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The gut microbiome and Alzheimer's disease: Complex and bidirectional interactions

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Abstract

Structural and functional alterations to the gut microbiome, referred to as gut dysbiosis, have emerged as potential key mediators of neurodegeneration and Alzheimer disease (AD) pathogenesis through the "gut -brain" axis. Emerging data from animal and clinical studies support an important role for gut dysbiosis in mediating neuroinflammation, central and peripheral immune dysregulation, abnormal brain protein aggregation, and impaired intestinal and brain barrier permeability, leading to neuronal loss and cognitive impairment. Gut dysbiosis has also been shown to directly influence various mechanisms involved in neuronal growth and repair, synaptic plasticity, and memory and learning functions. Aging and lifestyle factors including diet, exercise, sleep, and stress influence AD risk through gut dysbiosis. Furthermore, AD is associated with characteristic gut microbial signatures which offer value as potential markers of disease severity and progression. Together, these findings suggest the presence of a complex bidirectional relationship between AD and the gut microbiome and highlight the utility of gut modulation strategies as potential preventative or therapeutic strategies in AD. We here review the current literature regarding the role of the gut-brain axis in AD pathogenesis and its potential role as a future therapeutic target in AD treatment and/or prevention.

Keywords

Gut microbiome; Alzheimer disease; Age; Lifestyle; Prevention

1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia in individuals above the age of 65 years, and results in progressive memory and cognitive impairment, behavioral changes, and functional decline (Tarawneh and Holtzman, 2012). From a neuropathological perspective, AD is characterized by the abnormal aggregation of extracellular amyloid, in the form of amyloid plaques, and intracellular hyper-phosphorylated tau protein in the form of neurofibrillary tangles, eventually leading to synaptic dysfunction and neuronal death

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(Price et al., 2001). As populations are aging, and in the absence of effective methods for disease prevention or treatment, AD has become a global health epidemic and a major cause of morbidity and mortality among elderly (Tarawneh and Holtzman, 2012).

Late-onset sporadic AD is a multifactorial disease that results from a complex interaction of genetic, lifestyle, and environmental factors (Tarawneh and Holtzman, 2012). Among the environmental factors implicated in AD pathogenesis, rapidly growing evidence from animal and human data suggests an important role for the gut microbiome in the onset and progression of AD pathology and supports the notion that alterations to the gut microbiome can influence central nervous system (CNS) homeostasis and disease pathogenesis through a "gut -brain axis" (Carabotti et al., 2015) (Fig. 1).

The human intestines contain approximately 1000 species and 7000 strains of bacteria which constitute the gut flora, with gram-positive or gram-negative *Firmicutes* (including the genus *Lactobacillus*, *Clostridium*, and *Eubacterium*) and gram-negative *Bacteroidetes (*including *Bacteroides* and *Prevotella)* being the most predominant (Huttenhower et al., 2012; Askarova et al., 2020). Dysregulation of the gut microbiome reflected by changes in the diversity and frequency of microorganism taxa and species which constitute the gut flora, also referred to as "gut dysbiosis", has been associated with abnormal brain protein aggregation, inflammation, immune dysregulation, and impaired neuronal and synaptic activity in animal and human studies of AD (Gubert et al., 2020; Cryan et al., 2020). Furthermore, studies suggest that the presence of AD pathology is associated with characteristic changes to the gut microbiome leading to relatively disease-specific metabolic signatures which may serve as potential AD biomarkers (Vogt et al., 2017).

In this review, we will summarize the current and rapidly growing literature regarding the complex, and often bidirectional, relationship between the gut microbiome and AD, and describe various disease mechanisms and pathways by which the gut microbiome may contribute to AD pathogenesis from both animal and clinical studies. We also review effects of aging and environmental factors including diet, exercise, sleep, and stress on the gut-brain axis, and discuss potential strategies for gut modulation which may have a beneficial role in future AD prevention or treatment trials. Finally, we discuss limitations of previous studies of the gut microbiome in AD and provide directions for future research.

2. Evidence supporting the bi-directional relationship between the gut microbiome and AD

2.1. Animal studies

Data from animal studies support the notion that the gut microbiome contributes to cognitive impairment and the progression of AD pathology, including amyloid and tau aggregation, immune dysregulation, and neuroinflammation (Kowalski and Mulak, 2019; Wang, 2022). Significant alterations to the gut microbiome which may result from dietary changes, medication use, or infection have also been directly associated with synaptic dysfunction and cognitive or behavioral impairment in animal models of AD (Gareau, 2014).

Infection with *Enterobacteria* exacerbated AD pathology in a *Drosophila* AD model by promoting immune hemocyte recruitment into the brain, inflammation, and tumor necrosis factor (TNF)- and c-jun N-terminal kinase (JNK)-mediated neurodegeneration (Wu et al., 2017). Increased gut bacterial load and higher circulating levels of antimicrobial peptides targeting gram-negative bacteria have been reported in *Drosophila* tauopathy models, suggesting the presence of an enhanced innate immune response to gut flora (Rydbom et al., 2021). The gut microbiome also regulates the trafficking of interleukin (IL) 17-producing γδ-T cells from the gut into the meninges which triggers astrocytic release of IL-17, chemokine receptor 6 (CCR6)-mediated neuroinflammation, and synaptic dysfunction (Cipollini et al., 2019). In a study by Wang et al., intestinal dysbiosis induced by 1 month of ampicillin administration was associated with reduced hippocampal expression of the N-methyl-D-aspartic acid (NMDA) receptor, increased anxiety, and spatial memory impairment in rats, while the enrichment of the gut microbiome with *Lactobacillus fermentum NS9* ameliorated these changes (Wang et al., 2015a). Infection with the pathogenic bacteria *Citrobacter rodentium* resulted in stress-induced memory disturbances in a C57BL/6 mouse model (Gareau et al., 2011). Additionally, in germ-free Swiss-Webster mice deprived of intestinal bacteria, spatial and working memory impairments were accompanied by reduced brain-derived neurotrophic factor (BDNF) expression which is associated with impaired synaptic plasticity (Gareau et al., 2011).

Other alterations to the gut microbiota have been shown to be beneficial in improving cognition or reducing AD pathology (Kowalski and Mulak, 2019). Treatment of *APP/PS1* mice with antibiotics significantly reduced Aβ deposition and increased soluble Aβ levels even in older mice and was associated with less reactive gliosis around amyloid plaques, altered microglial morphology, and lower levels of peripheral inflammatory mediators (Minter et al., 2016, 2017). Prebiotic supplementation of *APP/PS1* transgenic mice with oligosaccharides derived from *Morinda officinalis* maintained gut microbiota diversity, reduced Aβ pathology, and ameliorated neuronal apoptosis (Xin et al., 2018). Significant improvement in cognitive deficits was reported in specific pathogen-free Sprague-Dawley rats when their diets were enriched with *Lactobacillus helveticus NS8* (Liang et al., 2015). The administration of both *Lactobacillus* and *Bifidobacterium* improved memory and learning deficits and reduced oxidative stress associated with intra-hippocampal injection of Aβ in a rat model of AD (Athari Nik Azm et al., 2018). Other studies have shown that the probiotic *Bifidobacterium longum 1714* improved cognitive function in male BALB/c mice (Savignac et al., 2015) and that transplantation of fecal microbiota from wild-type to AD transgenic mice was associated with reduced amyloid and tau pathologies and improved cognition (Kim et al., 2020).

In a study by Neufeld et al., germ-free mice exhibited improved behaviors and lower anxiety associated with reduced expression of the NMDA receptor subunit, NR2B, in the central amygdala, increased BDNF, and decreased serotonin receptor 1 A (5HT1A) hippocampal expression compared to their conventionally-reared specific pathogen-free counterparts (Neufeld et al., 2011). When *APP/PS1* mice are engineered to become germ-free, a decrease in Aβ pathology is observed, while colonizing germ-free *APP/PS1* mice with microbiota from conventionally raised transgenic mice increases brain Aβ pathology (Harach et al., 2017). In another study, the oral administration of *Bifidobacterium breve*

A1 strain prevented Aβ-induced cognitive impairment and attenuated behavioral deficits in an AD mouse model (Kobayashi et al., 2017). Similarly, in a rat AD model induced by intraperitoneal injection of D-galactose, treatment with *Lactobacillus plantarum* MTCC 1325 reduced Aβ plaque formation, restored brain acetylcholine levels, and improved cognition (Nimgampalle and Kuna, 2017). In these studies, molecular and pathological changes associated with cognitive improvement include decreased plasma levels of corticosterone and adrenocorticotropic hormone (ACTH), normalization of serotonin and norepinephrine brain expression, increased hippocampal BDNF expression, and reduced neuronal apoptosis (Askarova et al., 2020). Table 1 summarizes the main findings from animal studies examining the relationship between AD and the gut microbiome.

Evidence supporting a bi-directional relationship between the gut microbiome and AD is mostly derived from transgenic AD animal studies which examine the temporal relationship between gut microbiome structure and AD pathology in strictly controlled specific pathogen-free settings. Studies have shown that AD pathology influences the gut microbiome shifting it towards configurations that overlap with those seen in autism and inflammatory disorders (Bäuerl et al., 2018). Alterations to the gut microbiome in *APP/PS1* transgenic AD mice compared to wild-type mice include increases in *Bacteroidetes* and *Tenericutes* phyla and reductions in *Actinobacteria, Firmicutes, Verrucomicrobia*, and *Proteobacteria* which are observed as early as 8 months of age (Harach et al., 2017). Alterations in gut microbiota with aging and increased gut amyloid precursor protein (*APP*) expression have also been reported in 5xFAD mice (Brandscheid et al., 2017). Interestingly, data from AD animal models suggest that the gut microbiome of AD mice is enriched with pro-inflammatory species (e.g. *Escherichia-Shigella*, *Desulfovibrio, Akkermansia*, and *Blautia*) and that gut dysbiosis is present early in life, increases with age, and often precedes the first signs of cortical Aβ deposition or microglial activation (Chen et al., 2020). Therefore, it has been postulated that AD pathology or AD-causing mutations in mouse models induce gut microbiome alterations which subsequently may contribute to further AD progression in a “forward-feedback” loop. This notion is supported by observations that gut microbial changes are often observed prior to brain amyloid aggregation, and that animals with absent intestinal flora develop less amyloid pathology than those with existing or replaced gut microbiomes (Harach et al., 2017; Chen et al., 2020; Dodiya et al., 2019, 2020). Further research is needed to clarify the extent to which AD mutations or brain AD pathology influence the gut microbiome and the mechanisms that underlie these changes.

2.2. Clinical studies

Consistent with animal data, results of clinical studies support an important role for the gut microbiome in AD pathogenesis and the presence of a gut microbiome “signature” for AD (Vogt et al., 2017). Numerous studies report the increased prevalence of bacterial lipopolysaccharide (LPS) in AD brain lysates compared to controls, including the accumulation of LPS in neocortical and hippocampal neurons and its co-localization with Aβ in amyloid plaques and perivascular Aβ aggregates (Zhan et al., 2016; Zhao et al., 2017a,b). Associations with other pathogens, including *Chlamydia pneumoniae, Borrelia burgdorferi*, spirochetes, herpes simplex type 1, and several others have also been reported in post-mortem AD brains (Hammond et al., 2010; Miklossy, 2016; Zhan et al., 2016).

However, causal relationships and a full understanding of the mechanisms by which the gut microbiota influence brain pathology cannot be elucidated from post-mortem studies.

Conversely, recent studies in living individuals with AD have provided important insights into the role of the gut microbiome in AD pathology. Significant differences in the composition of the gut microbiomeat both the phylum and species levels-have been observed in individuals with AD compared to healthy controls in cross-sectional studies (Vogt et al., 2017; Kowalski and Mulak, 2019). In a recent study of individuals with late-onset AD and matched controls, which utilized bacterial 16 S ribosomal RNA (rRNA) gene sequencing of stool samples (Vogt et al., 2017), reductions in gut microbial diversity and significant differences in the abundance of 82 operational taxonomic units (OTUs) were observed in AD compared to controls, including differences at the phylum, family, and genus levels. Differences at the phylum level included a decreased abundance of *Firmicutes* and *Actinobacteri*a, and an increased abundance of *Bacteroidetes*. Within *Firmicutes*, AD samples showed less abundance of the families *Ruminococcaceae*, *Turicibacteraceae*, *Peptostreptococcaceae*, *Clostridiaceae*, and *Mogibacteriaceae*, and the genera *SMB53* (family *Clostridiaceae)*, *Dialister*, *Clostridium*, *Turicibacter*, and *cc115* (family *Erysipelotrichaceae*), and more abundance of the family *Gemellaceae* and the genera *Blautia*, *Phascolarctobacterium*, and *Gemella* compared to controls. Within *Bacteroidetes*, *Bacteroidaceae* and *Rikenellaceae* at the family level, and *Bacteroides* and *Alistipes* at the genus level were more abundant in AD. Within *Actinobacteria*, AD samples had lower abundance of the *Bifidobacteriaceae* at the family level and *Bifidobacterium* and *Adlercreutzia* at the genus level. Conversely, the genus *Bilophila* in the phylum *Proteobacteria* was more abundant in AD samples compared to controls. Furthermore, gut microbial alterations correlated with disease severity and cerebrospinal fluid (CSF) markers of amyloid (i.e., lower CSF Aβ42/Aβ40 levels) and tau (higher CSF p-tau181 levels) pathology with the strongest correlations being observed with *Blautia*, *SMB53* and *Dialister* bacterial load. In this cohort, increased *Bacteroides*, and decreased *Turicibacter* and *SMB53*, bacterial populations also correlated with higher CSF YKL-40 levels, reflective of more severe astrocytic activation in AD (Vogt et al., 2017). Differences in intestinal populations of *Bacteroides, Actinobacteria, Ruminococcus, Lachnospiraceae*, and *Selenomonadales* phyla have also been reported in other cohorts (Zhuang et al., 2018). Consistent with these reports, a systematic meta-analysis of 11 observational and pre-interventional studies, which included 805 individuals with AD and healthy controls, found that individuals with AD dementia had lower gut microbial diversity compared to controls, more abundance of *Proteobacteria*, *Bifidobacterium*, and *Phascolarcobacterium*, and lower abundance of *Firmicutes*, *Clostridiaceae*, *Lachnospiraceae*, and *Rikenellaceae* compared to controls (Hung et al., 2022). Conversely, this meta-analysis suggested no significant differences in gut microbial diversity between individuals with mild cognitive impairment (MCI) and healthy controls. For several microbiota (i.e., *Proteobacteria, Phascolarcobacterium*, and *Clostridiaceae*), altered microbial abundance was found to scale with progression from normal cognition to MCI to AD dementia.

Higher intestinal levels of the pro-inflammatory *Escherichia-Shigella*, and lower levels of the anti-inflammatory *Eubacterium rectale*, have been associated with peripheral markers of inflammation, including interleukin (IL)-1β, IL-6, C-X-C motif chemokine ligand-2

[CXCL2], and NLRP3 (NOD-like Receptor [NLR] Family Pyrin Domain-Containing Protein 3) inflammasome in cognitively impaired older adults with amyloidosis compared to those without amyloidosis and healthy controls (Cattaneo et al., 2017). Other reports suggest that AD is associated with significant elevations in serum IgG antibodies targeting *Fusobacterium nucleatum* and *Prevotella intermedia* (Sparks Stein et al., 2012). Studies examining the associations of *Helicobacter pylori* (*H. pylori*) with AD have been conflicting. While previous studies suggest possible associations of *H.pylori* infection with AD, and higher CSF or serum *H. pylori*-specific IgG antibody titers with more severe cognitive impairment (Kountouras et al., 2009; Roubaud-Baudron et al., 2012), these findings were not confirmed in a recent large population-based study which showed no association between *H. pylori* infection and dementia risk (Fani et al., 2018).

In addition to quantitative and qualitative differences in microbial taxa, functional differences in the gut microbiome across different taxa and species have also been reported in association with AD pathology (Liu et al., 2019a). In one study which conducted functional pathway analyses of the gut microbiome using KEGG (Kyoto Encyclopedia of Genes and Genomes) and PICRUSt (Phylogenetic Investigation of Communities by Reconstruction of Unobserved States), the gut microbiome of individuals with AD was enriched with orthologs involved in LPS biosynthesis (glycan biosynthesis and metabolism) and the bacterial secretion system (membrane transport), while orthologs related to N-glycan biosynthesis, phenylalanine, tyrosine, and tryptophan biosynthesis and histidine metabolism were downregulated in AD compared to healthy controls (Liu et al., 2019a). Other studies have shown that disease-specific signatures for AD can be identified by combining clinical data with gut microbial features. The AlzBiom study combined taxonomic and functional gut microbial assessments measured by shotgun metagenomics with clinical data from 75 amyloid-positive individuals with AD dementia and 100 healthy controls. Findings from this study suggested the presence of an AD-specific signature consisting of 18 genera, 17 Gene Ontology features, and 26 KEGG ortholog features, which when combined with clinical data (i.e., age, sex, body mass index, and the apolipoprotein E4 [*APOE4*] genotype) discriminated AD from controls with a diagnostic accuracy of 80–92% (Laske et al., 2022).

A recent study which utilized 16 S Ribosomal RNA sequencing to examine the gut microbiome found that gut microbiome alterations were detectable in the early preclinical stages prior to the onset of cognitive impairment (e.g., increased relative abundance of *Bacteroidetes* and decreased abundance of *Firmicutes* and class *Deltaproteobacteria*). When the gut microbiome profile was combined with cognitive status and plasma Aβ levels, the combination of these markers differentiated preclinical AD from healthy controls with a diagnostic accuracy of 87% (Sheng et al., 2022).

Cognitively impaired individuals with AD, including those with MCI, exhibit distinctive gut metabolomic signatures compared to healthy controls. CSF levels of the gut metabolite, trimethylamine N-oxide (TMAO), are elevated in individuals with AD (Vogt et al., 2018), and correlate with CSF markers of amyloid (i.e. CSF Aβ42) and tau (i.e. p-tau181) pathology, and neurodegeneration (i.e. total tau and neuro-filament light chain). Plasma TMAO levels are also elevated in aging mice and may reflect oxidative stress and mitochondrial dysfunction associated with senescence (Li et al., 2018). Studies which

examined fecal metabolomics have found significant differences in the levels of tryptophan metabolites, especially those involving indole derivatives and serotonin synthesis, and lithocholic acid in stool samples from AD compared to controls, which correlated with gut dysbiosis and cognitive impairment (Wu et al., 2021; Pappolla et al., 2021). Levels of the tryptophan metabolite, indole-3-pyruvic acid, predicted AD pathology and were progressively higher in MCI and AD dementia compared to healthy controls. Conversely, the indole derivatives, acting as the aryl hydrocarbon receptor (AhR) ligands, were reduced in the presence of AD pathology (Wu et al., 2021). In this study, levels of 5 short-chain fatty acids (formic acid, acetic acid, propanoic acid, 2-methylbutyric acid, and isovaleric acid) were found to be strongly predictive of clinical progression from MCI to AD dementia (Wu et al., 2021). Altered CSF levels of tryptophan metabolites were also reported in other AD cohorts (Kaddurah-Daouk et al., 2011). The main findings from clinical studies examining the relationship between AD and the gut microbiome are summarized in Table 2.

In contrast to animal studies which provide direct evidence for brain AD pathology influencing the gut microbiome, elucidating the temporal relations between AD pathology and gut microbial alterations in clinical cohorts is particularly challenging given the limited number of studies, small cohorts, unstandardized study methods in cohort characterization and microbiome analyses, and the cross-sectional study design which limits the ability to track gut microbial alterations associated with healthy aging across middle and late life, and contrast them to those associated with disease onset or progression. Therefore, while several studies have shown quantitative and qualitative differences in the gut microbiome of individuals with AD compared to controls, in the absence of longitudinal evaluations, it remains unclear whether these are the cause or result of AD pathology. Examination of gut microbial alterations early in life in individuals with dominantly inherited forms of AD (autosomal dominant AD [ADAD]; caused by autosomal dominant mutations in *APP*, presenilin-1 [*PSEN1*], or presenilin-2 [*PSEN2*]) represents an excellent opportunity to elucidate the effects of AD -causing mutations on gut microbiota early in life prior to the onset of AD pathology in the brain and to differentiate these from gut microbiota associated with healthy aging. Unfortunately, there is a scarcity of data regarding the gut-brain axis in ADAD cohorts, which, therefore, represents an important area for future research. Nevertheless, a few recent studies have examined the gut microbiome in individuals with Down's syndrome (i.e., Trisomy 21), almost all of whom develop AD pathology by the fifth decade of life due to the presence of an additional copy of *APP* on chromosome 21. Findings from a study of Chinese children with Down's syndrome suggested the presence of significant differences in the structure and diversity of the gut microbiome compared to controls, including a lower abundance of *Acidaminococcaceae* and increased modules involved in peptidases and pyrimidine metabolism (Ren et al., 2022). Importantly, gut microbiota alterations were closely associated with the severity of cognitive impairment in this cohort. Similar studies which include fluid or imaging markers of AD pathology in dominantly inherited (i.e., ADAD) or genetic forms (i.e., Trisomy 21) of AD will better elucidate the bi-directional relationship between AD-causing mutations and the gut microbiome prior to the development of significant AD pathology. Furthermore, longitudinal studies of well-characterized AD cohorts, encompassing those with early-onset inherited and late-onset sporadic forms of the disease, will provide valuable insight into the extent

to which microbial alterations in cognitively normal older adults may serve as predictive markers for AD pathology and/or viable targets for potential disease modification.

Despite their anatomical continuity, studies suggest that the oral and gut microbiome profiles are distinct, being separated by the “oral-gut barrier”, and interdependently influence AD pathology (Park et al., 2021). There is growing evidence from epidemiological and experimental studies that the oral microbiome may also be associated with AD pathology and cognition (Kowalski and Mulak, 2019; Sureda et al., 2020). Periodontal disease is observed with higher frequency in patients with neurodegenerative disorders and has been associated with the severity of cognitive impairment in epidemiological studies (Ide et al., 2016). Individuals with periodontitis of 10 years were found to have a 1.7-fold increased risk of developing AD in one study (Chen et al., 2017), and those with periodontitis and gingivitis were at a higher risk of developing all-cause dementia in another study (Tzeng et al., 2016). Noble et al. found that higher serum titers of periodontal anti--*Actinomyces naeslundii* and anti-*Eubacterium nodatum* IgG were associated with a higher, and lower, risk for AD, respectively (Noble et al., 2014). Kamer et al. reported associations between periodontal disease and brain Aβ load using the positron emission tomography (PET) amyloid ligand Pittsburgh Compound B in cognitively normal older adults (Kamer et al., 2015). In a recent report, antibodies for *Porphyromonas gingivalis*, the most common pathogenic periodontal bacteria, were elevated in the serum of AD patients and an enzyme, gingipain, produced by *P. gingivalis*, was found in post-mortem AD brains (Singhrao and Olsen, 2019; Dominy et al., 2019). Other studies demonstrate differences in the prevalence of the *Moraxella*, *Leptotrichia*, and *Sphaerochaeta* genera in AD compared to controls (Liu et al., 2019b), and associations between oral dysbiosis and the progression of AD pathology (Bathini et al., 2020), or conditions such as diabetes mellitus (DM) and atherosclerosis which are associated with a higher risk for AD (de Groot et al., 2017; Fåk et al., 2015). While these findings suggest the presence of a potential association between oral bacteria and AD, there is limited data to support a cause-effect relationship and further research in this area is warranted.

3. Proposed mechanisms linking the gut microbiome to AD

Gut dysbiosis contributes to AD pathogenesis and cognitive impairment via several mechanisms, including immune dysregulation, neuroinflammation, disruption of the intestinal and blood-brain barriers, amyloid and tau aggregation and toxicity, and impaired synaptic plasticity, neuronal excitability, and neurogenesis. Fig. 2 represents an overview of the various mechanisms by which the gut microbiota and gut toxins or metabolites exert peripheral and central effects leading to cognitive impairment.

3.1. Immune system dysregulation

Emerging evidence from genetic, histopathological, and mechanistic studies supports an important role for immune dysregulation as a central and primary substrate in AD pathogenesis (Kinney et al., 2018; Lutshumba et al., 2021). Disturbances in innate immunity including cytokine signaling, immune cell proliferation and migration, and microglial activation are observed in animal models of AD (Heneka et al., 2015). Recent findings

from large-scale genetic analyses in humans suggest that over half of the AD risk loci are significantly enriched or uniquely expressed in immune cells (Wightman et al., 2020). Genetic variants in the microglial receptor, triggering receptor expressed on myeloid cells-2 (TREM2), are associated with a 2–3-fold higher risk for AD (Abduljaleel et al., 2014). The gut microbiome influences innate and adaptive immunity, including a role in innate immune system priming through the formation of gut-associated lymphoid tissue and influencing adaptive local and systemic immune responses (Galland, 2014). Alterations to the gut microbiome are associated with increased penetration of peripheral Th1 immune cells into the blood-brain-barrier (BBB), increased microglial activation, Aβ aggregation, and cognitive decline in AD mouse models (Galland, 2014). The gut microbiome may alter the peripheral immune response through the release of cytokines, complement and major histocompatibility complex (MHC) proteins, and microbial toxins or metabolites, including LPS, polysaccharide A (PSA), and butyrate (van Olst et al., 2021).

LPS is a bacterial endotoxin which is produced by several gram-negative bacteria (e.g. *Bacteroidetes*), and is detected in amyloid plaques and peri-vascular Aβ aggregates in human AD brains (Zhan et al., 2016). Neocortical and hippocampal LPS levels are 7 and 21-fold higher, respectively, in lysates of AD brains compared to age-matched controls (Zhao et al., 2017a) and LPS colocalizes with amyloid within plaques and surrounding blood vessels (Zhan et al., 2016). LPS induces systemic inflammation through several pathways including the activation of Toll-like receptor (TLR) 4 signaling with the subsequent release of proinflammatory cytokines (e.g., IL-1, IL-6, and tumor necrosis factor-α [TNF-α]) and the activation of T helper17 (Th17) cells which contribute to neurodegeneration via activation of the apoptotic Fas pathway in neurons (Cani et al., 2007; Tristão et al., 2017; Zhang et al., 2013; Lukiw, 2016). LPS produced by *Bacteroides fragilis* activates the nuclear factor kappa B (NF-κB) pathway and induces the transcription of pro-inflammatory miRNAs, which interfere with microglial functions (Lukiw, 2016). As an example, miRNA-34a inhibits the ability of microglia to phagocytose Aβ (Bhattacharjee et al., 2016). Another mechanism by which LPS contributes to brain amyloid aggregation involves disrupting Aβ flux across the BBB and reducing brain amyloid clearance into the periphery (Jaeger et al., 2009) (see section on Amyloid and Tau Aggregation). Intraperitoneal injection of LPS increased brain Aβ levels, reduced neuronal counts, and induced cognitive deficits in C57BL/6J mice (Kahn et al., 2012; Zhao et al., 2019). In another study, intraventricular LPS administration with ascorbic acid increased the immunoreactivity of intraneuronal Aβ (Hauss-Wegrzyniak and Wenk, 2002). LPS-injected mice display cognitive deficits and higher brain and peripheral levels of pro-inflammatory cytokines (i.e., TNF-α and IL-1β), higher levels of prostaglandin E2 and nitric oxide (NO), and lower levels of the anti-inflammatory cytokines IL-4 and IL-10 (Zhao et al., 2019). Treatment with the TLR-4 specific inhibitory peptide, VIPER, prevented LPS-mediated inflammation and ameliorated cognitive impairment in these models (Zhao et al., 2019).

P-glycoprotein (P-gp) is an efflux transporter which is expressed in the brain endothelium (van Assema et al., 2012) and intestinal barrier and is involved in amyloid clearance across the BBB (Wang et al., 2016a; Cirrito et al., 2005). AD is associated with reduced brain endothelial expression and impaired function of P-gp which contributes to amyloid aggregation, and with lower levels of P-gp in the intestinal epithelium compared to healthy

controls and individuals with other dementias (Chiu et al., 2015; Haran et al., 2019). Several constituents of the gut microbiome, mainly gram-negative *Bacteroides*, alter P-gp levels with variable effects observed across different species; increased abundance of *B. dorei* is associated with higher P-gp levels, while lower P-gp levels are associated with a higher abundance of *B. fragilis and B. vulgatus* (van Olst et al., 2021). Furthermore, in a clinical study, stool samples from individuals with AD had lower p-gp levels than controls and resulted in lower p-gp levels from in vitro samples of healthy controls and individuals with other dementias (Haran et al., 2019). In addition to its role in amyloid clearance, P-gp exerts regulatory homeostatic functions which suppress the immune response to gut bacteria by exporting endocannabinoids, and balance inflammatory pathways mediated by multidrug-resistant protein 2 [MRP2]/hepoxilin A3 (Szabady et al., 2018). Therefore, gut dysbiosis may contribute to brain amyloid deposition and altered immune homeostasis through p-gp dysregulation and the loss of its physiological transport and immunomodulatory functions.

Gram-negative *Bacteroides fragilis* also produce the capsular carbohydrate, PSA. PSA triggers a regulatory immune response via the toll-like receptor-2 (TLR-2) which includes activation of dendritic cells and regulatory T cells, suppression of Th17 cells, and decreased production of IL-17 (Shen et al., 2012). Conversely, CD4 + stimulation by PSA was associated with increased secretion of pro-inflammatory cytokines (interferon [IFN]-γ, TNF-α, IL-6 and CXCL10), and increased surface expression of anti-inflammatory mediators (Lag3, Tim3, and PD1) in one study suggesting complex, and possibly dual, effects of PSA on inflammatory pathways (Alvarez et al., 2020).

Short-chain fatty acids (SCFA), such as butyrate, acetate, and propionate, play an important role in maintaining the structural and functional integrity of the gut microbiome, and mediating many of its immunomodulatory functions (Tan et al., 2014). Multidimensional data-driven models which utilize a systems-based approach identified over 8000 important interactions of microbial metabolites with AD pathways and ranked SFCAs among the most highly prioritized microbial metabolites associated with AD (Wang et al., 2021a). *F. prausnitzii, E. rectale, and Lachnospiraceae* are among the most important butyrate-producing gut bacteria and exert important regulatory effects on the peripheral immune system (Liu et al., 2018; Atarashi et al., 2013). Butyrate administration increases transforming growth factor (TGF)-β-dependent differentiation of Treg cells in cell cultures (Kespohl et al., 2017), inhibits NF-κB signaling in the intestinal epithelium (Segain et al., 2000), and is associated with higher plasma TGF-β levels and lower plasma IL-6, IL-17, and IL-23 levels (Zhang et al., 2016). Dendritic cell cultures treated with butyrate demonstrate increased IL-10 production by CD4 + cells, decreased IL-17 production, and reduced differentiation of naïve T cells into pro-inflammatory IFN-γ-producing phenotypes (Gurav et al., 2015; Kaisar et al., 2017). In LPS-treated rats, butyrate administration is associated with reduced expression of cytokine-induced neutrophil chemoattractant (CINC) 2αβ, TNF-α, and NO (Vinolo et al., 2011). Butyrate has been shown to mitigate inflammation in LPS-treated macrophages via inhibition of histone deacetylase, subsequent downregulation of IL-6, IL-12, and NO synthase 2, and G-protein receptor mediated inhibition of the NF-kB signaling pathway (Siddiqui and Cresci, 2021). While butyrate exerts predominantly anti-inflammatory effects under normal physiological conditions, interestingly-higher doses of butyrate may trigger inflammation via induction of IFN- γ and T-bet expression (Kespohl

et al., 2017). SCFAs can also modulate T cell fate through G-coupled protein receptor signaling (GPR41/GPR43) and epigenetic modifications (Kim et al., 2013). Carriers of the *APOE4* allele, the most significant genetic risk factor for AD, have significantly lower abundance of butyrate-producing *Ruminococcacaea* compared to *APOE*2/3 carriers (Tran et al., 2019).

Another mechanism by which the gut microbiome may influence brain pathology is through altered metabolism of bile acids. Serum and stool levels of secondary bile acids, which are produced through the deconjugation of primary bile acids by gut bacteria, are elevated in the presence of high anaerobic content of gut microbiota (Heinken et al., 2019). In a study of 1464 individuals with MCI or dementia due to AD and healthy controls, lower levels of cholic acid, and higher levels of the 7α-dehydroxylated counterpart, deoxycholic acid, were observed in AD compared to controls (MahmoudianDehkordi et al., 2019). Furthermore, higher levels of deoxycholic acid damage the tight junctions of the intestinal barrier and contribute to cognitive impairment by BBB disruption and translocation into the brain (Quinn et al., 2014; Raimondi et al., 2008; Stenman et al., 2013).

In addition to the generation of toxic metabolites, recent studies suggest that gut dysbiosis may influence peripheral immunity via amino acid secretion. High levels of phenylalanine and isoleucine (Phe/Ile) increase Th1 cells and promote neuroinflammation, while treatment with GV-971, a marine-derived oligosaccharide, reconditions the gut microbiota and reduces detrimental effects of amino acids on peripheral immunity (Wang et al., 2019). In a study by Wang et al (Wang et al., 2019), gut dysbiosis, reflected by an increased ratio of *Firmicutes* to *Bacteroidetes*, was evident at 7 months of age and coincided with an increase in the number of pro-inflammatory microglia and infiltrating peripheral Th1 cells and Aβ-mediated synaptic dysfunction in 5xFAD compared to wild-type mice. Similar increases in peripheral Th1 infiltration were observed in wild-type mice that were co-housed with, or received fecal microbiota transplantation (FMT) from, 5xFAD mice. Interestingly, higher blood and fecal levels of phenylalanine and isoleucine (*Phe/Ile*) were observed in 5xFAD mice compared to wild-type mice, which normalized with the oral administration of GV-971 (Wang et al., 2019). Treatment with GV-971 was also associated with lower brain Aβ burden, fewer brain Th1 cells, and less activated microglia in 5xFAD mice and improved cognitive function in *APP/PS1* mice (Seo et al., 2019; Wang et al., 2019).

3.2. Leaky gut

Inflammation is associated with disruption of the intestinal epithelial barrier which facilitates the flux of bacterial constituents, endotoxins, and inflammatory cells into the circulation, a condition often referred to as “leaky gut” (Marizzoni et al., 2017). While certain gut species such as *Lactobacillus plantarum*, *Escherichia coli Nissle*, and *Bifidobacterium infantis* enhance the expression of tight junction proteins (Bischoff et al., 2014), others such as the *Bacteroides fragilis* toxin disrupt the intestinal barrier (Choi et al., 2016; König et al., 2016). Gut hyperpermeability assays have demonstrated changes in tight junction proteins such as E-cadherin, occludin, and zonula occludens (ZO-1) proteins in AD, which facilitate the translocation of bacterial endotoxins into the circulation (“endotoxemia”) (Andŕe et al., 2019). Serum samples from individuals with dementia

have increased markers of gut permeability, such as serum diamine oxidase (DAO) levels, and increased inflammatory mediators including the soluble cluster of differentiation 14 (sCD14) levels compared to controls (Stadlbauer et al., 2020). Measurements of calprotectin concentrations in the stool may also offer a useful surrogate for gut inflammation (Walsham and Sherwood, 2016). Calprotectin is an inherently amyloidogenic calcium-binding protein which consists of a heterodimer of S100A8/A9 (Walsham and Sherwood, 2016) and can aggregate into oligomers and fibrils that resemble those of Aβ and induce Aβ fibrillization in vitro (Wang et al., 2014a; Zhang et al., 2012). S100A9 induces microglial activation via TLR4 and the receptor for glycation end-products (RAGE) pathways and promotes oligodendrocyte precursor cell apoptosis via activation of the NF-kB pathway (Wang et al., 2014a; Wu et al., 2018). CSF and brain calprotectin levels are increased in AD (Kowalski and Mulak, 2019), and mediate increased amyloid plaque formation in individuals with TBI (Wang et al., 2018).

3.3. Neuroinflammation, IL-17, and kynurenine pathways

Neuroinflammation is a well-documented pathological substrate of AD; increased numbers of activated microglia and reactive astrocytes are observed in human AD brains in the vicinity of amyloid plaques (Cattaneo et al., 2017; Cerovic et al., 2019). Abnormal amyloid and tau aggregation stimulate microglia, trigger the release of inflammatory cytokines and recruitment of inflammatory cells into the brain (Wang et al., 2015b). Gut dysbiosis is closely associated with activation of the NLRP3 inflammasome and higher peripheral levels of pro-inflammatory markers (Cattaneo et al., 2017). Transplantation of transgenic mice with fecal samples from individuals with AD is associated with NLRP3 induction, hippocampal microglial activation, and cognitive impairment (Shen et al., 2020). Furthermore, neuroinflammation is associated with downregulation of TREM2, leading to reduced microglial phagocytic ability of amyloid and increased amyloid aggregation (Pistollato et al., 2016; Zhao and Lukiw, 2013). Repeated exposure to bacterial toxins such as LPS may prime microglia and exacerbate microglial response to Aβ in the brain (Friedland, 2015). The secretion of meso-diaminopimelic acid (meso-DAP) from bacterial cell walls triggers the nucleotide-binding oligomerization domain-containing protein 1 (NOD1) receptor signaling and NOD1-mediated activation of bone marrow neutrophils (Clarke et al., 2010).

In AD mouse models, Aβ recruits neutrophils by increasing the affinity of the lymphocyte function association antigen-1 (LFA-1) integrin to the brain endothelium (Zenaro et al., 2015). In the brain, neutrophils increase IL-17 production which amplifies neutrophil recruitment and contributes to neurodegeneration and cognitive deficits (Cipollini et al., 2019). Blocking LFA-1 integrin or depleting neutrophils reverses cognitive deficits in mice (Zenaro et al., 2015). Increased production of reactive oxygen species due to Aβ also stimulates IL-17 secretion. IL-17 plays an important role in mediating neuroinflammation in AD and is synergistic with the pro-inflammatory effects of cytokines (Cipollini et al., 2019); CSF, serum, and hippocampal IL-17 levels are increased in AD animal models (Milovanovic et al., 2020), and their neutralization with anti-IL-17 antibodies ameliorates Aβ-mediated neuroinflammation, as evidenced by lower levels of the astrocytic markers

(e.g., glial fibrillary acidic protein [GFAP], S100b, and myeloperoxidase-[MPO]), and improves cognitive functions (Cristiano et al., 2019).

Interestingly, gut microbiome alterations triggered by a high salt diet induce brain endothelial dysfunction and cognitive impairment in mice via intestinal Th17 cell polarization even in the absence of brain inflammation (Faraco et al., 2018). One proposed mechanism for this includes toxic effects of IL-17, produced by Th17 cells, on brain endothelium leading to impaired endothelial eNOS synthesis and disturbed neurovascular coupling (Faraco et al., 2018). Furthermore, high salt may have both direct effects on Th17 cell polarization as well as indirect effects mediated by gut microbiome alterations including the depletion of *Lactobacillus murinus* (Wilck et al., 2017). Data from clinical studies are consistent with animal studies and suggest that serum IL-17 and IL-23 levels, and the expression of the Th17 transcription factor RORγt, are higher in AD compared to controls and that Th17 cell counts correlate with CSF markers of amyloid pathology (i.e., CSF Aβ42/Aβ40) (Chen et al., 2014; Oberstein et al., 2018). Fig. 3 summarizes the main effects of IL-17 in AD pathogenesis including its relationship with the gut microbiome.

Gut dysbiosis is also associated with higher extracellular levels of the high-mobility group box 1 (HMGB1), an important non-histone nucleoprotein which has highly preserved functions in transcriptional regulation, telomere maintenance, and DNA repair (Andersson et al., 2018; Festoff et al., 2016). The extracellular exosome-mediated release of HMGB1 from the intestines into the peripheral circulation in the setting of altered gut microbiota acts as a danger-associated molecular pattern which alarms the immune system and triggers TLR-4 and NF-KB inflammatory pathways and the peripheral release of inflammatory mediators (e.g. IL-1, IL-6, and TNF-α) (Fitzgerald and Kagan, 2020). Furthermore, HMGB1 is recognized by RAGE receptor on neutrophils, monocytes, and endothelium leading to chronic low-grade inflammation and impaired BBB permeability (Liu et al., 2021; Hudson and Lippman, 2018).

Another, albeit less understood, mechanism by which the gut microbiome contributes to CNS inflammation is the dysregulation of the kynurenine pathway involved in tryptophan metabolism. Under physiological conditions, tryptophan metabolism via the kynurenine pathway results in the formation of 4 key metabolites, 3-hydroxykynurenine (3-HK), quinolinic acid (QA), kynurenic acid (KA) and picolinic acid, which play important roles in neuroplasticity (Savitz, 2020). However, in the presence of gut dysbiosis, altered ratios of these metabolites have detrimental effects leading to microglial activation, neuroinflammation, and dysregulated calcium-mediated excitotoxicity (Lugo-Huitrón et al., 2013; Guillemin, 2012). One of the key enzymes of the kynurenine pathway, indoleamine 2,3-dioxygenase 1 (IDO-1), is activated by the pro-inflammatory cytokine, IFN-γ, and co-localizes with Aβ plaques (Arora et al., 2020). The administration of *Lactobacillus johnsonii* to bio-breeding rats was associated with reduced endogenous IDO-1 resulting in less tryptophan breakdown, and the diversion of tryptophan towards pathways involved in serotonin synthesis (Valladares et al., 2013).

Taken together, these findings support the notion that neuro-inflammation is an important mechanism by which gut dysbiosis can influence brain pathology and immune homeostasis

and has led to the proposition of a microbiome-gut-*inflammasome*-brain axis (Kamer et al., 2015; Shukla et al., 2021).

3.4. Blood-brain barrier disruption

The BBB, which is composed of endothelial tight junctions surrounded by pericytes and astrocytic end-foot processes, plays an important role in brain homeostasis (Sweeney et al., 2018). Disruption to the BBB, including loss of pericytes and endothelial tight junctions, is reported in even the earliest stages of AD, and is associated with increased amyloid pathology due to impaired Aβ clearance (Sweeney et al., 2018). Animal studies suggest that BBB alterations may precede Aβ and tau aggregation or neuronal loss (Szu and Obenaus, 2021). Similarly, clinical studies suggest that BBB dysfunction in the hippocampus (Montagne et al., 2015) and cortical regions is an early event in AD pathogenesis which precedes brain atrophy and cognitive decline (van de Haar et al., 2016). Toxic Aβ oligomers accelerate BBB damage by disrupting endothelial tight junctions, creating a vicious cycle that further promotes Aβ aggregation. Individuals with AD have imaging evidence of age- and disease-dependent BBB breakdown which correlates with memory loss and learning deficits and CSF markers of pericyte injury (Montagne et al., 2015).

There is growing evidence that a healthy gut microbiome is essential for BBB integrity as well as normal neuronal development (Fung et al., 2017). Gut dysbiosis is associated with increased BBB permeability in animal studies which improves after restoring gut microbial homeostasis (Braniste et al., 2014). Lower expression of the tight junction proteins, claudin-5 and occludin, and subsequent BBB disturbances have been documented in adult germ-free mice (i.e., which lack a gut microbiome), and are ameliorated with their conventionalization through fecal microbiota transplantation from pathogen-free adult mice or colonization with *Bacteroides thetaiotaomicron*, or *Clostridium tyrobutyricum* which produces butyrate (Braniste et al., 2014). Low-dose penicillin exposure in mice early in life was associated with increased hippocampal endothelial expression of the tight junction proteins, occludin and claudin-5, in one study (Leclercq et al., 2017), and treatment of senescence accelerated mice P8 (SAMP8) with probiotics was associated with increased brain expression of claudin-1, occludin, and zonula occludens-1 (ZO-1) in another study (Yang et al., 2020).

3.5. Amyloid and tau aggregation

Several pro-inflammatory bacteria such as *Escherichia coli* and *Bacillus subtilis* secrete large quantities of the amyloid peptide *curli*, which aids in bacterial adhesion and other bacterial surface functions (Friedland and Chapman, 2017; Hufnagel et al., 2013; Schwartz and Boles, 2013). *Curli* is composed of a subunit of CsgA amyloid precursor protein which shares many structural similarities to Aβ peptides, and can be recognized by the TLR2 receptor on macrophages (Rapsinski et al., 2015; Tükel et al., 2005). Activation of TLR2 by *curli* results in the activation of bone-marrow macrophages and T-lymphocytes and increased pro-inflammatory cytokines such as IL-6, IL-8, IL-17, and IL-22 (Rapsinski et al., 2015; Nishimori et al., 2012). The infiltration of the brain with these peripheral inflammatory mediators activates the TLR2/1 and NF-κB signaling pathways in the brain leading to inflammation, including increased production of IL-1β (Friedland, 2015). In one study, the

oral administration of a *curli*-producing strain of *E.coli* in rats was associated with increased brain astrogliosis (Chen et al., 2016a). Therefore, bacterial amyloid in the gut may prime the immune system, enriching its response to endogenous brain amyloid proteins (Friedland and Chapman, 2017).

Additionally, the formation of amyloid proteins in the gut wall may facilitate their retrograde transport into the brain via the gut-brain axis (Eisele et al., 2010). While the mechanisms that control amyloid spread from the gut into the brain remain to be elucidated, transport of amyloid into the brain may be facilitated by several cell types including neurons, astrocytes, fibroblasts, and microglia (Espargaró et al., 2016). In the brain, Aβ seeding is followed by amyloid accumulation and spread to neuroanatomically connected regions and induces conformational changes of other protein molecules into the β-pleated structure, further exacerbating amyloid propagation, resembling the transcellular spread seen with prion and tau proteins (Eisele et al., 2010; Sowade and Jahn, 2017). Consistent with these findings, mice overexpressing human amyloid α-synuclein demonstrate increased brain synuclein pathology and exacerbated behavioral and motor deficits following their colonization with curli-producing *E.coli* (Sampson et al., 2020). Treatment of these mice with a gut-restricted amyloid inhibitor prevented curli-mediated exacerbation of synuclein aggregation and associated behavioral deficits (Sampson et al., 2020).

Interestingly, recent studies have shown that tau misfolding and aggregation may be facilitated by extracellular bacterial DNA, including *B. burgdorferi, P. gingivalis, C. albicans*, and *E. coli* (Tetz et al., 2020). The *E. coli* (K99 strain) and *P. gingivalis* are detectable in brain parenchyma and vasculature in post-mortem AD samples, including the hippocampus (Dominy et al., 2019; Zhan et al., 2016). These bacterial strains demonstrate facultative intracellular properties which create a favorable environment for interactions with the intracellular tau pathways. It has been postulated that bacterial DNA is transported to the outer membrane or released following prophage induction into the neuronal cytosol where it acts as a seed for intracellular tau aggregation (Tetz et al., 2020).

3.6. Direct effects on neuroplasticity and hippocampal learning processes

Several studies suggest direct effects of gut dysbiosis on synaptic and neuronal plasticity and modulation of hippocampal learning processes. In a study by Chu et al., antibiotic-treated mice had impaired extinction learning compared to their untreated counterparts which was attributed to reduced dendritic spine growth and remodeling and reduced activity of signal-encoding neurons in the medial prefrontal cortex (Chu et al., 2019). When gnotobiotic (i.e., germ-free) mice were colonized with diverse gut microbiota at different developmental stages, a reversal of impaired extinction learning was only observed in mice that were colonized after birth, while gnotobiotic mice colonized during weaning or adulthood did not demonstrate any cognitive benefits. Furthermore, CSF, serum, and fecal levels of 4 bacterial metabolites (phenyl sulfate, pyrocatechol sulfate, 3-[3-sulfooxyphenyl] propanoic acid, and indoxyl sulfate) were found to be differentially altered in germ-free mice compared to controls or those with restored microbiota.

Other studies provide evidence to support a role for gut dysbiosis in modulating cortical and hippocampal neuronal activity. Aβ toxicity is associated with impaired function and

expression of the Na + and K + -ATPase transporters within neuronal membranes leading to impaired energy metabolism and increased oxidative stress (Ugbode et al., 2017). D-galactose administration in rats results in significant reductions in membrane-bound ATPase in the cortex and hippocampus and cognitive impairment, which are almost completely reversed with the administration of *Lactobacillus plantarum* MTCC1325 (Mallikarjuna et al., 2016). Taken together, these findings support the notion that gut microbiota and bacterial metabolites play an important role in learning and neuronal plasticity during the early developmental stages. Consistent with data from animal studies, results from a clinical trial of individuals with AD suggested cognitive benefits and reduced brain insulin resistance in those treated with probiotics containing *Lactobacillus acidophilus, Lactobacillus casei*, *Bifidobacterium bifidum, and Lactobacillus fermentum (*Akbari et al., 2016).

4. Age, lifestyle, and the gut microbiome

Several studies utilizing metagenomics suggest that lifestyle may influence the gut microbiome to a larger extent than genetic factors, and significantly contribute to a higher risk for AD (Hills et al., 2019; Rothschild et al., 2018). We herein review evidence supporting a link between aging or lifestyle factors (i.e., sleep, diet, stress, and exercise) and the gut microbiome, and how gut dysbiosis may mediate the effect of lifestyle factors on AD pathogenesis.

4.1. Aging

Healthy aging is associated with structural and functional changes in the gut microbiome (Salazar et al., 2017; Nagpal et al., 2018), including an increase in the number of facultative anaerobes and changes in species dominance with a relative stability of total anaerobic counts (Askarova et al., 2020; Mariat et al., 2009). One study reported lower abundance of *Bifidobacterium* and *Lactobacillus* in older compared to younger adults, and a relative predominance of the *Bifidobacterium adolescentis* species (Hopkins and Macfarlane, 2002). As *Bifidobacterium* and *Lactobacillus* are involved in the production of the inhibitory neurotransmitter γ-Aminobutyric acid (GABA), and as intestinal GABA levels appear to correlate with brain GABA levels, it has been postulated that the lower abundance of *Bifidobacterium* and *Lactobacillus* in older age results in impaired synaptogenesis and cognitive impairment due to altered GABA activity in the brain (Junges et al., 2018; Strandwitz, 2018). Other age-associated changes in the gut microbiome include increased prevalence of *Prevotella, Eubacterium rectale, Clostridium coccoides*, and *Ruminococcus*, proteolytic bacteria, such as *Fusobacteria* and *Propionibacteria* (Hopkins and Macfarlane, 2002; Woodmansey et al., 2004), and pro-inflammatory enterobacteria, streptococci, staphylococci, and yeast.

4.2. Sleep

The bi-directional link between midlife sleep disturbance or impaired circadian rhythms and late-life AD has been established in several epidemiological and mechanistic studies (Musiek et al., 2015; Wu et al., 2003; Uddin et al., 2020; Sabia et al., 2021). Sleep has important effects on amyloid clearance due to an increase in interstitial space which may be disturbed by even short periods of sleep restriction (Kang et al., 2009; Xie et al., 2013).

Sleep disruption is a common symptom, being reported in 20–55% of individuals with AD, and may precede cognitive symptom onset by several years (Webster et al., 2020; Zhou et al., 2019). Recent studies have shown that chronic sleep fragmentation over 4 weeks increases hippocampal Aβ accumulation in mice (Duncan et al., 2022). Loss of central circadian rhythms disturbed daily oscillations of interstitial Aβ levels in the hippocampus, and targeted deletion of the core clock gene *Bmal1* increased *APOE* expression and amyloid plaque formation (Kress et al., 2018). Data from clinical studies also support important effects of sleep disturbance on brain amyloid pathology. Normal diurnal variations in CSF Aβ42 levels in healthy adults are obliterated, and brain Aβ accumulation is increased, by even relatively short periods of sleep deprivation in humans (Shokri-Kojori et al., 2018; Ooms et al., 2014).

Sleep deprivation has also been shown to directly influence the gut microbiome (Poroyko et al., 2016; Bowers et al., 2020), providing another potential mechanism, in addition to amyloid aggregation, by which sleep disturbance may contribute to AD pathogenesis. Chronic sleep disruption shifts gut microbial structure and function in mice (Bowers et al., 2020). In humans, partial sleep deprivation is associated with an increased gut *Firmicutes/Bacteroidetes* ratio in healthy young adults, higher abundance of the *Coriobacteriaceae* and *Erysipelotrichaceae*, and lower abundance of *Tenericutes*, families (Benedict et al., 2016). Circadian rhythm disturbances have also been shown to alter gene expression within the gut microbiota, being associated with increased expression of genes involved in the synthesis and transportation of LPS, and suppression of genes involved in immune regulation (Deaver et al., 2018). Interestingly, these changes strongly resemble genetic changes in the gut microbiome observed in AD (Liu et al., 2019a). In a study which implemented meta-transcriptomic analyses of stool samples, circadian rhythm disturbance in mice was associated with higher abundance of *Ruminococcus torques*, and lower abundance of *Lactobacillus johnsonii*, which have negative and positive effects on the gut barrier integrity, respectively (Deaver et al., 2018). Reversible structural and functional changes in the gut microbiome were observed 48 h after acute sleep deprivation in rats in another study (Wang et al., 2022). Conversely, healthy sleep patterns correlated with a larger number of *Verrucomicrobia* and *Lentisphaerae* in stool samples and better cognitive performance in a clinical study of healthy older adults (Anderson et al., 2017). Despite these interesting findings, associations between sleep disturbance and gut microbiome morphology have not been replicated by other studies (Zhang et al., 2017a).

Other studies have examined the opposite direction of this relationship including the effect of the gut microbiome on sleep efficiency. In a recent clinical study, the diversity of the gut microbiome was found to be closely associated with increased sleep efficiency and total sleep time and negatively correlated with wake after sleep onset (Smith et al., 2019). An abundance of several taxa, including *Lachnospiraceae*, *Corynebacterium*, and *Blautia* was associated with poor sleep efficiency (Smith et al., 2019).

Given the strong associations between the gut microbiome and immune system alterations, disturbances in cytokines and other inflammatory mediators represent a potential important link between gut dysbiosis, sleep disturbance, and AD pathogenesis. It remains unclear whether the complex and multi-directional association between chronic sleep disturbance,

immunity, and the gut microbiome may be influenced by other factors such as age, sex, obesity, and the metabolic syndrome. Validation of these findings in larger studies and further research in this area is warranted.

4.3. Diet

The “Western diet” consisting of a high amount of saturated fat and added sugar has been linked to a higher risk for AD in several epidemiological studies (Weisburger, 1997), and an increased risk for AD has accompanied the transition of non-Western populations to “Westernized” diets. These observations are supported by preclinical studies that demonstrate a strong association between high fat diet and dementia risk (Studzinski et al., 2009; Sanguinetti et al., 2018; Sah et al., 2017; Nam et al., 2017). The association between chronic dietary changes and a higher risk for DM, obesity, and AD is well-established and is -at least-partially mediated by an increased risk for cerebrovascular pathology. However, recent studies suggest that dietary changes may significantly alter the gut microbiome within days to weeks, thereby providing an additional mechanism by which diet may contribute to AD pathogenesis. In addition to their association with a higher incidence of vascular risk factors (e.g., DM, obesity, and the metabolic syndrome), other mechanisms by which dietary factors influence the risk for AD pathology appear to be mediated by alterations to the gut microbiome, including increased gut inflammation, oxidative stress, dysregulated NRF2 (nuclear factor erythroid 2-related factor 2) signaling, and increased neuronal apoptosis (Studzinski et al., 2009; Sanguinetti et al., 2018; Sah et al., 2017; Nam et al., 2017). A high fat diet (HFD) increased amyloid deposition in 12-month-old *APP23* mice and was associated with altered brain lipid levels and lower expression of genes involved in synaptic plasticity and neuronal growth (Nam et al., 2017).

Interestingly, other studies in AD transgenic mice have shown that a HFD and genetic predisposition to AD are associated with similar gut metabolomic profiles, including higher levels of fecal ribose, lactate, ketones, trimethylamine (TMA), and TMAO, and lower levels of choline and unsaturated fatty acids (Sanguinetti et al., 2018). Gut microbiome changes in HFD-fed mice included higher cecal levels of *Clostridium* and *Staphyloccosus* species, and higher colonic abundance of *Firmicutes compared to Bacteroidetes*, *Roseburia*, *Coprobacillus*, and *Dorea* phyla, and *Rikenellaceae, Lachnospiraceae, and Enterococcaceae* families (Sanguinetti et al., 2018). Additionally, a HFD can lead to chronic elevation of circulating LPS levels referred to “metabolic endotoxemia” and contributes to chronic low-grade inflammation, insulin resistance, and DM (Mohammad and Thiemermann, 2021).

Higher ileal and colonic *Firmicutes/Bacteroidetes* ratios and lower abundance of *Actinobacteria, Proteobacteria, and Verrucomicrobia* have been observed in mice fed a refined high-fat or a refined low-fat diet compared to chow-diet fed mice (Dalby et al., 2017). In another study, the transition from a standard chow diet to a refined low fiber diet in mice was associated with loss of *Bacteroidetes* and increased *Clostridia* and *Proteobacteria* within one week, with limited additional impact of high or low dietary fat on gut microbiota composition, suggesting that fiber intake may be more closely associated with gut microbiota composition than dietary fat intake (Morrison et al., 2020).

4.4. Exercise

A sedentary lifestyle has been linked to cognitive decline in several studies, while exercise has been shown to have protective effects on brain health including a lower risk of AD (Fenesi et al., 2017). Growing evidence from animal studies suggests that physical activity slows the progression of AD pathology, including reduced amyloid and tau aggregation and inflammation, and improves lipid metabolism, neurogenesis, and cognitive function (Kim et al., 2019; Zeng et al., 2020; Rossi Daŕe et al., 2020). In one study, 12 weeks of exercise on a treadmill were associated with improved mitochondrial function, increased neurogenesis, and reduced amyloid pathology in an AD mouse model (Kim et al., 2019). Other studies have shown that physical activity is associated with reduced soluble hippocampal Aβ and TNF-α, and increased hippocampal BDNF levels (Bashiri et al., 2020; Zeng et al., 2020). A single session of physical exercise after learning improved memory consolidation in rat AD models generated by direct-hippocampal injection of Aβ (Rossi Daŕe et al., 2020). Physical exercise has also been shown to combat negative effects of a HFD on brain health including HFD-induced neuroinflammation, neuronal apoptosis, and hypothalamic microglial activation (Kim et al., 2017; Yi et al., 2012). Wu et al. demonstrated that 4 weeks of treadmill running before intraperitoneal LPS injection inhibited LPS-induced dopamine deficiency, loss of dopaminergic neurons, and motor dysfunction in male C57BL/6J mice (Wu et al., 2011).

Together, these findings support important protective roles for physical activity on brain health through several mechanisms including reduced oxidative stress, inflammation, amyloid and tau pathology, and improved neurogenesis and mitochondrial functions (Chen et al., 2016b). Recent evidence suggests that another potential mechanism by which exercise supports brain health is through modulation of the gut microbiome (Abraham et al., 2019; Fernandez et al., 2018; Mitchell et al., 2019). Physical activity has been associated with increased abundance of butyrate-producing bacteria and higher fecal butyrate levels which have homeostatic and anti-inflammatory effects and reduce LPS translocation into the bloodstream (Abraham et al., 2019; Mitchell et al., 2019). Increased diversity within the *Firmicutes* phyla has been consistently reported with physical activity across studies (Mitchell et al., 2019). In a study by Motiani et al (Motiani et al., 2020), sprint interval and moderate-intensity continuous training were associated with favorable changes in the gut microbiome of sedentary individuals with diabetes or pre-diabetes, including an increase in the *Bacteroidetes* phyla, a decrease in *Firmicutes/Bacteroidetes* ratio, and lower levels of systemic (e.g., TNF-α) and intestinal (e.g., LPS-binding protein) inflammatory mediators.

4.5. Stress

Stress, including environmental (e.g., noise, toxins, pollutants, or climate change), physical (e.g., sleep disturbance) or psychological (e.g., fear or anxiety) stressors, have been associated with several neurodegenerative disorders including AD (Gubert et al., 2020). Animal studies suggest that environmental stress is associated with neuroinflammation and altered expression of amyloid and tau proteins (Chong et al., 2005; Futch et al., 2017; Gubert et al., 2020; Machado et al., 2014; Ricci et al., 2012). Transgenic mice overexpressing corticotropin-releasing hormone (CRH) have increased hippocampal tau

pathology, and CRH antagonism reduces both amyloid and tau aggregation in animal models (Carroll et al., 2011; Futch et al., 2017; Gubert et al., 2020).

Stress may influence the gut microbiome through activation of the hypothalamic-pituitary (HPA) axis (Misiak et al., 2020). Stress-induced HPA axis activation increases gut permeability and intestinal expression of corticotropin-releasing factor (CRF; CRH) receptor type 1 in rats (Vicario et al., 2012). Probiotics reduce HPA axis dysfunction associated with stress, and improve mood, learning, and memory functions in animal models (Misiak et al., 2020; Eutamene et al., 2007; Gareau et al., 2007). Consistent with these findings, anxiolytic effects of probiotics containing *Lactobacillus helveticus R0052* and *Bifidobacterium longum R0175* due to lower cortisol levels have been observed in clinical studies (Messaoudi et al., 2011).

In a recent study, traffic-related air pollution (TRAP) was associated with gut dysbiosis including reduced microbial diversity, lower abundance of *Lactobacillus* and *Ruminococcus flavefaciens*, lower *Firmicutes/Bacteroidetes* ratio, and altered bile acid production at 10 months of age in a rat AD (i.e., TgF344) model (Dutta et al., 2022). In this model, TRAP was associated with increased amyloid and tau aggregation, neuronal loss, and cognitive deficits. Importantly, TRAP-mediated effects on gut dysbiosis and AD pathology appeared to be age-, sex-, and host genotype-dependent, supporting the presence of a dynamic interplay between genetics and environmental factors on the gut-brain axis.

Other studies have found that electromagnetic field exposure was associated with gut dysbiosis (i.e., lower *Firmicutes*/*Bacteroidetes* ratio) and depression-like behavior in mice (Tai et al., 2020; Luo et al., 2021). Additionally, heavy metal exposure (e.g., manganese, aluminum, and cadmium) has also been linked to gut dysbiosis in animal studies (Tinkov et al., 2021; Pineton de Chambrun et al., 2014). In one study, exposure of adult mice to cadmium for 8 weeks resulted in gut-microbiota shifts with decreased abundance of *Prevotella* and *Lachnoclostridium* and increased *Escherichia coli-Shigella* (Yang et al., 2021). In another study, the oral administration of benzo-[a]-pyrene for 4 weeks was associated with an increase in pro-inflammatory (e.g., *Desulfovibrionaceae*), and a decrease in anti-inflammatory (e.g., *Lactobacillus* and *Akkermansia*), taxa (Ribière et al., 2016).

The relationship between the gut microbiome and the HPA axis appears to be bi-directional. Gut dysbiosis may lead to higher levels of circulating cytokines, including IL-1β, IL-6, and TNF-α, or LPS (Vakharia and Hinson, 2005), which can then penetrate the BBB and activate the HPA axis (Banks, 2005), while SCFAs may suppress HPA axis activity via gene down-regulation (van de Wouw et al., 2018). Furthermore, studies suggest an association between stress related to chronic noise exposure and increased hippocampal and prefrontal tau pathology (Manikandan et al., 2006; Cui et al., 2009, 2012a, 2012b), upregulation of enzymes involved in Aβ synthesis (i.e., *APP*, β- and γ-secretases) (Cui et al., 2015), and a possible role for CRF in dysregulated Aβ and tau pathologies (Gai et al., 2017; Kang et al., 2007). Interestingly, these studies suggest that chronic noise may promote AD pathology via gut dysbiosis. In a study by Cui et al., SAMP8 mice exposed to chronic noise had higher abundance of *Firmicutes* and lower abundance of *Bacteroidetes* at the phylum level, higher levels of *Candidatus Jettenia* and *Denitratisoma* at the genus level, impaired brain and

intestinal endothelial tight junctions, and higher levels of peripheral inflammatory mediators compared to controls (Cui et al., 2018).

4.6. Environment, epigenetics, and the gut microbiome

With an estimated 100 trillion various microbes in the human intestine, the gut microbiome encodes 100-fold more unique genes than the human genome, making it an important component of the human epigenetic landscape. Epigenetic modifications represent an important mechanism by which the gut microbiome may mediate the effects of environmental factors (e.g., diet, toxins, air pollution, and environmental stress) on AD risk and progression. Gut microbiota and their associated metabolites have been shown to, directly and indirectly, modulate enzymatic pathways involved in epigenetic mechanisms such as histone modifications, DNA methylation, and chromatin plasticity, which contribute to AD pathogenesis and cognitive impairment (Nagu et al., 2021). For example, gut bacterial metabolites, such as SFCAs and folate, can modulate histone acetylation and DNA methylation, respectively, which in turn regulate the expression of several genes involved in the amyloid pathway (e.g., β-secretase, *APP*, and *PSEN1*) (Nagu et al., 2021; Chen et al., 2022). Furthermore, SCFAs can directly influence cognitive functions via modulation of histone deacetylase activity. In a study which conducted integrated gut-microbiome hippocampal DNA methylation analyses of *APP* knock-in mouse models, a positive correlation was observed between amplicon sequence variants within the *Lachnospiraceae* family and hippocampal *APOE4* methylation (Kundu et al., 2021). Together, these findings support the presence of a dynamic cross-talk between epigenetics and the gut microbiome, in which the gut microbiome may influence the expression of AD-susceptibility genes via epigenetic mechanisms and/or epigenetic AD markers may alter intestinal physiology and influence the growth or activity of certain gut microbiota.

5. Modulating the gut microbiome for AD prevention and treatment

Modulation of the gut microbiome represents a potential strategy for AD prevention and treatment as it may reduce inflammation, oxidative stress, amyloid or tau aggregation, and help restore neurogenesis, blood-brain barrier integrity, and improve or stabilize cognitive and behavioral functions (Bonfili et al., 2021; Wang and Dykes, 2022). Potential treatment or prevention strategies of gut microbiome modulation and the mechanisms by which these may influence AD pathology are summarized in Fig. 4.

5.1. Dietary modification

Evidence supporting a link between dietary factors, the gut microbiome, and AD risk has generated interest in identifying brain-healthy diets. Diets rich in unsaturated fats, fruits, vegetables, and whole grains such as the Mediterranean diet are associated with improved cognition, reduced brain atrophy in regions vulnerable to AD pathology, higher plasma carotenoid levels and paraoxonase activity, higher SCFA levels, increased gut microbial diversity, and lower peripheral markers of inflammation (e.g., C-reactive protein) in several studies, supporting a positive role for the Mediterranean diet in reducing atherogenesis and supporting brain health (Blum et al., 2006; Kincaid et al., 2021; Meslier et al., 2020; Mosconi et al., 2014; Wang et al., 2021b). The Mediterranean diet has been associated with

preserved cognition in older adults and with a lower risk for AD in epidemiological studies (Valls-Pedret et al., 2015; Yusufov et al., 2017). In one study of over 16,000 middle-aged and older adults who were followed over 20 years, the Mediterranean diet was associated with a 20% lower risk for dementia (Andreu-Reinón et al., 2021). Gut microbial alterations associated with the Mediterranean diet include a lower *Firmicutes/Bacteroidetes* ratio, and increased abundance of butyrate-producing bacteria such as *F. prausnitzii* and *E. rectale* and the butyrate-producing genus *Roseburia* (Ghosh et al., 2020; Nagpal et al., 2019a).

Consistent with these findings, gut microbial alterations associated with the Mediterranean diet, typically including a high intake of fiber, vitamins (e.g., B1, B9, and B6) and minerals (copper, manganese, magnesium, iron, and potassium), were associated with improved cognition and reduced frailty in another study (Ghosh et al., 2020). Similar diets, such as the Dietary Approaches to Stop Hypertension (DASH) diet, also have beneficial effects on brain health when combined with exercise (Blumenthal et al., 2019). Diets that combine elements from both the Mediterranean and DASH diets (e.g., The Mediterranean-DASH Intervention for Neurodegenerative Delay [MIND]), which is rich in fruits, vegetables, whole grains, low-fat dairy, and lean protein, may be more effective in delaying cognitive decline (Morris et al., 2015). Dietary elements rich in Vitamin D3 (e.g., dairy and fish) (Brown et al., 2003) promote the neural growth factor protein, and those rich in flavonoids (e.g., grapes, citrus, and green tea) or the polyunsaturated fatty acid, docosahexaenoic acid (e.g., fish) may reduce amyloid and tau pathology and neuroinflammation (Ayaz et al., 2019; Szczechowiak et al., 2019).

Other diets that may have protective effects on brain health include the ketogenic diet which is very low in carbohydrate and high in fat, mimicking the effects of the fasting state and promoting the production of ketones through incomplete oxidization of fatty acids (Dewsbury et al., 2021). In AD mouse models, ketones reduce oxidative stress, prevent intracellular uptake of Aβ, and improve synaptic plasticity (Yin et al., 2016). Furthermore, the ketogenic diet has been shown to alter the gut microbiome, reduce AD pathology, and improve cognition (Carranza-Naval et al., 2021). The combination of the Mediterranean and ketogenic diets is associated with increased SCFA production by gut microbiota, improved CSF markers of amyloid and tau, and better cognitive performance (Kawas et al., 2021; Nagpal et al., 2019b). Intermittent fasting has also been shown to promote hippocampal neurogenesis through activation of glycogen synthase kinase (GSK)-3β and increased BDNF, increase insulin sensitivity, reduce inflammation, and promote autophagy and protein clearance in animal studies (Baik et al., 2020; Park et al., 2020). Preliminary clinical studies also suggest protective effects of intermittent fasting on memory in older adults (Witte et al., 2009).

5.2. Probiotics

Probiotic supplementation improves gut microbial diversity, supports the integrity of the intestinal and BBB, mitigates brain amyloid accumulation, and can help reduce inflammation, and improve cognition in animal studies (Athari Nik Azm et al., 2018; Kobayashi et al., 2017). In one study, the oral administration of *B. longum NK46* was effective in restoring gut dysbiosis and reducing LPS production resulting in reduced

inflammation and improved cognition in AD transgenic mice (Lee et al., 2019). Other studies in AD transgenic mice have shown that probiotics containing *B. lactis*, *L. casei*, *B. bifidum*, and *L. acidophilus* suppress inflammation by inhibiting TLR4- and RIG-I-mediated NF-κB pathways (Yang et al., 2020). Probiotic supplements (containing *B. bifidum* and *L. plantarum*) combined with exercise-training reduced Aβ toxicity and improved spatial learning in a rat AD model (Shamsipour et al., 2021).

In combination with 12-weeks of memantine treatment, probiotics containing *L. plantarum* decreased hippocampal Aβ levels, reduced peripheral TMAO levels, and promoted neural plasticity (Wang et al., 2020a). Other studies suggest beneficial effects for probiotics containing *Clostridium butyricum* in reducing brain Aβ deposits and mitigating microglial activation and inflammation via increased butyrate levels (Sun et al., 2020). Butyrate production by *Agathobaculum butyriciproducens SR79* was associated with lower brain Aβ deposits and improved cognition in *APP/PS1* mice (Go et al., 2021).

Data from clinical trials have generally been consistent with animal studies regarding beneficial effects of probiotics on brain health. Positive effects on cognition were reported following adherence to a 12-week diet rich in probiotics including *Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifidobacterium bifidum*, and *Lactobacillus fermentum* (Akbari et al., 2016), or consuming milk fermented with kefir grains in clinical trials (Ton et al., 2020). Studies in humans also support an important role for butyrate in regulating neuronal growth and synaptic differentiation (Goswami et al., 2018; Silva et al., 2020). Probiotics including *B. bifidum BGN4* and *B. longum BORI*, or those including *B. breve A1*, were associated with cognitive benefits in community-dwelling older adults in 2 studies (Kim et al., 2021; Kobayashi et al., 2019). However, the effects of probiotics on cognitive function in individuals diagnosed with AD have been conflicting. While one clinical study suggested that the combination of probiotics (including *L. acidophilus*, *B. bifidum*, and *B. longum*) and selenium was associated with improved cognition in AD (Tamtaji et al., 2019), and another study showed significant cognitive benefits in association with 12-weeks of probiotic supplementation (mainly *Lactobacillus* and *Bifidobacterium* strains) (Akbari et al., 2016), these results were not replicated by other studies (Krüger et al., 2021).

A possible mechanism by which probiotics promote brain health is mediated by their strong anti-oxidant effects. Sirtuin-1 (SIRT-1) is a nicotinamide adenine dinucleotide (NAD)-dependent histone deacetylase which plays an important role in protecting cells from reactive oxygen species. SIRT-1 levels are reduced in human AD brains and in senescent mice resulting in increased predisposition to oxidative stress (Julien et al., 2009). Administration of a probiotic supplement containing *Streptococcus thermophilus, Bifidobacterium longum, B. breve, B. infantis, Lactobacillus acidophilus, L. plantarum, L. paracasei, L. delbrueckii subsp. bulgaricus, and L. brevis* was associated with significantly higher SIRT-1 expression and activity in AD transgenic mice, increased deacetylation of the SIRT-1 substrate, retinoic acid receptor-β (RARβ), and increased synthesis of ADAM-10, an *APP*-cleaving α-secretase involved in the non-amyloidogenic pathway, ultimately, reducing Aβ synthesis (Bonfili et al., 2018).

Results of studies are promising regarding potential protective effects of probiotics on brain health in older age. However, further research is warranted to validate these findings and provide further mechanistic insight for the effects on cognition or AD pathology and to elucidate whether such cognitive benefits extend to individuals who have evidence of AD pathology.

5.3. Prebiotics

Prebiotics are short-chain carbohydrates which can modify the composition or function of gut microbiota. Some prebiotics act as fermentation substrates for SFCA-producing microbiota such as *Bifidobacteria* and *Lactobacilli*, while others, such as fructo-oligosaccharides (FOS), have direct beneficial effects on synaptic plasticity. In a study by Sun et al., FOS supplementation was associated with upregulation of the pre-synaptic protein, synapsin-1, expression and modulation of the glucagon-like peptide (GLP-1) pathway in AD transgenic mice, leading to improved brain insulin sensitivity, reduced phosphorylation of the JNK pathway, and improved cognition (Sun et al., 2019b). Other studies have examined a similar oligosaccharide, xylo-oligosaccharide (XOS), in AD transgenic mice with post-hepatectomy cognitive dysfunction which demonstrate increased inflammation and BBB permeability and significant alterations to the gut microbiome. XOS administration reversed loss of the BBB integrity by upregulation of tight-junction proteins (e.g. ZO-1), reduced inflammation and microglial activation, restored the gut microbiome, and improved cognitive function (Han et al., 2020). Synbiotics (combinations of prebiotics and probiotics) including XOS and *Lactobacillus paracasei* HII01 were associated with reduced hippocampal oxidative stress and microglial activation in obese insulin-resistant rats (Chunchai et al., 2018).

Other prebiotics with potential positive effects on brain health and the gut microbiome include lactulose, dietary polyphenols (e.g., ferulic acid), and non-digestible fibers (e.g., inulin and oligofructose)(Constante et al., 2017; Lee et al., 2021). Lactulose has been shown to reduce inflammation and promote autophagy and insulin sensitivity in animal and human studies (Lee et al., 2021; Lupien-Meilleur et al., 2016). Ferulic acid (FA) is a phenolic compound which exerts strong anti-oxidant and anti-inflammatory effects and promotes neuronal stem cell proliferation through increased production of nerve growth factor (NGF) and BDNF (Nabavi et al., 2015; Lindsay, 1988; Meng et al., 2018). Large amounts of FA are produced by probiotic species such as *Lactobacillus fermentum* NCIMB 5221 and *Bifidum animalis* (Westfall et al., 2017). Pretreatment with FA was found to reduce neuroinflammation, cortical and hippocampal Aβ levels, and act as a scavenger for reactive oxygen species in AD transgenic mice (Sgarbossa et al., 2015).

It is important to note that while probiotics and prebiotics may have promising beneficial effects on cognition in animal studies, more research is needed before they can be incorporated into routine clinical practice. It will be critical to determine the extent to which, if any, they are effective in the presence of brain disease, and the optimal dose and formulation which would provide the most acceptable risk-benefit ratio. In particular, it will be important to evaluate the safety of these agents across different patient populations, including vulnerable populations (e.g., elderly, critically ill, and immunosuppressed), as

some have been associated with serious side effects including sepsis, immune reactivity, and antibiotic resistance. Other limitations that will need to be addressed before these agents can be widely accepted in medical practice include the large variability in individuals' response to these supplements and the unpredictability of their effects on gut homeostasis within and across individuals.

5.4. Antibiotics

Antibiotics have been shown to ameliorate inflammation, oxidative stress, and AD pathology in animal studies (Yulug et al., 2018). Interestingly, several animal studies suggest that these effects may be sex-dependent (Minter et al., 2016; Kaur et al., 2021). Antibiotic treatment was associated with reduced Aβ plaques and reduced microglial activity in male, but not female, *APP/PS1* mice (Minter et al., 2016; Dodiya et al., 2019). Antibiotic-treated male mice have lower levels of pro-inflammatory cytokines such as IL-1β and IL-17A while the opposite effect was observed in antibiotic-treated female mice (Dodiya et al., 2019).

Results of clinical studies examining the effects of antibiotics on the gut microbiome and cognition in AD have been conflicting. High doses of D-cycloserine administered over 4 weeks (100 mg) was associated with improved cognition in individuals with AD, while lower doses (15 mg) produced no cognitive benefit (Tsai et al., 1999, 1998). Reduced rates of cognitive decline were observed after a 3-month treatment with a combination of doxycycline and rifampicin compared to placebo in another study (Loeb et al., 2004). However, these results were not replicated in a longer study which included 12-months of antibiotic treatment (Molloy et al., 2013).

5.5. Butyrate treatment

Butyrate administration or the colonization of germ-free mice with butyrate producing *Clostridium tyrobutyricum* is associated with beneficial effects on BBB integrity and reduced LPS-mediated inflammation and IL-1β production in mice (Braniste et al., 2014; Jiang et al., 2021). Higher butyrate levels were associated with cognitive improvement and reduced tau pathology in mice; however, their effects on Aβ aggregation appear to be stage-dependent (Fernando et al., 2020; Govindarajan et al., 2011). There is limited data regarding the effects of butyrate treatment in humans.

5.6. Fecal microbiota transplantation

There is growing evidence to suggest that FMT is safe and effective in treating gastrointestinal disease such as recurrent colitis (Khanna et al., 2017; Hazan, 2020). Due to its ability to alter the gut microbiome, FMT has also been proposed as a potential mechanism to modulate the gut-brain axis and reduce the risk of neurological disorders, including AD. Data from several animal studies suggest that FMT may effectively alter the mouse gut microbiome and influence brain pathology. In one study, transplantation of germ-free C57BL/6N humanized mice with fecal samples from an individual with AD reproduced the donor microbiota and influenced mouse behavior (Fujii et al., 2019). Other studies have shown that FMT can reduce Aβ and tau pathologies and improve cognitive deficits in AD transgenic mice through restoration of gut microbial homeostasis and increased SCFA production (Ho et al., 2018; Kim et al., 2020; Zhan et al., 2018). While these animal

data are promising, FMT as a potential treatment option in humans remains controversial. More research is warranted to determine the safety and efficacy of FMT in humans, and rigorous screening methods for donor infections and recipient susceptibility will need to be incorporated into the design of clinical trials of FMT.

6. Discussion and future directions

Growing evidence supports an important role for the gut microbiome in AD pathogenesis and mediating cognitive impairment through several mechanisms including disturbance to the intestinal and blood-brain barriers, dysregulated immune response, neuroinflammation, amyloid and tau aggregation, oxidative stress, and direct effects on synaptic function, and neuronal function or survival. Importantly, animal data suggest that gut microbial alterations may be present early in life and precede AD pathology and synaptic loss, highlighting the potential value of gut modulation as a preventative or early treatment strategy in AD. Recent animal studies provide important insight into the mechanisms by which the gut-brain axis influences the onset and progression of AD pathology. While various modalities of gut modulation have shown promise in reducing AD pathology or cognitive decline in preclinical studies, more studies are needed before these findings can be translated into human studies. This is particularly important as inherent gut microbiota composition and the effects of gut microbial alterations on AD pathology may vary significantly between animals and humans (e.g., increased *Firmicutes*:*Bacteroidetes* ratio has been reported in 5xFAD mice (Wang et al., 2019) while both increased and decreased *Firmicutes*:*Bacteroidetes* ratios have been reported in clinical studies of AD) (Vogt et al., 2017; Saji et al., 2019).

Other confounding factors in the interpretation of animal data include variations in the gut microbiome of transgenic AD models due to variations in target promotors, differences in the presence or severity of other AD pathologies (e.g., amyloid or tau), or examination of AD models at different stages of disease. For example, in one study which examined gut microbiota of a tauopathy animal model (*P301L*), AD transgenic mice had a lower *Firmicutes*:*Bacteroidetes* ratio compared to wild-type mice (Sun et al., 2019a), while this ratio was increased in several other transgenic AD models of amyloid deposition (Bäuerl et al., 2018; Wang et al., 2019). Furthermore, other confounding factors which may limit the translation of preclinical data into human studies include differential effects of age, sex, diet, and comorbidities on the gut microbiome, which have not been adequately controlled for in all studies (Jašarevíc et al., 2016).

Most animal and clinical studies examining the role of the gut microbiome on AD pathogenesis do not adjust for sex or directly examine biological differences between males and females. Significant sex-based differences in gut microbial diversity and composition, as well as differences in immune and inflammatory responses, are evident and vary according to the female reproductive stage, with shifts towards pro-inflammatory gut microbial phenotypes in post-menopausal females (Korf et al., 2022). These differences can, at least partially, be explained by a combination of hormonal and genetic factors related to the sex chromosomes, although the mechanisms that underlie such sex differences are not yet fully understood. Sex differences in the gut microbiome are also reported in preclinical studies, in which dietary and environmental factors can be controlled. However, the specific sex-based

differences in these models vary by strain, which suggests that hormonal factors or sex chromosomes alone do not fully account for these differences, and that other factors such as host genetics or differential response to environmental stimuli also play an important role. Sex-dependent differences in the effects of gut modulation on brain health offer a unique opportunity to delineate mechanistic differences in disease pathogenesis between men and women and interactions of sex with genetic and lifestyle risk factors for AD and should be integrated into future studies of the gut-brain axis.

Despite a rapidly growing number of studies examining the gut microbiome in animal AD models, data from clinical studies remain limited. So far, clinical studies have been limited by small cohorts and the scarcity of longitudinal analyses. The relatively poor reproducibility of findings across studies may be attributed to large variations in study methodology, as well as difficulty controlling for environmental factors such as diet, stress, and sleep which are known to influence gut microbial composition and metabolic activity. Genetic factors may also significantly influence the gut microbiome; therefore, validation of findings across different cohorts will require important attention to the racial and ethnic composition of study cohorts as well as their geographical locations which may confound the interpretation of these findings and their generalizability to other populations.

As environmental factors (e.g., diet, stress, and sleep) are important confounding factors in clinical or animal studies of the gut microbiome, there has been increasing interest in identifying guidelines or best practice recommendations for microbiome study design to minimize their effects on study outcomes. Recommendations include longitudinal sampling from participants and the collection of personal history (including diet, stress, sleep, and other environmental exposures) for several days prior to sampling. Longitudinal sampling from individuals accounts for intra-individual differences, which collectively reflect dietary and other short-term environmental exposures for a particular individual, and averaging these changes helps reduce intra-individual noise associated with these exposures. An average of 3–5 days of sampling has been recommended based on studies in healthy adults; however, this may vary by study design. By reducing within-person noise, longitudinal analyses improve study power and reduce the need to enroll significantly larger cohort sizes to reliably measure disease or intervention-associated outcomes (Johnson et al., 2020).

Although gut modulation represents an exciting opportunity for future research, it is worth mentioning that a few areas of investigation into the modulation of the gut-brain axis as a preventative or therapeutic strategy in AD are controversial (Goyal et al., 2021). For example, while a few studies have demonstrated positive effects of probiotics on cognition, results have been contradictory as to whether these benefits are a direct consequence of gut microbial alterations (Hanage, 2014; Hooks et al., 2018; Kristensen et al., 2016; Reid et al., 2019). This highlights the importance of improving the design of future preclinical studies to provide direct mechanistic evidence to support gut modulation as an effective strategy for disease modification, and expand the current repertoire of association studies to those that can better elucidate cause-effect relationships between gut modulation and clinical or biomarker-based outcomes of AD.

Another highly controversial topic pertains to the safety of FMT as a gut modulation strategy (Wang et al., 2016b). Despite evidence supporting its general safety as an investigational gut modulation strategy for gastrointestinal disease (e.g., recurrent *Clostridium difficile* infections) with strict donor screening, it is important to note that serious adverse events, including death or life-threatening infections, have been reported (Wang et al., 2016b). These appear to be mostly related to FMT use from banked stool samples where screening for multi-drug resistant organisms was not routinely performed. In 2019 and 2020, the United States Food and Drug Administration (FDA) issued safety warnings due to reports of severe illness caused by enteropathogenic *Escherichia coli* (EPEC) and *Shigatoxin-producing E. coli* associated with the use of FMT products (FDA, 2019–2020). It is also important to note that transmission of SARS-CoV-2 is a potential risk associated with FMT as the virus has been shown to remain viable in the stool even after resolution of respiratory symptoms (Xiao et al., 2020; Wang et al., 2020b). Other safety considerations pertain to the use of FMT in the treatment of chronic immune-mediated conditions, in which a pathological immune response to allogenic FMT strains is more likely to occur, and the risk of aspiration or bowel perforation during the procedure (Khoruts and Weingarden, 2014). Importantly, there is limited evidence to support effective timing and dosing regimens of FMT products and their possible interactions with antibiotic treatment or dietary modifications. Therefore, there is a need for well-designed and validated protocols for donor selection and screening to guide FMT use in clinical or research settings.

7. Conclusions

Emerging evidence from animal and clinical studies suggests a potential role for gut dysbiosis in AD pathogenesis via the gut-brain axis. Potential mechanisms by which the gut microbiome may contribute to AD pathogenesis include immune dysregulation, neuroinflammation, promoting amyloid and tau aggregation and spread, impaired BBB, as well as direct effects on synaptic plasticity and neuronal functions. Recent studies also suggest the presence of characteristic microbial signatures for AD. The effects of gut dysbiosis on brain pathology are influenced by unmodifiable factors including age, sex, and genetics as well as modifiable environmental factors including diet, exercise, environmental stress, and sleep disruption which may influence the gut-brain axis via epigenetic mechanisms. Inadequately controlling for these variable factors has limited the reproducibility of study findings across different cohorts or animal models. While addressing this may be challenging in clinical study design, it represents an important area for future mechanistic animal research.

Gut modulation offers a potential opportunity to modify AD risk; however, further research is needed to establish its safety in humans. Rigorous screening measures to ensure safety of gut microbial alterations, and a better understanding of the long-term effects of such modulation on brain and systemic health, will be needed before gut modulation may be safely implemented in clinical practice. Furthermore, there is a paucity of data regarding the effects of gut modulation on CSF or imaging markers of AD pathology, including brain atrophy and global or regional amyloid and tau aggregation. Understanding the extent to which animal data can be translated into clinical studies and the differential effects of age,

sex, and metabolic risk factors on the gut-brain axis will be crucial in the design of future clinical studies.

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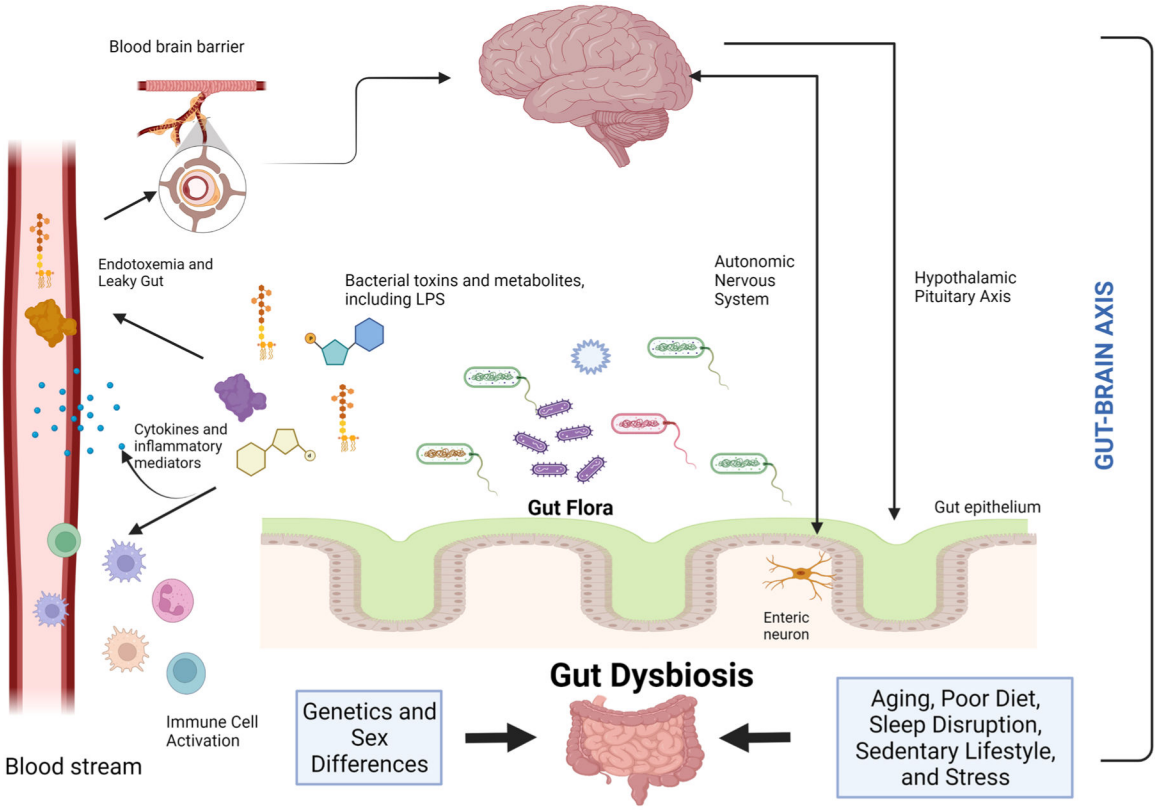

Fig. 1.

The Gut-Brain Axis. A schematic diagram demonstrating interactions between the brain and the gut via the gut-brain axis, including interactions mediated by gut secretion of toxins and metabolites, and gut modulation of the immune system leading to migration of immune cells and inflammatory markers across the blood-brain barrier. The central nervous system modulates gut motility and secretion via the enteric nervous system and the hypothalamic-pituitary axis. LPS, lipopoly-saccharide. Created with BioRender.com.

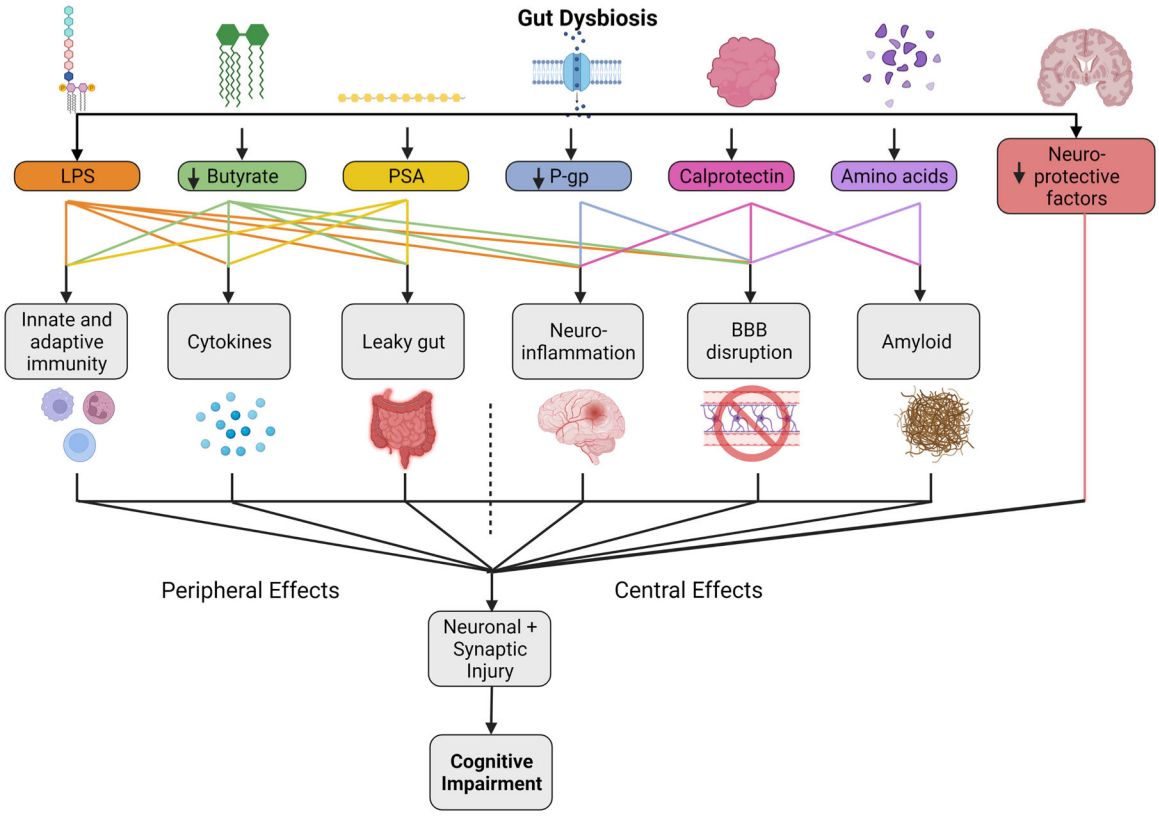

Fig. 2.

Potential mechanisms by which the gut microbiome contributes to AD pathogenesis. Animal and clinical studies suggest several mechanisms by which the gut microbiome contributes to the onset and progression of AD pathology, including modulation of innate and adaptive immunity, neuroinflammation and the release of cytokines and other inflammatory mediators, increased blood-brain barrier permeability, reduced integrity of the intestinal barrier leading to “leaky gut” which facilities the translocation of toxins into the circulation, increased protein aggregation including amyloid, tau, and synuclein, and direct effects on synaptic plasticity, memory, and learning processes. LPS, lipopolysaccharide; PSA, polysaccharide A; p-gp, p-glycoprotein. Created with BioRender.com.

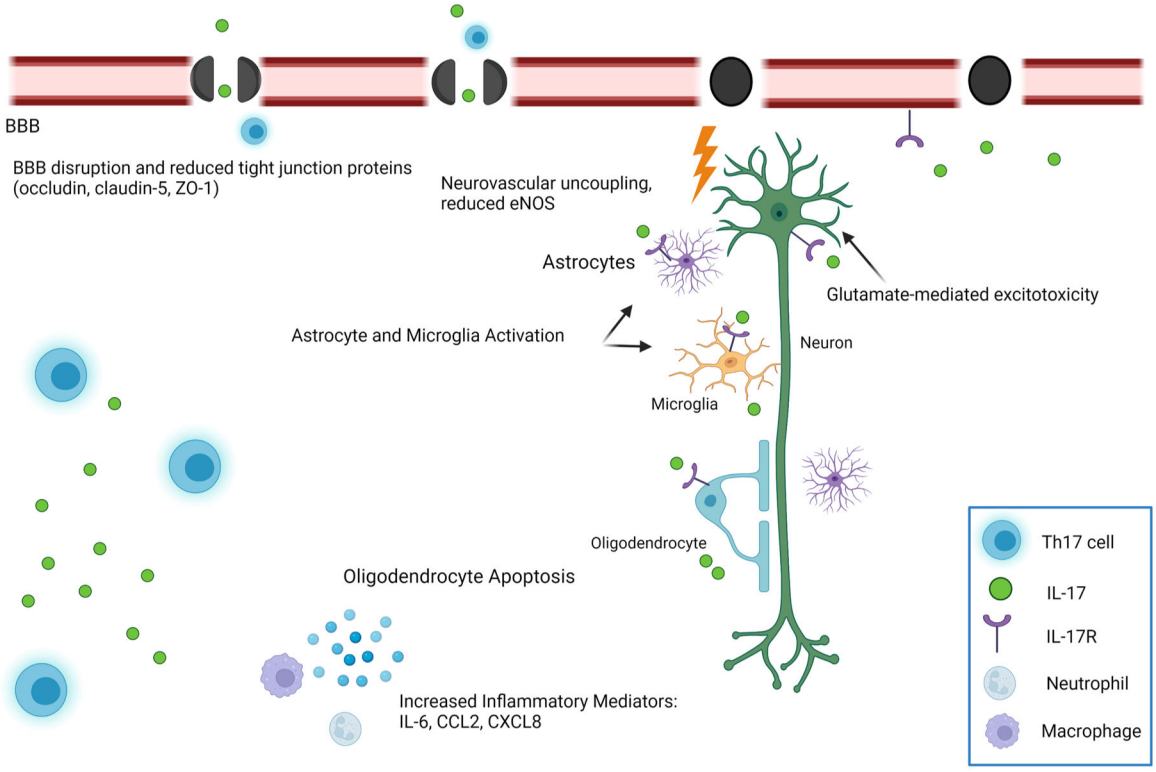

Fig. 3.

The Role of Interleukin-17 (IL-17) in AD Pathogenesis. One of the important inflammatory mediators by which gut dysbiosis contributes to AD pathogenesis is IL-17, produced by Th17 cells. IL-17 promotes neuronal and oligodendrocyte apoptosis, neuroinflammation through activation of astrocytes and microglia, neurovascular uncoupling, and increased calcium-mediated excitotoxicity, eventually leading to neuronal loss. Created with BioRender.com.

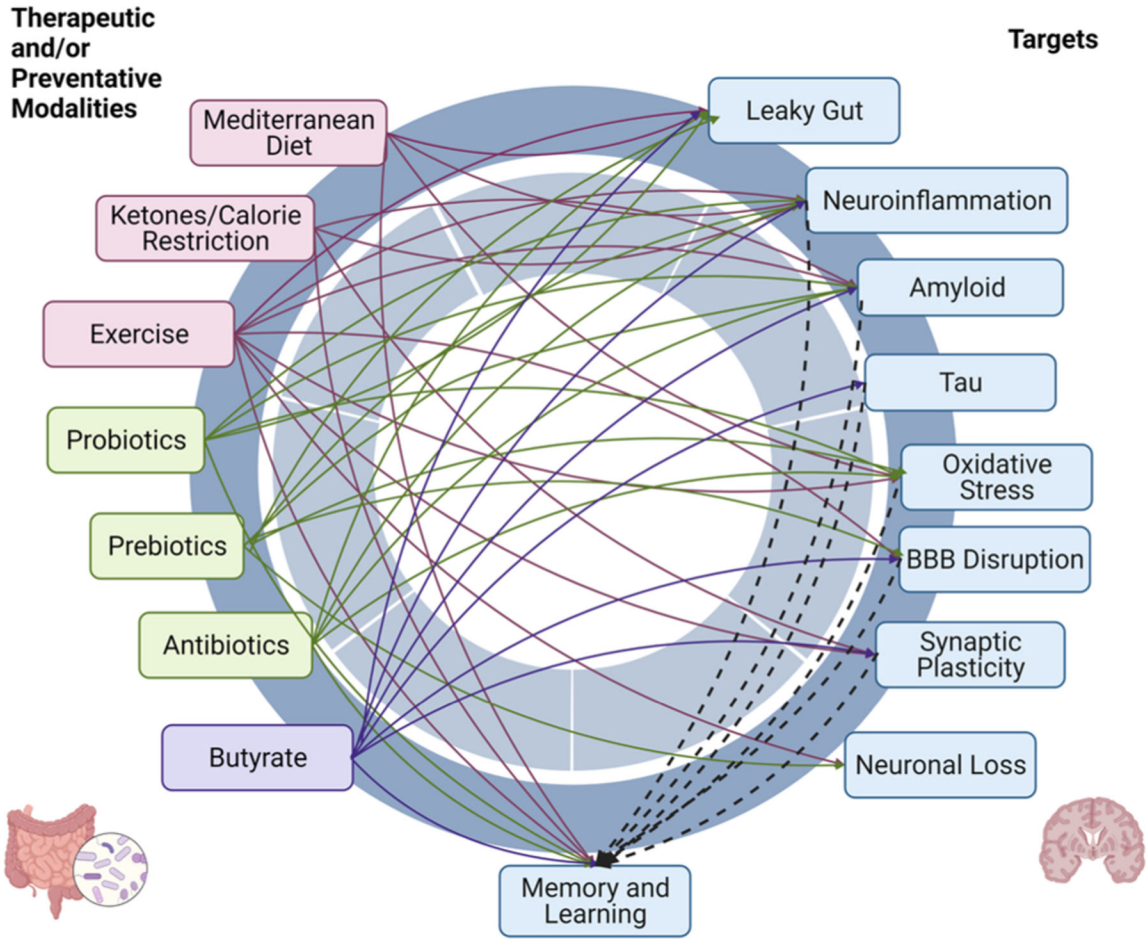

Fig. 4.

Proposed Modalities of Gut Modulation with Potential Benefits in AD Prevention or Treatment. Gut modulation through dietary modification, exercise, supplementation with probiotics, prebiotics, or the short chain fatty acid butyrate, and use of antibiotics have been investigated as potential strategies for AD prevention or treatment. This matrix summarizes the mechanisms by which each of these modalities influences AD pathogenesis. Further research is warranted to determine the safety and efficacy of other modalities, such as fecal microbiota transplantation (FMT). BBB, blood-brain barrier. Created with BioRender.com.

Table 1

Summary of Animal Studies.

APP/PS1 mice	• Shifts in gut microbiota profile in Tg mice; ↑*Proteobacteria*, ↑*Erysipelotrichaceae*; ↑*Firmicutes*: *Bacteroidetes ratio* with age (Bäuerl et al., 2018)
	• AD associated with shifts of the gut microbiome towards profiles that resemble those seen in autism and inflammatory disorders (Bäuerl et al., 2018)
	• Altered gut microbial diversity with ↑ *Proteobacteria* and *Verrucomicrobia* at 12 months of age; ↓SCFA (Zhang et al., 2017b)
	• ↓ Microbial diversity, ↓spatial memory, ↑*Odoribacter and Helicobacter* (genus level), and ↓ *Prevotella* in Tg mice at 6 months of age (Shen et al., 2017)
	• Altered gut microbiota composition with antibiotic treatment (e.g., ↑*Lachnospiraceae)*, including early post-natal antibiotic treatment (Minter et al., 2016, 2017)
	• Altered peripheral inflammatory mediators in antibiotic-treated Tg mice (Minter et al., 2016)
	• ↓ Cerebral Aβ in antibiotic-treated or germ-free Tg mice (Harach et al., 2017; Minter et al., 2016, 2017); associated with ↑ soluble Aβ levels in some studies (Minter et al., 2016, 2017)
	• ↓ Aβ plaques, ↓ plaque-localized glial reactivity, and significantly altered microglial morphology in antibiotic treated Tg mice (Minter et al., 2016, 2017)
	• Early post-natal antibiotic treatment associated with ↓brain Aβ deposition, and ↓ plaque-localized microglia and astrocytes (Minter et al., 2017)
	• ↑ Cerebral Aβ in germ-free Tg mice when colonized with microbiota from conventionally raised Tg mice; colonization with microbiota from WT mice was associated with smaller changes in cerebral Aβ pathology (Harach et al., 2017)
	• Supplementation with oligosaccharides from *Morinda officinalis* associated with ↓ Aβ pathology, ↓ neuronal apoptosis, and ↓ brain edema (Xin et al., 2018)
3xTg AD-mice	• Probiotic supplementation associated with ↓ peripheral inflammatory mediators, brain Aβ deposition, and cognitive deficits (Bonfili et al., 2017)
5xFAD mice	• Age associated with changes in fecal microbiota composition; ↓ trypsin proteins in fecal samples; human *APP* expression detected in gut (not only brain) (Brandscheid et al., 2017)
	• ↑ *Firmicutes*: *Bacteroidetes ratio*; infiltration of microglia and Th1 cells into brain (Wang et al., 2019)
	• Treatment with GV-971 and antibiotics associated with ↓microglial activity (Wang et al., 2019)
	• Antibiotic treated mice had ↓ hippocampal Aβ, ↓ blood glucose, ↑serum glucagon, and ↓ RAGE (Guilherme et al., 2021)
	• Germ-free and antibiotic-treated 5xFAD mice displayed ↓ hippocampal Aβ-associated memory loss; germ-free 5x FAD mice had ↑ microglial Aβ uptake in early disease stages compared to antibiotic-treated mice (Mezö et al., 2020)
	• Distinct microbiota-dependent gene profiles related to phagocytosis and microglial activity states identified in hippocampal microglia of germ-free and antibiotic-treated mice (Mezö et al., 2020)
AD mouse model (intra-cerebroventricular Aβ injection)	• Oral administration of *Bifidobacterium breve* strain A1 prevented Aβ-induced cognitive dysfunction and ↓Aβ-induced hippocampal gene expression (Kobayashi et al., 2017)
APOE−/− mice	• Infection with *Porphyromonas gingivalis* and complement activation observed in mouse brain (Poole et al., 2015)
APP NL-F and APP NL-G-F Mice	• Behavioral and cognitive performance associated with the gut microbiome in 6 mo-old mice; *APP* genotype modulated this association (Kundu et al., 2021)
	• Stool from 6-month-old $App^{NL\text{-}G\text{-}F}$ mice or $App^{NL\text{-}G\text{-}F}$ crossed with human *APOE4*-targeted replacement mice sufficient to induce behavioral phenotypes in 4–5 month-old germ-free C57BL/6 J mice 4 weeks following inoculation (Kundu et al., 2022)

C57BL/6 Mice	•	Infection with the pathogenic bacteria *Citrobacter rodentium* resulted in stress-induced memory disturbances (Gareau et al., 2011)
Swiss Webster Germ-free mice	•	Improved behaviors and lower anxiety in germ-free mice compared to conventionally-reared specific pathogen-free counterparts (Neufeld et al., 2011)
P301L mice	•	↓ *Firmicutes: Bacteroidetes ratio* (Sun et al., 2019a)
Rat Models	•	AD rat model generated by the intraperitoneal injection of D-galactose: *Lactobacillus plantarum* MTCC 1325 ↑acetylcholine levels and ↓ Aβ plaques and cognitive deficits (Nimgampalle and Kuna, 2017)
	•	AD rat model generated by the intrahippocampal injection of Aβ: *Lactobacillus* and *Bifidobacterium* improved memory and learning (Athari Nik Azm et al., 2018)
	•	Intraperitoneal infiltration with *Helicobacter pylori* is associated with ↑ cerebral Aβ and impaired spatial memory (Wang et al., 2014b)
	•	1 month of ampicillin administration associated with gut dysbiosis, ↓ hippocampal NMDA receptor expression, ↑anxiety, and spatial memory impairment in rats; *Lactobacillus fermentum NS9* ameliorated these changes (Wang et al., 2015a)
Drosophila models	•	*Enterobacteria* infection ↑ hemocyte recruitment in brain and exacerbated AD pathology; attenuation of hemocyte recruitment ↓ inflammation and AD pathology (Wu et al., 2017)

Abbreviations: APP, amyloid precursor protein; PS1; presenilin-1; Tg, transgenic; RAGE, Receptors for Advanced Glycation End-products; APP NL-F Mice, Human amyloid precursor protein (hAPP) knock-in mice which contain the Swedish and Iberian mutations; APP NL-G-F, Human APP knock-in mice which contain the Arctic mutation as third mutation; APOE, apolipoprotein E; NMDA, N-methyl-D-aspartate; SCFA, short-chain fatty acids; Aβ, amyloid-β peptide.

Table 2

Summary of Clinical Studies.

Post-mortem AD brains	•	Bacterial LPS found in human AD brains including neocortex and hippocampus with levels (3–7)-fold and >20-fold greater in AD compared to controls, respectively (Zhao et al., 2017a,b)
	•	LPS and Escherichia coli K99 colocalize with Aβ in plaques and perivascular aggregates (Zhan et al., 2016)
	•	LPS from *Porphyromonas gingivalis* detected in AD brains (Poole et al., 2013)
	•	LPS accumulates in neocortical neurons in AD and impairs transcription in neuronal-glial primary co-cultures (Zhao et al., 2017b)
	•	16S rRNA sequencing shows increased bacterial populations in AD brains (Emery et al., 2017)
	•	*Chlamydia pneuomoniae* present in same brain regions as Aβ plaques and neurofibrillary tangles (Hammond et al., 2010)
	•	*Borrelia burgdorferi* DNA detected in Aβ plaques (Miklossy, 2016)
Living AD Human Participants	•	↑ Pro-inflammatory *Escherichia/Shigella* which correlated with IL-1 β, inflammasome complex (NLRP3), and CXCL2; ↓ abundance of anti-inflammatory *Eubacterium rectale*; ↓ *Bacteroides fragilis* in AD (Cattaneo et al., 2017)
	•	↓ Microbial diversity; ↓*Firmicutes*, ↓*Bifidobacterium*, and ↑*Bacteroidetes* in AD (Vogt et al., 2017)
	•	*Bacteroides* correlated with CSF YKL-40 levels reflective of astrocyte activation (Vogt et al., 2017)
	•	↑ *Actinobacteria*, ↑ *Enterococcaceae, Lactobacillaceae, Ruminococcaceae*; ↓ *Bacteroidetes, Bacteroidaceae*, Lachnospiraceae, *Veillonellaceae* (Zhuang et al., 2018)
	•	↓ *Firmicutes, Clostridia*, *Lachnospiraceae*, *Ruminococcaceae*; ↑ *Proteobacteria* and *Enterobacteriaceae* in AD vs controls (Liu et al., 2019a)
	•	↑ *Bifidobacterium, Blautia, Dorea, Escherichia, Lactobacillus, Streptococcus*; ↓ *Alistipes, Bacteroides, Parabacteroides, Paraprevotella, Sutterella* in AD vs controls (Li et al., 2019)
	•	↑ *Alistipes, Bacteroides, Barnesiella, Collinsella, Odoribacter*; ↓ *Eubacterium, Lachnoclostridium, Roseburia in AD* vs *controls* (Haran et al., 2019)
	•	Kynurenine: tryptophan ratio↑ with probiotic supplementation (Leblhuber et al., 2018)
	•	Plasma LPS levels ↑ in AD and correlate with blood monocyte/macrophage activation (Zhang et al., 2009)
	•	Serum and CSF *H. pylori-specific* IgG antibody levels ↑ in AD and correlate with AD severity (Kountouras et al., 2006)
	•	Serum IgG antibody levels against *Fusobacterium nucleatum* and *Prevotella intermedia* ↑ in AD (Sparks Stein et al., 2012)
	•	Probiotic supplementation associated with improved cognition (Akbari et al., 2016)
	•	↑ Titer of periodontal anti-*Actinomyces naeslundii* IgG associated with ↑ AD risk; ↑ titer of anti-*Eubacterium nodatum* associated with ↓ AD risk (Noble et al., 2014)
	•	↑ Functional orthologs involved in LPS biosynthesis and bacterial secretion; ↓ orthologs related to N-glycan biosynthesis, phenylalanine, tyrosine, and tryptophan biosynthesis and histidine metabolism (Liu et al., 2019a)
	•	CSF TMAO ↑ in AD and correlates with CSF markers of amyloid, tau, and neuronal injury (Vogt et al., 2018)
	•	Differences in tryptophan metabolites, indole derivatives, serotonin precursors, and lithocholic acid in stool samples from AD compared to controls; metabolite levels correlate with cognitive impairment (Wu et al., 2021; Pappolla et al., 2021).

Abbreviations: LPS, lipopolysaccharide; TMAO, trimethylamine-N-oxide; CSF, cerebrospinal fluid; Aβ, amyloid-β peptide.