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The Microbiota–Gut–Brain Axis in Alzheimer's Disease: A Review of Taxonomic Alterations and Potential Avenues for Interventions

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Abstract

Objective: The gut microbiome is a complex community of microorganisms that inhabit the gastrointestinal tract. The microbiota–gut–brain axis encompasses a bidirectional communication system that allows the gut to influence the brain via neural, endocrine, immune, and metabolic signaling. Differences in the gut microbiome have been associated with psychiatric and neurological disorders, including Alzheimer's Disease (AD). Understanding these AD-associated alterations may offer novel insight into the pathology and treatment of AD.
Method: We conducted a narrative review of clinical studies investigating the gut microbiome in AD, organizing the results by phyla to understand the biological contributions of the gut microbial community to AD pathology and clinical features. We also reviewed randomized clinical trials of interventions targeting the microbiome to ameliorate AD symptoms and biomarkers.
Results: Alpha diversity is reduced in patients with AD. Within Firmicutes, taxa that produce beneficial metabolites are reduced in AD, including *Clostridiaceae, Lachnospiraceae, Ruminococcus,* and *Eubacterium.* Within Bacteroidetes, findings were mixed, with studies showing either reduced or increased abundance of *Bacteroides* in mild cognitive impairment or AD patients. Proteobacteria that produce toxins tend to be increased in AD patients, including *Escherichia/Shigella.* A Mediterranean-ketogenic dietary intervention significantly increased beneficial short-chain fatty acids and taxa that were inversely correlated with changes in AD pathological markers. Probiotic supplementation with *Lactobacillus spp.* and *Bifidobacterium spp.* improved cognitive function and reduced inflammatory and metabolic markers in patients with AD.
Conclusions: The gut microbiome may provide insight into AD pathology and be a novel target for intervention. Potential therapeutics include probiotics and dietary intervention.

Keywords: microbiome; bacteria; short-chain fatty acids; probiotics; dementia; mild cognitive impairment

Introduction

Alzheimer's Disease (AD) currently has no cures and only limited therapies are available. As the global aging population increases, the prevalence of AD is expected to rise, making AD a critical public health concern worldwide (Alzheimer's Association, 2021; Fratiglioni, De Ronchi, & Agüero-Torres, 1999). There is an urgent need to further elucidate modifiable mechanisms of pathology in order to provide better, more effective treatments for AD. A major difficulty in developing effective treatments for AD stems from ambiguity in understanding the precise biological mechanisms which cause AD (Kumar, Singh, & Ekavali., 2015). The microbiota–gut–brain (MGB) axis has the potential to influence the brain through a bidirectional

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communication system consisting of neural, immune, endocrine, and metabolic pathways (Jiang, Li, Huang, Liu, & Zhao, 2017). Emerging evidence in the developing field of gut microbiome may offer new insights into the pathology and treatment of AD.

The human microbiota represents the complex communities of microorganisms, including bacteria, eukaryotes, archaea, and viruses, living symbiotically, commensally, and sometimes pathogenically within the human body (Ursell, Metcalf, Parfrey, & Knight, 2012). The number of microbial cells at least equals or outnumbers the human cells in the body, and the number of microbial genes outnumbers the genes present in the human genome by 100:1 (Gill et al., 2006; Qin et al., 2010; Savage, 1977; Sender, Fuchs, & Milo, 2016). Thus, the microbiome, protein products, and downstream effects have significant implications for human health. Humans have co-evolved with microbiomes and rely on them to perform functions that bodily cells cannot, including digestion of food ingredients and accessing nutrients from the diet, metabolism of drugs, biosynthesis of vitamins, maintenance of gut epithelial cells, and development and modulation of the immune system (Sonnenburg & Sonnenburg, 2019; Turnbaugh et al., 2007). The vast majority of microbes reside in the distal intestines or gut. When the balance of the gut microbiome is disrupted, known as dysbiosis, it can lead to increased gut permeability and systemic inflammation. Such alterations can negatively impact physical and mental health and has been linked with obesity, diabetes, cardiovascular disease, and a wide range of neuropsychiatric disorders, including AD (Askarova et al., 2020; Carranza-Naval et al., 2021).

A growing body of literature indicates that gut microbial composition is altered in AD and that therapeutic interventions incorporating the microbiome may be a viable target for protecting against or mitigating the effects of AD. In this review, results of known studies associating the gut microbiome with AD are organized by phyla to clarify the biological relevance of the contributions of the gut microbial community relating to AD and identify relationships with clinical features including cognition and neuropathology. In addition, studies are reviewed that have examined interventions targeting the gut microbiome's role in moderating biomarkers associated with AD pathology. This is the first known review to offer this unique perspective.

Microbiota–Gut–Brain Axis

The microbiome is part of a complex network termed the gut–brain axis, which represents the bidirectional communication between the central nervous system (CNS) and the gastrointestinal (GI) tract. This system allows for central control and maintenance of GI homeostasis and links peripheral intestinal functions with emotional and cognitive functions. There are multiple direct and indirect pathways by which the microbiome can modulate the gut–brain axis, including neural, endocrine, immune, and metabolic signaling, which incorporates the CNS, sympathetic and parasympathetic divisions of the autonomic nervous system, hypothalamic–pituitary–adrenal (HPA) axis, and enteric nervous system (ENS; Cryan & Dinan, 2012). The ENS, often called the "second brain," comprises a network of neuron and glial cells that innervate the GI tract and coordinates many aspects of GI functions, including permeability, motility, secretion, mucus production, and intestinal immunity (Carabotti, Scirocco, Maselli, & Severi, 2015; Macfarlane & Dillon, 2007). The ENS and the CNS communicate via the vagus nerve, whereby efferent signals regulate GI function and afferent signals can produce anxiogenic and anxiolytic effects, among other reflexes (Forsythe, Bienenstock, & Kunze, 2014; Ma et al., 2019). Metabolic endotoxemia is another mechanism by which the gut can impact the brain. A healthy intestinal barrier functions as a highly selective barrier preventing translocation of bacteria and toxins from the gut into the bloodstream (Hollander, 1999). Endotoxemia occurs when the intestinal barrier is compromised, causing microbes to pass into systemic circulation increasing plasma lipopolysaccharide (LPS) concentration. A resultant inflammatory response is triggered, and cytokines are released, which can have effects systemically and also directly on the CNS by passing through the blood–brain barrier (BBB), which may lead to neuroinflammation and neurodegeneration (Morris et al., 2018). Corticosteroids released due to HPA activation can affect gut permeability, immune function, and microbiota composition. Lastly, bacteria within the microbiome synthesize a wide range of metabolites essential for host health, including short-chain fatty acids (SCFA), precursor molecules, neurotransmitters (e.g., γ-aminobutyric acid [GABA], noradrenaline, dopamine, serotonin, and acetylcholine), and regulate neurotrophic factors (e.g., brain-derived neurotrophic factor [BDNF]; Cryan & Dinan, 2012). Microbiome-derived neurotransmitters act locally within the ENS and can signal to the brain via the vagus nerve (Chen, Xu, & Chen, 2021). Precursor molecules produced by the microbiome cross the BBB and become incorporated into brain-derived neurotransmitters (Chen et al., 2021).

Studies of gnotobiotic or germ-free (GF) animals have suggested causal links between the gut microbiota and behavior including cognition (reviewed in Cryan & Dinan, 2012). GF animals are born and reared in a sterile environment to prevent the colonization of bacteria and other microorganisms. They are crucial to understanding the contributions of intestinal microbiota on various phenotypes (Al-Asmakh & Zadjali, 2015). For instance, GF animals exhibit altered social interactions, anxiety-like behavior, motor activity, and HPA stress responses to acute stress compared with control mice (Crumeyrolle-Arias et al., 2014; Heijtz et al., 2011; Sudo et al., 2004). Importantly, some deficiencies in GF animals were reversed with reconstitution with the microbiota of conventional animals (Sudo et al., 2004). Moreover, translational studies have also shown that GF

animals transplanted with microbiotas from clinical patients with psychiatric disorders, such as major depressive disorder and schizophrenia, display increased behavioral changes consistent with depression and schizophrenia in addition to altered neurochemistry, compared with mice transplanted with microbiotas from healthy control participants (Zheng et al., 2016, 2019). Of particular relevance to aging and Alzheimer's disease, colonization of GF mice with microbiota of old conventional mice promotes greater endotoxemia, systemic inflammation, impaired spatial learning and memory, and altered hippocampal synaptic plasticity and neurotransmission, compared with colonization from young mice (D'Amato et al., 2020; Fransen et al., 2017). These are among many studies that have established the importance of the intestinal microbiota and gut–brain axis in neuropsychiatric disorders, including AD (Goyal, Ali, & Singh, 2021).

Altogether, biological studies elucidating the MGB as well as evidence from gnotobiotic animal studies revealing a role of gut bacteria in affective and cognitive behavior suggest that the microbiome may provide insight into AD pathology and be a novel target for intervention.

Diversity and Compositional Alterations in Alzheimer's Patients

The microbiome can be characterized on multiple levels. Understanding these different measures is essential to appreciating the gut microbiome's contributions to health and disease. Global patterns in microbiome community structure are assessed using measures of diversity. Alpha diversity represents species richness or evenness within a given sample, which can be compared across individuals or groups (Walters & Martiny, 2020). Beta diversity captures the similarity (or dissimilarity) between pairs of samples in a group through a distance matrix based on species abundance data (Anderson, Ellingsen, & McArdle, 2006). In addition to diversity metrics, the microbiome can also be characterized by taxa that are differentially abundant across samples or groups (Rinninella et al., 2019).

In the following section, we present findings from studies of the gut microbiome in clinical populations with AD. First, we report data related to overall alpha and beta diversity. Then, we describe findings of differentially abundant taxa grouped by various phyla, which highlights the unique and biologically significant role of each phylum to AD (see Table 1). Patients with AD exhibit differences within three principal phyla: Firmicutes, Bacteroidetes, and Proteobacteria. Fewer alterations have been reported within Actinobacteria and Verrucomicrobia, but these phyla are relatively less abundant (Forster et al., 2019).

Diversity

The gut microbiome is a complex and dynamic ecosystem. Like many ecosystems, a standard measure of health is diversity. While diversity alone cannot measure the total health of an ecosystem, having a highly diverse ecosystem provides stability by allowing the ecosystem to adapt to a changing environment supplying symbiotic and commensal organisms resources to survive and keeps problematic, invasive, and pathogenic species at low and manageable levels (Bäckhed et al., 2012; Hooper et al., 2005). Studies of normal aging have demonstrated that the gut microbiome increases in alpha diversity (Badal et al., 2020). In terms of beta diversity, the composition of the microbiome grows increasingly unique between individuals with age, with decreases in core abundant taxa and increases in rare taxa (Wilmanski et al., 2021). In contrast, unhealthy aging is associated with reduced diversity (Kim and Benayoun, 2020; Mariat et al., 2009) and preservation of core abundant taxa (Wilmanski et al., 2021). In AD, alpha diversity is reduced (Vogt et al., 2017; Li et al., 2019; Liu et al., 2019), and beta diversity is significantly different between patients and controls (Guo et al., 2021; Haran et al., 2019; Li et al., 2019; Liu et al., 2019; Vogt et al., 2017).

Firmicutes

Firmicutes contains many families and genera of bacteria that ferment indigestible carbohydrates (i.e., dietary fiber), producing health-promoting metabolites such as SCFAs (Duncan, Louis, & Flint, 2007; Huang et al., 2018). SCFAs are crucial for maintaining intestinal barrier function by providing nutrients to epithelial cells, regulating host immune function, and protecting against endotoxemia (Leung, Rivera, Furness, & Angus, 2016; Stilling et al., 2016). Patients with AD exhibit decreased SCFA-producing taxa including *Lachnospira*, *Ruminoclostridium 9*, *Clostridiaceae*, *Lachnospiraceae*, and *Ruminococcus*, compared with healthy controls (Guo et al., 2021; Haran et al., 2019; Liu et al., 2019; Vogt et al., 2017; Zhuang et al., 2018). These taxa have also been associated with better cognitive performance on the Mini Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) across AD, Mild Cognitive Impairment (MCI), and healthy control individuals (HC; Guo et al., 2021; Li, Zhu, Zhang, & Qin, 2018; Liu et al., 2019).

One SCFA in particular, butyrate, is critical for intestinal barrier function because it is the preferred energy source for the colonic epithelial cells. It also helps maintain the immune system and has anti-inflammatory properties (Rivière, Selak, Lantin,

Table 1. Summary of phylogenetic differences in gut microbiome in Alzheimer's Disease patients

Phylum	Class	Order	Family	Genus	reference
↓Firmicutes	*Clostridia*	*Eubacteriales*	**↓*Lachnospiraceae*** in AD	**↓*Lachnospira*** in AD and MCI **↑ *Blautia and Dorea*** in AD **↓*Lachnoclostridium*** in AD **↓ *Butyrivibrio (Butyrivibrio hungatei and Butyrivibrio proteoclasticus)*** in AD	(Guo et al., 2021; Haran et al., 2019; Li et al., 2019;Vogt et al., 2017 ; Zhuang et al., 2018)
			Eubacteriaceae	Species **↓ *E. Rectale*** peripheral inflammatory state and amyloidosis ***E. eligens*** ↑in MCI then ↓in AD **↓*E. eligens, E. hallii, and E. rectale*** in AD	(Cattaneo et al., 2017; Guo et al., 2021; Haran et al., 2019)
			Oscillospiraceae	**↑*Ruminococcus*** in AD **↑*Subdoligranulum*** in AD **↓*Ruminoclostridium 9*** in AD and MCI	(Guo et al., 2021; Zhuang et al., 2018)
			↓*Peptostreptococcaceae* in AD		(Vogt et al., 2017)
			↓*Clostridiaceae* in AD	**↓ *SMB53 and Clostridium*** in AD **↓ *Clostridium* sp.** in AD	(Haran et al., 2019; Vogt et al., 2017)
	↑*Bacilli* in AD	*Lactobacillales*	*Streptococcaceae*	**↑*Streptococcus*** in AD	(B. Li et al., 2019; Zhuang et al., 2018)
			↑*Lactobacillaceae*	**↑*Lactobacillus*** in AD but ↓ in amyloid burden	(Li et al., 2019)
	Erysipelotrichia	*Erysipelotrichales*	**↓*Turicibacteraceae*** in AD	**↓*Turicibacter*** in AD	(Vogt et al., 2017)
			Erysipelotrichaceae	↓ *cc115* in AD	(Vogt et al., 2017)
	↓*Negativicutes* in AD	*Veillonellales*	*Veillonellaceae*	**↓ *Dialister In AD***	(Vogt et al., 2017; Zhuang et al., 2018)
		Acidaminococcales	*Acidaminococcaceae*	**↑*Phascolarctobacterium*** in AD	(Vogt et al., 2017)
↑↓Bacteroidetes	**↓*Bacteroidia*** in AD	*Bacteroidales*	**↓↑*Bacteroidaceae*** in AD	***Bacteroides*** ↓ (5 Studies: 2 AD, 1 AD and MCI, and 1 Dementia) ↑ (3 Studies:1 MCI and 2 AD) **↑*B. Fragilis*** in AD	(Cattaneo et al., 2017; Guo et al., 2021; Haran et al., 2019; Li et al., 2019; Saji, Murotani, et al., 2019; Saji, Niida, et al., 2019; Vogt et al., 2017; Zhuang et al., 2018)
			Odoribacteraceae	**↓*Odoribacter spp.*** in AD	(Haran et al., 2019)
			Tannerellaceae	**↓*Parabacteroides*** in AD	(Li et al., 2019)
			↑*Rikenellaceae* in AD	***Alistipes*** ↓↑in AD	(Li et al., 2019; Vogt et al., 2017)
			Prevotellaceae	**↓*Paraprevotella*** in AD **↑*Prevotella*** in AD	(Guo et al., 2021; Li et al., 2019)
↑Proteobacteria	**↑*Gammaproteobacteria*** increases from HC to MCI to AD	**↑*Enterobacterales*** increases from HC to MCI to AD	**↑*Enterobacteriaceae*** increases from HC to MCI to AD	**↑*Escherichia/Shigella*** Peripheral inflammation and amyloidosis **↑*Escherichia*** in AD **↑ *Klebsiella spp.*** in AD	(Cattaneo et al., 2017; Haran et al., 2019; Li et al., 2019; Liu et al., 2019)
	Betaproteobacteria	*Burkholderiales*	*Sutterellaceae*	**↓ *Sutterella*** in AD	(Li et al., 2019)
	Deltaproteobacteria	*Desulfovibrionales*	*Deltaproteobacteria*	**↑ *Bilophila*** in AD	(Vogt et al., 2017)
↑↓Actinobacteria	**↑ *Actinobacteria*** in AD	*Bifidobacteriales*	**↓*Bifidobacteriaceae***	**↓↑*Bifidobacterium*** in AD	(Li et al., 2019; Vogt et al., 2017)
	Coriobacteriia	*Eggerthellales*	*Eggerthellaceae*	**↓*Adlercreutzia*** in AD **↑*E. lenta*** in AD	(Haran et al., 2019; Vogt et al., 2017)

Bold text and shaded cell indicate reported alteration in taxa.

Abbreviations; ↓: decrease; ↑: increase; AD: Alzheimer's Disease; HC: healthy control; MCI: Mild Cognitive Impairment.

Leroy, & De Vuyst, 2016). AD patients have decreased relative abundance of species that produce butyrate, such as *Eubacterium rectale*, *Eubacterium eligens*, and *Eubacterium halli*, compared with healthy controls, along with decreased levels of butyrate enzyme encoding genes (Haran et al., 2019). Furthermore, one study that compared healthy controls, MCI, and AD patients found an increase in *E. eligens* in MCI patients only, perhaps suggesting that this microbe may be protective in MCI versus AD (Guo et al., 2021).

In addition to its essential role in maintaining barrier function, butyrate has been shown to directly interfere with the accumulation of neurotoxic beta-amyloid (Aβ) aggregation in vitro (Ho et al., 2018). Aβ aggregation is a hallmark neuropathological feature of AD. It is an accumulation of misfolded proteins in the brain that interfere with cell communication, causing an immune response, inflammation, neurodegeneration, and ultimately cell death. One study measured Aβ by amyloid positron emission tomography imaging (Cattaneo et al., 2017) and others measured Aβ through cerebrospinal fluid (CSF; Nagpal, Neth, Wang, Craft, & Yadav, 2019; Vogt et al., 2017). Cattaneo and colleagues observed decreased *E. rectale* in Aβ positive patients compared with Aβ negative patients and healthy controls, and Nagpal and colleagues found a negative association of butyrate with CSF Aβ-42 in patients with MCI (Cattaneo et al., 2017; Nagpal et al., 2019).

Firmicutes also contains species that produce other beneficial metabolites. *Lactobacillus* produces GABA, the main inhibitory transmitter in the brain (Barrett, Ross, O'Toole, Fitzgerald, & Stanton, 2012) and acetylcholine (Lyte, 2011). Studies have shown improved cognition in AD patients when treated with *Lactobacillus* as a probiotic (Akbari et al., 2016; Leblhuber, Steiner, Schuetz, Fuchs, & Gostner, 2018). *Clostridium sporogenes* produces indole propionic acid (IPA; Dodd et al., 2017). IPA has been shown to inhibit endotoxemia in preclinical studies (Zhao et al., 2019) and to have a neuroprotective role against the damage and cell death caused by Aβ (Chyan et al., 1999). Abundance of *Clostridium* was lower in AD patients compared with healthy controls (Vogt et al., 2017). Of note, other genera in Firmicutes produce neurometabolites, including *Bacillus* spp. (noradrenaline and dopamine) and *Streptococcus* and *Enterococcus* (serotonin); however, these taxa have not been reported to be different in AD studies (Lyte, 2011).

Firmicutes is a large and diverse phylum, also containing genera that can have effects detrimental to health. Levels of *Blautia* (Li et al., 2019; Vogt et al., 2017) and *Dorea* (Li et al., 2019) have been found to be increased in AD patients compared with healthy controls. In preclinical studies using mouse models of AD, these genera have been shown to secrete membrane vesicles that contain fragmented bacterial DNA and other molecules into the bloodstream contributing to endotoxemia (Li et al., 2019; Park et al., 2017). Higher levels of *Blautia* and *Dorea* were also associated with lower MMSE scores across AD, MCI, and HC groups (Li et al., 2019). Although many taxa within Firmicutes provide protective roles in AD pathology, care must be taken to make sure specific genera and species within Firmicutes are accounted for due to the phylum's diverse assortment of species.

Bacteroidetes

The Bacteroidetes phylum includes anaerobic gram-negative bacteria characterized by having an outer layer of LPS. Bacteroidetes has a complex role within the human body, particularly the genus *Bacteroides*, which has a vital role within the ecosystem of the gut but may cause detrimental effects when translocated. Many species within *Bacteroides* provide nutrients, maintain gut barrier integrity, regulate the immune system, and prevent colonization by pathogens (Wexler, 2007). However, others within *Bacteroides* can produce enterotoxins that directly interfere with the gut barrier function (Lukiw, 2016; Wexler, 2007). When gram-negative bacteria such as *Bacteroides* translocate, LPS not only contributes to endotoxemia but also colocalizes in the brain with Aβ plaques (Zhan, Stamova, & Sharp, 2018). Chronic infection or exposure to LPS may trigger immune system dysregulation resulting in overproduction and aggregation of Aβ (Kowalski & Mulak, 2019; Welling, Nabuurs, & van der Weerd, 2015). Interestingly, Aβ in preclinical studies has been shown to protect against bacterial and fungal infection, suggesting that Aβ may have a protective role in innate immunity (Kowalski & Mulak, 2019; Vijaya Kumar et al., 2016). The dual protective/damaging role of Aβ is similar to other antimicrobial peptides—though normally protective, they can lead to host cell toxicity, chronic inflammation, and degeneration when dysregulated (Cao, Chtarbanova, Petersen, & Ganetzky, 2013; Reinholz, Ruzicka, & Schauber, 2012; Yamaguchi et al., 2007). In addition, *Bacteroides* has previously been found to be linked with chronic illnesses that are known risk factors for AD, such as diabetes (Larsen et al., 2010), and other neurodegenerative disorders such as Parkinson's Disease (Keshavarzian et al., 2015). In advanced aging, maintaining high relative abundance of core genera, in particular, *Bacteroides* has been associated with decreased survival after a 4-year follow-up (Wilmanski et al., 2021).

Findings related to *Bacteroides* in AD are mixed. Some studies found decreased levels of *Bacteroides* in patients in AD compared with cognitively healthy controls (Cattaneo et al., 2017; Guo et al., 2021; Li et al., 2019; Saji et al., 2019; Zhuang et al., 2018), whereas other studies found increased levels in patients with MCI and AD (Haran et al., 2019; Saji et al., 2019; Vogt et al., 2017). Abundance of *Bacteroides* was positively associated with CSF biomarkers, p-tau, and p-tau/Aβ42 and YKL-40, irrespective of diagnostic group (Vogt et al., 2017). When participants were grouped by enterotypes, the *Bacteroides* group had

a larger proportion of MCI diagnosed patients (55.7% MCI) than the other enterotype groups (e.g., 6.6% MCI in *Prevotella* group; Saji, Murotani, et al., 2019). Moreover, individuals in the *Bacteroides* group were characterized by greater white matter hyperintensities and cortical and hippocampal atrophy compared with other enterotypes. Studies have reported mixed results on the association between Bacteroidetes taxa and scores on cognitive screeners such as the MMSE and MoCA, with some studies reporting a positive association and others reporting a negative association (Guo et al., 2021; Liu et al., 2019; Saji, Murotani, et al., 2019).

Proteobacteria

The Proteobacteria phylum contains the *Enterobacteriaceae* family, which includes the proinflammatory *Escherichia/Shigella* and *Klebsiella* genera, mostly known for the widely studied species *Escherichia coli*. Similar to Bacteroidetes, Proteobacteria contains many gram-negative bacteria that can lead to endotoxemia. In addition, *E. coli* and *Klebsiella* spp. form their own extracellular amyloid protein called curli, which helps the bacteria form biofilms (Chapman et al., 2002; Friedland & Chapman, 2017; O'Toole, Kaplan, & Kolter, 2000). Biofilms are an adaptation for the survival of bacteria by providing protection from host immunity and the harsh gut environment while facilitating other microbe activity such as obtaining nutrients, communicating with other microbes, and enhancing reproductive strategies (Srivastava, Gupta, Kumar, & Kumar, 2017). However, these bacterially derived amyloids can cause problems for the human host, as they may act as a prion, a misfolded protein that triggers other normal proteins to fold abnormally, cross-seeding neuronal Aβ found in AD patients (Friedland & Chapman, 2017). Along with LPS, *E. coli* fragments have been found to colocalize with Aβ in the brains of AD patients on postmortem autopsy (Zhan et al., 2016). Supporting the potential role of Proteobacteria in AD, studies suggest that levels of Proteobacteria increase in a dose-dependent fashion, with healthy controls having lowest abundance, followed by patients with MCI, and highest abundance in patients with AD (Liu et al., 2019; Nagpal et al., 2019). Levels of *Escherichia/Shigella* were higher in AD patients who are Aβ positive, compared with patients who are Aβ negative and HC (Cattaneo et al., 2017). In addition, increased levels of *Escherichia/Shigella* were associated with greater peripheral inflammatory markers and amyloidosis (Cattaneo et al., 2017). Lastly, the species *Klebsiella pneumoniae* is elevated in AD patients when compared with patients with other types of dementia and HC (Haran et al., 2019).

Other

Actinobacteria are generally reported to have associations with positive health effects; particularly, the genus *Bifidobacterium*, commonly found in probiotics, may help maintain intestinal barrier function, have anti-inflammatory effects, and decrease LPS levels (O'Callaghan & van Sinderen, 2016). One study found decreased *Bifidobacterium* in AD patients when compared with HC (Vogt et al., 2017), and another found treatment with a *Bifidobacterium* probiotic increased MMSE scores in patients with AD (Akbari et al., 2016).

In addition to bacterial taxa, the less studied, fungal taxa may be correlated with AD. One study has found that fungal taxa correlated with AD CSF biomarkers and gut bacteria in subjects with MCI (Nagpal et al., 2020).

Overall, patients with AD exhibit an altered gut microbiome, including reduced alpha diversity and taxa within the phylum Firmicutes that produce beneficial metabolites that are reduced in AD patients such as *Clostridiaceae*, *Eubacterium*, *Lachnospiraceae*, and *Ruminococcus.* Findings were mixed within Bacteroidetes, with studies showing either reduced or increased abundance of *Bacteroides* in MCI or AD patients. Toxin-producing Proteobacteria, including *Escherichia/Shigella*, is increased in AD patients. Understanding alterations of the gut microbiome within various stages of MCI and AD may provide a new perspective into AD pathology and possibly be an innovative plan for intervention.

Intervention

While many factors can influence the gut microbiome, the most readily modifiable are diet and lifestyle (Larroya-García, Navas-Carrillo, & Orenes-Piñero, 2019; O'Callaghan & van Sinderen, 2016). Probiotic, prebiotic, and dietary interventions on the gut–brain axis are collectively referred to as "psychobiotics" (Sarkar et al., 2016). Psychobiotics promote microbial production of beneficial metabolites, including SCFAs and neuroactive metabolites such as GABA and serotonin (Dinan, Stanton, & Cryan, 2013; Sarkar et al., 2016). Though clinical studies are sparse on psychobiotic intervention in AD, a handful of studies have begun to show insight into how enriching the microbiome may protect against AD progression. Here, we focus on studies of randomized clinical trials (RCTs) as they are the most scientifically rigorous design for intervention studies and considered the gold standard for evaluating the effectiveness of interventions (Akobeng, 2005).

Diet

In recent human history, modernization of the human diet has caused a switch from seasonally available fruits and vegetables to calorie-dense, nutrient-poor processed foods (Sonnenburg & Sonnenburg, 2019). This transition has been associated with alterations of the microbiota, as highlighted by studies comparing Westernized diets to more traditional diets (Clemente et al., 2015; Gomez et al., 2016; Larroya-García et al., 2019). Consumers of Western diets exhibit decreased alpha diversity, decreased fiber degrading bacteria that produce SCFAs, and increased mucus degrading bacteria. Notably, this shift also parallels the increased prevalence of AD worldwide. Mounting evidence from ecological and observational studies has shown that Western diets are strongly associated with risk of AD and other chronic diseases (Grant, 2016). In Japan, rates of AD have significantly risen with nutritional transition from a traditional Japanese diet to a more Western diet (Grant, 2014). This finding is supported by studies showing that high-fat diets exacerbate AD-related pathology and cognitive impairment in preclinical animal models of AD (Sah, Lee, Jang, & Park, 2017; Sanguinetti et al., 2018; Thériault, ElAli, & Rivest, 2016). On the other hand, plant-based diets are associated with increased alpha diversity, SCFA-producing microbes, and conjugated linoleic acid (CLA; McDonald et al., 2018). CLA is produced by lactic acid fermenting bacteria, including *Lactobacillus plantarum* (Kishino et al., 2013) and *Bifidobacterium* spp. (Coakley et al., 2003), and has anti-inflammatory properties (Reynolds & Roche, 2010). In cell culture studies, CLA has been found to be protective against neurotoxins such as reactive oxygen species and A$\beta_{1–42}$ (Lee et al., 2013). Prospective studies suggest that diets high in fruits, vegetables, low-fat dairy products, and fish may slow cognitive decline and reduce risk of AD (Solfrizzi et al., 2011).

To our knowledge, there has been only one RCT investigating the effects of dietary intervention on the gut microbiome in clinical populations with MCI/AD. Nagpal and colleagues conducted a 6-week intervention of the Modified Mediterranean Keto Diet (MMKD) in older adults with MCI compared with cognitively normal older adults (Nagpal et al., 2019, 2020). The MMKD is a combination of the Mediterranean diet (high fiber, moderate fish and poultry, and low red meats, dairy, and sweets) and the ketogenic diet (very low carbohydrate and high fat; Scarmeas, Stern, Tang, Mayeux, & Luchsinger, 2006; Uddin et al., 2020); it emphasizes healthy fats and proteins and allows carbohydrates from vegetables and fruit (Scarmeas et al., 2006). The MMKD diet was compared with the American Heart Association Diet, which consisted of a low fat, higher carbohydrate meal plan. Results revealed that MMKD influences the gut microbiome and metabolites differently in participants with MCI and compared with healthy controls. While alpha diversity was not significantly altered, there were differential changes in taxonomic composition, including *Bifidobacteriaceae* and *Bifidobacterium*, which were significantly reduced in the MMKD treatment group and with a greater reduction in MCI individuals than controls. Following intervention, both diets decreased the metabolite lactate and increased propionate; this was especially seen in the MCI-MMKD group. Elevated levels of lactate have previously been reported in the brain and CSF of AD patients (Liguori et al., 2015, 2016). Butyrate was also increased following MMKD in MCI and healthy controls combined. Results suggest that MMKD may differentially affect the microbiome of MCI patients by altering production of metabolites that can impact cognitive function. In addition, changes in the microbiota and metabolites after MMKD correlated both positively and negatively with changes in CSF AD biomarkers Aß-42, Aß-40, tau, and tau-p181. In MCI, post-MMKD, *Enterobacteriaceae* and *Tenericutes* were increased and negatively correlated with changes in Aß-42 and *Mollicutes* was negatively correlated with tau-p181. In contrast, *Rikenellaceae* and *Parabacteroides* were positively correlated with changes in Aß-42 and *Sutterella* was positively correlated with tau-p181.

Probiotics

Probiotics are supplements or foods containing microorganisms that confer health-promoting effects when administered in adequate amounts (Hill, Bhattacharjee, Pogue, & Lukiw, 2014). Preclinical studies in animal models of AD have shown that probiotic supplementation can ameliorate neuropathology and cognitive performance, including improved novel object recognition and spatial memory, restoration of hippocampal function, reduced Aβ accumulation, and increased acetylcholine levels in the cerebral cortex and hippocampus (Bonfili et al., 2017; Musa et al., 2017; Nimgampalle & Kuna, 2017). The success of these studies has bolstered the investigation of probiotic supplementation in human-based trials.

There have been five RCTs of probiotics in relation to AD (Agahi et al., 2018; Akbari et al., 2016; Hwang et al., 2019; Kobayashi, Kuhara, Oki, & Xiao, 2019; Tamtaji et al., 2019). Each of these studies spanned 12 weeks of treatment and used probiotic formulations with at least one strain of lactic acid bacteria (e.g., *Lactobacillus* and *Bifidobacterium*), which contain species that synthesize GABA and other neurometabolites (Barrett et al., 2012; Lyte, 2011). Four out of the five studies found that probiotic supplementation significantly improved cognitive performance in participants with subjective memory complaints, MCI, and AD, relative to placebo groups (Akbari et al., 2016; Hwang et al., 2019; Kobayashi et al., 2019; Tamtaji et al., 2019).

Akbari et al. (2016) demonstrated that supplementation of probiotic milk containing *Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifidobacterium bifidum*, and *Lactobacillus fermentum* led to significantly improved MMSE scores and reduced

inflammatory and metabolic markers, such as high-sensitivity C-reactive protein (hs-CRP) and insulin resistance, in AD patients compared with placebo. Hwang et al. (2019) found that the supplementation of *L. plantarum* C29-fermented soybean (DW2009) in patients with MCI was associated with improved global cognition, which included verbal memory, sustained attention, and working memory on the Computerized Cognitive Function Test System (Ha et al., 2002), compared with placebo. Improvements in cognition were also associated with increased serum levels of BDNF. Tamtaji et al. (2019) found that co-supplementation of probiotics with selenium was effective in improving MMSE scores, compared with selenium only and placebo groups. Additionally, probiotic plus selenium supplementation also resulted in reduced hs-CRP and increased antioxidant capacity. Kobayashi et al. (2019) did not find group differences in MMSE or Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) total score following administration of single strain *Bifidobacterium breve* A1 in older adults with subjective memory complaints. However, stratified analysis with subjects with verified MCI revealed improved immediate and delayed memory recall on the RBANS in the *B. breve* A1 treatment group. On the other hand, Agahi et al. (2018) found that probiotic supplementation with *L. fermentum*, *L. plantarum*, and *Bifidobacterium lactis* or *L. acidophilus, B. bifidum*, and *Bifidobacterium longum*, compared with placebo, did not improve cognition on the Test Your Memory test or biomarkers of inflammation or oxidative stress in patients with AD. A hypothesized reason for the negative result is that a majority of participants had test scores in the range of severe impairment, suggesting that probiotic supplementation may be less effective at later stages of disease progression, making early intervention a crucial factor (Agahi et al., 2018).

While the exact mechanisms by which probiotics may exert beneficial cognitive effects are unknown, data suggest that changes are related to reduction of malondialdehyde, neuroinflammation, oxidative stress, and metabolic risk (Den, Dong, Chen, & Zou, 2020). Additionally, probiotics may modulate certain neurotransmitters and neurotrophic factors such as GABA or BDNF that confer neuroprotective effects. Notably, GABA has been shown to protect multiple parts of the brain from effects associated with AD pathogenesis and cognitive decline (Cho et al., 2014; de Jong et al., 2012; Wu & Sun, 2015) and BDNF has been associated with improvements in cognition, working memory through hippocampal activation, and protection against neuroinflammation (Egan et al., 2003).

Though a majority of reported studies found that probiotics had beneficial effects in cognition, many of these studies suffered from small sample sizes, homogenous treatment groups, and incomprehensive biomarker assessments (Den et al., 2020). Therefore, further research is needed to better understand the efficacy of probiotic supplementation on AD.

Prebiotics

At this time, there are no known clinical studies of prebiotics supplementation in AD. However, one preclinical study of fructooligosaccharides in an AD model demonstrated the downregulation of AD-biomarkers, decreased neuroinflammation, and improved memory and learning abilities on the Morris water maze test (Chen et al., 2017).

Conclusion

Both AD pathology and the microbiome have complex and dynamic associations with various factors, including age, genetics, health status, environment, diet, and lifestyle. AD is a slowly progressive disease with disease pathology starting approximately 20 years before symptoms begin to emerge (Alzheimer's Association, 2021). MCI patients can remain without progression for many years (Koepsell & Monsell, 2012), offering an extended period time to detect and intervene. Rapid advances in our understanding of the gut microbiome and the MGB axis present an exciting opportunity to better elucidate the pathophysiology of AD and potential avenues for intervention. Clinical studies show MCI and AD patients exhibit altered microbiome composition compared with healthy individuals: individuals with AD show decreased alpha diversity, lower abundance of taxa that produce beneficial metabolites, and higher abundance of proinflammatory and toxin-producing taxa. Similar alterations of the microbiome are also associated with clinical features of AD, including cognition, biomarkers, and neuropathology, suggesting that the gut microbiome may be a vital part of the complex pathophysiology of AD. In addition, preclinical and clinical studies suggest that by modulating neurometabolites and improving biomarkers associated with AD probiotics may be a potential low-risk treatment, providing protective effects and improving cognition.

However, limitations of the emerging field urge caution in the interpretation of results. Currently, clinical studies are limited with only small sample sizes. These studies also contain a high degree of variability in study design with differences in participant grouping. Studies had a range of clinical groups that varied from study to study, including MCI, AD, all-cause dementia, or presence/absence of AD biomarkers. All studies used at least one cognitive measure (e.g., MMSE, MoCA, etc.), and while most studies included additional measures such as neuroimaging or biomarker assessments, some did not, which limits our ability to understand how the microbiome may be associated with specific clinical features of the disease. While some studies supported the idea that gut dysbiosis was increased from MCI to AD (Guo et al., 2021; Liu et al., 2019), many studies failed to examine

the microbiome at different clinical stages or severity of disease progression, limiting a more nuanced understanding of whether the degree of dysbiosis may correlate with disease severity. Additionally, later states of AD severity may be more resistant to treatment, partly due to irreversible loss of synapses (Agahi et al., 2018; Brewer, 2010). Indeed, probiotic interventions in patients with advanced AD proved to be less effective (Agahi et al., 2018). Also, memory complaints before progression to MCI may not be responsive to probiotic treatment (Kobayashi et al., 2019). These results suggest that probiotic treatment may be most effective for MCI and early stages of AD and less effective before progression to MCI and severe, later stages of AD.

It is also important to note that data from clinical studies show alterations in microbial diversity and composition in AD and MCI patients relative to HC. The bidirectionality of the MGB and cross-sectional nature of most studies in this review limit the interpretations of causality. Whether these alterations cause or are caused by AD or other factors associated with AD has yet to be determined. Moreover, AD is a heterogeneous and multifactorial disease, and patients often exhibit many co-morbid conditions, including obesity, type 2 diabetes, and cardiovascular disease. Similar alterations of Firmicutes, Bacteroidetes, and Actinobacteria, as well as LPS-induced systemic inflammation and metabolic endotoxemia, have also been observed in these disorders (Carranza-Naval et al., 2021; Naseer et al., 2014; Trøseid, Andersen, Broch, & Hov, 2020). More research is needed to disentangle microbial alterations related to AD itself versus other medical and lifestyle risk factors.

Microbiomes are complex ecosystems, interacting with each other and their environment within the human host (Foster, Schluter, Coyte, & Rakoff-Nahoum, 2017). The presence or absence of one individual type of bacteria may or may not be of great consequence, depending on how it affects the ecosystem as a whole. This environment is exceedingly complex and is affected not only by the microorganisms present but also by the lifestyle, diet, genetic factors, immune system function, and the presence of other disease (Askarova et al., 2020; Hall, Tolonen, & Xavier, 2017). An adaptive trait of any ecosystem is its resilience to external perturbations and the ability to return to homeostasis after a stressful event. Communities typically exhibit "functional redundancy" in that a metabolic function can be performed by multiple coexisting, taxonomically distinct organisms (Fernández et al., 1999). States of disease or dysbiosis, as in AD, may be less resilient and less able to compensate for stress-related disruptions in community function. Analytical methods aimed to understand the functional metabolic pathways of a microbe or microbial community may provide more insights into such taxonomic alterations and how they might contribute to cognition and other clinical and pathologic features of AD.

Methodologies used also had a high degree of variability, with different sequencing techniques for microbial community identification (e.g., 16S rRNA, shotgun metagenomics, qPCR) and a range of methods for biomarker and metabolite detection. The field would benefit from standardization of study design and methodology to increase reproducibility. In addition, the complex and dynamic nature of the microbiome requires studies with larger sample sizes and longitudinal designs to elucidate causal relationships and deeper characterization clinical cohorts to better understand moderating and mediating effects of cofactors such as medication and disease-related factors.

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Conflict of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this report.

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