Neurotherapeutics 21 (2024) e00475

Contents lists available at ScienceDirect

Neurotherapeutics

journal homepage: www.sciencedirect.com/journal/neurotherapeutics

Review

The brain pathobiome in Alzheimer's disease

Nanda Kumar Navalpur Shanmugam [a,b], William A. Eimer [a,b,*], Deepak K. Vijaya Kumar [a,b], Rudolph E. Tanzi [a,b]

[a] Genetics and Aging Research Unit, Henry and Allison McCance Center for Brain Health, MassGeneral Institute for Neurodegenerative Disease, Charlestown, MA, 02129, USA

[b] Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA, 02129, USA

Introduction

Overview of Alzheimer's disease

Alzheimer's Disease (AD) is a neurodegenerative disorder that leads to progressive cognitive decline, severely impacting memory, cognition, and behavior. It is the most common cause of dementia, accounting for 60–80 % of cases worldwide. Typically affecting older adults, AD begins with mild memory loss and gradually progresses to more severe cognitive impairments, making it increasingly difficult for individuals to perform everyday tasks, eventually leading to a loss of independence. It is ultimately fatal, with the average lifespan after diagnosis ranging from four to eight years, though some may live with the disease for up to 20 years [1].

The pathology of AD is complex and not yet fully understood, but it is primarily characterized by two key features: the accumulation of amyloid-β (Aβ) plaques and the formation of neurofibrillary tangles composed of tau protein in the brain [2]. These pathological changes are thought to lead to widespread neuronal loss, brain atrophy, and a breakdown in neural networks essential for cognitive function. Additionally, studies have identified the importance of neuroinflammation and vascular changes as significant contributors to the disease. Chronic inflammation in the brain, driven by the activation of microglia (the brain's immune cells) and vascular issues such as reduced blood flow and the breakdown of the blood-brain barrier, exacerbate neuronal damage [2–5].

The recent failure of drug treatments clearing Aβ and the identification of microbial involvement in other neurodegenerative diseases have reignited the interest in microbial involvement in AD pathology. This chapter reviews the concept of pathobiomes and how microbes may be involved in AD. The evidence for and challenges to the microbial hypothesis are evaluated by examining the gut-brain axis, microbes with known associations with AD, and existing therapeutic tools. While not a new concept, the rise in evidence for microbial involvement in AD presents an important hypothesis that could open up novel methods of treatment and diagnosis with a more complete elucidation of the microbes and pathways involved.

Concept of the pathobiome

The pathobiome refers to the dynamic and complex ecosystem of microorganisms, including bacteria, viruses, fungus, and their collective genetic material that coexist within a host organism and are involved in disease processes. Unlike the microbiome, which describes a host's overall community of beneficial microbes, the pathobiome specifically focuses on the microbial components and interactions contributing to disease development, progression, or exacerbation. This concept challenges the traditional notion of one pathogen causing one disease, acknowledging that the pathogenicity of certain microorganisms may result from multiple factors, such as microbial interactions, environmental conditions, or the host's immune response [6,7].

Relevance to neurodegenerative diseases

The concept of the pathobiome is increasingly relevant to neurodegenerative diseases, such as AD, Parkinson's Disease (PD), and amyotrophic lateral sclerosis (ALS) [8–10]. Emerging research suggests that disruptions in the gut microbiome, a vital component of the pathobiome, can influence neuroinflammatory processes and contribute to neurodegeneration [11–14]. Alterations in gut microbiota have been linked to increased gut lining permeability (“leaky gut”), which may allow harmful substances and microbes to enter the bloodstream and eventually reach the brain, triggering inflammation and neuronal damage [15]. Additionally, certain viruses and bacteria have been implicated in

* Corresponding author.
E-mail addresses: nnavalpurshanmugam@mgh.harvard.edu (N.K. Navalpur Shanmugam), weimer@mgh.harvard.edu (W.A. Eimer), tanzi@helix.mgh.harvard.edu (R.E. Tanzi).

https://doi.org/10.1016/j.neurot.2024.e00475
Received 28 August 2024; Received in revised form 18 October 2024; Accepted 19 October 2024

neurodegenerative conditions by promoting chronic inflammation or directly infecting neural tissues. Understanding the growing role of the pathobiome in these diseases is essential to understanding neurodegenerative etiology.

The Microbiome and Brain Health

Gut-brain axis: role of the gut microbiome in brain function

The mammalian gastrointestinal tract (GI) has an extensive enteric nervous system (ENS). The comprehensive communication between the GI and central nervous system (CNS) is bidirectional, known as the gut/brain axis [16]. The gut/brain axis involves the ENS and CNS and the commensal microorganisms that reside in the gut, called the enteric microbiome. Microbial populations in a healthy gut, while variable from person to person, maintain diversity and volume, resulting in a mutually beneficial symbiotic relationship with the host [17].

Microbial metabolites generated by gut microbes are emerging as essential mediators of gut/brain interactions that modulate a broad range of brain functions. Moreover, metabolites generated by enteric microbes appear essential for normal brain health [17,18]. Postnatal development involves the establishment of the enteric microbiome and is characterized by shifting diversity in microbial populations [19]. Alternatively, a normal healthy microbiome in adulthood is stable [17]. However, late-life changes in the gut microbiome appear to be a normal part of aging but shift toward a less stable state. Mounting data link an abnormal increase in particular enteric microbes to a range of chronic late-life inflammatory diseases whose primary pathologies lie outside the gastrointestinal tract (GI), including disorders of the CNS [20,21]. Thus, enteric dysbiosis can play an important role in diseases found among the elderly. What remains unclear is whether enteric dysbiosis is the cause or an exacerbating factor for the pathologies mediating disease progression. Current research focuses on characterizing the shifts in microbial metabolites associated with dysbiosis in AD and the possible role this may play in β-amyloidosis, a hallmark AD pathology.

Mechanisms of communication: neural, endocrine, and immune pathways

Gut microbes release a range of neuromodulatory metabolites, including γ-aminobutyric acid (GABA), dopamine, serotonin, acetylcholine, butyrate, and short-chain fatty acids (SCFAs) [22,23]. These bacteria-derived neuromodulators enter the brain via afferent vagal nerve fibers that connect the ENS and CNS or cross the blood-brain barrier (BBB) into the brain from the portal circulation [24]. Lipopolysaccharides (LPS) and other microbial products generated by gut bacteria can also directly stimulate the ENS to signal the brain by binding neuronal cell surface toll-like receptor 4(TLR4) [25].

Microbial-derived neuromodulators and bacterial-induced nerve signals play a crucial role in maintaining brain homeostasis. Enteric dysbiosis, characterized by abnormal GI signaling, is associated with several neuropathologies, including AD amyloidogenic pathways [26]. Extended enteric dysbiosis also leads to leaky gut syndrome (LGS). In addition to normal signaling pathways, microbial products released into the circulation because of LGS may enter the brain and promote neuropathology [27,28]. Evidence suggests the disrupted enteric microbiome and the subsequent dysbiosis-mediated disruption in normal microbial signaling and increased generation of harmful microbial metabolic products are potential contributors to the neurodegenerative pathology [29,30].

Evidence linking microbiome alterations to cognitive decline

Studies have identified enteric dysbiosis in AD mouse models. Analysis of the enteric bacteria of transgenic AD mice (APP/PS1) by 16S rRNA sequencing revealed major shifts in microbial populations, including increased levels of Proteobacteria, and Verrucomicrobiota, and attenuation of Ruminococcus and Butyricicoccus bacterial groups [31,32]. Butyricicoccus bacteria are major producers of enteric butyrate, a molecule required for normal brain health. Dysbiosis in APP/PS1 mice is also accompanied by decreased gut bacterial metabolites [31]. Similarly, data from non-murine AD animal models, such as fruit flies, link disrupted enteric microbes with neurodegeneration. Intestinal dysbiosis caused by *E. coli* infection in AD fruit fly models leads to neuroinflammation and enhanced AD phenotype [33]. Evidence is also mounting that dysbiosis leads to the release of pathogenic microbial metabolites that can mediate harmful activities not only in AD but across multiple neurological disorders. GABA is among the neuromodulator molecules released by gut bacteria, and its dysregulation is linked to AD, anxiety, and depression. The neurotoxin β-N-methylamino-L-alanine (BMAA) is a glutathione-depleting molecule generated by intestinal cyanobacteria that is elevated, not only in AD but also ALS and PD [34].

While limited in number, there is growing evidence of microbial involvement in neurodegenerative diseases in humans. Data from a 2018 study suggest dysbiosis of Bacteroidetes, Firmicutes, and Bifidobacterium correlates to amyloidogenic shifts in Aβ40/42 ratio and p-tau markers in human cerebrospinal fluid (CSF) [10]. In another study, a SCFA-producing bacteria, *Eubacterium rectale,* decreased in elderly patients with symptoms of brain amyloidosis [35]. These initial human data suggest that reestablishing a healthy gut microbiome in AD patients may be a simple and effective strategy for attenuating the amyloidosis and neuroinflammation associated with the disorder [36–38]. The limited human data and findings from AD animal studies make a convincing case for further investigation into dysbiosis-mediated dyshomeostasis of microbiome-derived metabolites as a contributing factor in AD.

Interestingly, germ-free mice (mice raised without microbiota) exhibit altered brain development, cognitive deficits, and increased susceptibility to neuroinflammation when exposed to an inflammatory stimulus [39,40]. These findings suggest that a healthy microbiome is crucial for normal brain function, and disruptions can lead to cognitive impairments. Furthermore, studies have shown that transferring the microbiome from aged or diseased animals to younger ones can induce cognitive decline, providing direct evidence of the microbiome's dual role in both healthy brain development and neurodegeneration.

Impact of dysbiosis on neuroinflammation

Enteric microbe generation of SCFAs is essential for normal brain health, including butyrate, acetate, and propionate [41]. Enteric dysbiosis leads to attenuated SCFA generation and leads to neurological dysfunction and disease. In animal models, elevated SCFA is associated with reduced neurodegeneration [42–44]. Butyrate, released from the breakdown of low-digestible carbohydrates, is an essential neuroprotective SCFA. High butyrate levels are reported to protect against 6-hydroxydopamine-induced Parkinson's pathologies in mice [45]. Pertinent to AD, butyrate inhibits neuroinflammation and helps maintain blood-brain barrier (BBB) integrity [40]. During in vitro experiments, SCFAs inhibited Aβ aggregation [43]. While SCFAs appear protective, other enteric microbial molecules associated with dysbiosis promote pathologies linked to disease. For example, dysbiosis leads to increased generation of the microbial metabolite trimethylamine N-oxide (TMAO), which is linked to neurological dysfunction, including anxiety and cognitive deficits [46]. Notably, TMAO is reported to be elevated in the CSF of dementia patients [47]. Data is currently lacking on what changes in enteric microbial metabolites are associated with AD.

Gut-brain axis and amyloid pathology

Another critical link between microbiome alterations and cognitive decline is the gut microbiome's influence on Aβ pathology, a hallmark of AD. The gut microbiome influences the production and aggregation of Aβ through several pathways, including regulating immune responses, modulation of gut permeability, and the production of amyloid-like proteins by gut bacteria [37]. Dysbiosis by increased gut permeability,

or "leaky gut," allows bacterial endotoxins such as lipopolysaccharides (LPS) to enter the circulation [15,48]. LPS can cross the BBB, promote neuroinflammation, and enhance the production of Aβ plaques in the brain.

Antibiotic-induced alterations in the gut microbiomes of AD mouse models microbiome can reduce Aβ plaque deposition and neuroinflammation, suggesting a potential therapeutic target for modifying disease progression [49]. Additionally, fecal microbiota transplantation (FMT) from healthy donors has been shown to reduce Aβ pathology and improve cognitive function in AD mouse models [50], further supporting the role of the gut microbiome in modulating amyloid pathology.

The Pathobiome Concept in Alzheimer's Disease

Emerging hypotheses

The brain has traditionally been considered a sterile and immune-privileged organ. However, findings have recently emerged showing a persistent presence of microorganisms in both the normal and diseased human brain [14,51]. Recent advances have uncovered various pathogenic mechanisms preceding disease development and mediating disease progression. One exciting and emerging area of AD research has focused on the potential involvement of microbes (commensal and infectious) in AD etiology (microbes as early triggers of AD pathology) and AD neuropathogenesis (microbes exacerbating AD pathology) [12,52–54]. Brain infection stemming from bacteria, viruses, and fungi can drive neuroinflammation, leading to neurodegeneration [12,53,55]. In addition, our lab has shown that Aβ is an antimicrobial peptide (AMP) rapidly seeded by microbes to form Aβ deposits. We have previously provided *in vivo* proof of concept that Aβ′s AMP activity can serve as a means of brain host defense - microbes are trapped in protease-resistant Aβ fibrils that aggregate into Aβ plaques [56–61]. This evidence suggests the prolonged presence of microbe-induced Aβ deposits would then drive tangle formation and neuroinflammation, exacerbating neurodegeneration and ultimately leading to dementia.

Furthermore, it has been proposed that enteric dysbiosis may contribute to the development and progression of AD by influencing systemic inflammation, immune responses, and the production of metabolites that can affect brain function [40,44,46,62,63]. Ongoing comprehensive studies of this complex interplay between the microbiome, immune system, and neurodegeneration seek to facilitate the development of targeted therapeutic interventions to slow down or halt AD progression.

Microbial contributions to AD pathology

Certain organs and tissues, such as the brain, blood, heart, pancreas, and cerebrospinal fluid, have traditionally been considered sterile [64]. However, recent studies suggest the presence of microorganisms in these environments under both normal and pathological conditions. Despite this, the brain is still generally regarded as a sterile environment based on current evidence. Therefore, any microorganism (commensals or pathogens) gaining entry due to a breach of the blood-brain barrier or injury is considered non-beneficial. According to our current knowledge and understanding, the presence of any microbe in the brain is classified as an infection. To date, no precise mechanism has been identified for how infection may drive AD pathology, including β-amyloidosis. While microbes have been reported in AD brains, no single microbial pathogen has been consistently identified in AD cases. Individual studies of AD brain have typically focused on a particular microbial pathogen, for example, herpes simplex virus 1 (HSV1), Human herpesvirus 6 (HHV6) [55], or species of *Chlamydia, Borellia* and *Candida, Porphymonos gignivalis* [55, 65–69,113]. The mechanisms by which microbes can access the brain include the bloodstream, gut-brain axis, and the sinuses [11,16,29,36,43, 70,71]. Along with the evidence of microbial species present in the brain, studies have also reported microbial components to be present in the brain, such as lipopolysaccharides (LPS) from Gram-negative bacteria, fungal components, and HSV1 viral DNA [72,73]. Interestingly, these components were also co-localized around plaques in the human AD brain (Table 2) [74–76].

To further support evidence of microbial involvement in AD, bioinformatic studies have linked AD-associated GWAS genes to host-pathogen transcriptomic changes associated with several pathogens, including *Borrelia burgdorferi*, *Candida albicans*, *Chlamydia pneumoniae*, *Cryptococcus neoformans*, cytomegalovirus, Ebola virus, Epstein-Barr virus, hepatitis C, HSV-1, HERV-W, HIV-1, influenza, *Helicobacter pylori*, *Porphyromonas gingivalis*, *Trypanosoma cruzi*, *Toxoplasma gondii*, and Bornavirus [77]. These pathogens have been implicated in the modulation of amyloid-beta and tau proteins, suggesting a complex interplay between infections and AD pathology.

Notably, direct correlations have been observed between upregulated genes in the AD hippocampus and those of bacterial, viral, fungal, or protozoal origin at the transcriptomic level, particularly in microglial cells. Additionally, polymicrobial infections—bacterial, viral, and fungal—have been shown to upregulate host genes in the blood, brain, and cerebrospinal fluid (CSF) of AD patients [77]. Collectively, these findings support the hypothesis that infectious processes may precede cognitive decline in AD, underscoring the importance of further investigating the role of infections in the disease's etiology and progression. At the proteomic level, proteins involved in antimicrobial defense mechanisms, including those related to the complement system (C3, C4), toll-like receptors, and other immune signaling pathways, are overexpressed in AD brains. Antimicrobial pattern recognition, antiviral defense, and related immune response genes have also been identified as upregulated in the AD brain, blood, or CSF. These changes suggest an active immune response to potential microbial invasion, which may contribute to AD pathology.

Evidence Supporting the Brain Pathobiome in AD: Insights from Postmortem Brain Analyses

Recent studies have increasingly focused on the presence of microbial DNA, RNA, and proteins in postmortem brain tissues, highlighting the potential role of chronic infections in AD pathology. Specific attention has been given to pathogens such as *Chlamydia pneumoniae*, *Helicobacter pylori*, spirochetes, and *Porphyromonas gingivalis*, which have been linked to neuroinflammation and cognitive decline [14]. Microbial molecules and species associated with AD using postmortem brain analysis are listed in Tables 1 and 2. Multiple modes of identification have yielded associations of many different microbes with AD.

***Chlamydia* pneumoniae**, a bacterium known for causing respiratory infections, has been implicated in AD through its detection in postmortem brain tissues:

- **Microbial DNA and RNA:** Studies have identified *Chlamydia pneumoniae* DNA in AD brains, suggesting a role in chronic neuroinflammation. A study by Balin et al. (1998) [78] found that *C. pneumoniae* DNA was present in the brains of AD patients, supporting the hypothesis that respiratory infections may contribute to AD through persistent inflammatory responses and amyloid plaque formation [65,78].
- **Microbial Proteins:** Research also suggests that proteins from *C. pneumoniae* may influence AD pathology. The presence of these proteins could contribute to neuroinflammation and Aβ deposition, potentially exacerbating cognitive decline (Balin et al., 1998) [65, 78].

Helicobacter pylori, a bacterium primarily associated with gastritis and peptic ulcers, has also been linked to AD:

- **Microbial Proteins:** A study found a significantly higher prevalence of *Helicobacter pylori* infection in AD patients (88 %) compared to

Table 1
Microbes and their associated conditions in relation to cognition and neuroinflammation.

Microbe	Type	Associated Condition(s)	Cognitive/Neuroinflammatory Impact	References
Porphyromonas gingivalis	**Bacteria**	Periodontitis	Linked to neuroinflammation and cognitive decline, found in AD brains	[66]
Chlamydia pneumoniae	**Bacteria**	Respiratory infections	Associated with neuroinflammation, found in AD brains	[78]
Helicobacter pylori	**Bacteria**	Gastritis, peptic ulcers	Linked to cognitive impairment, possibly through systemic inflammation	[79]
Borrelia burgdorferi	**Bacteria**	Lyme disease	Cognitive deficits in "Lyme brain," linked to neuroinflammation	[95]
Streptococcus pneumoniae	**Bacteria**	Pneumonia and meningitis	Cognitive impairment	[97]
Mycobacterium tuberculosis	**Bacteria**	Tuberculous meningitis	Cognitive impairment associated with elevated cytokine levels	[99]
Neisseria meningitidis	**Bacteria**	Meningococcal meningitis	Cognitive deficits in survivors, including memory and attention issues	[41]
***Candida* spp.**	**Fungi**	Systemic candidiasis	Linked to neuroinflammation and cognitive dysfunction in AD	[90]
***Aspergillus* spp.**	**Fungi**	Invasive aspergillosis (cerebral aspergillosis	Cognitive disturbances linked to CNS involvement	[100]
Histoplasma capsulatum	**Fungi**	CNS histoplasmosis	Neuroinflammation and cognitive impairment, especially in endemic regions	[140]
Plasmodium falciparum	**Parasite**	Cerebral malaria	Causes significant cognitive impairment due to brain inflammation	[102]
Toxoplasma gondii	**Parasite**	Toxoplasmosis	Chronic infection linked to cognitive decline and psychiatric disorders	[104,141]
Trypanosoma brucei	**Parasite**	African trypanosomiasis (sleeping sickness)	Linked to neuroinflammation	[107,152]
Herpes simplex virus (HSV)	**Virus**	Herpes simplex encephalitis	Acute neuroinflammation leading to cognitive deficits	[142]
Human immunodeficiency virus (HIV	**Virus**	HIV-associated neurocognitive disorder (HAND)	Chronic neuroinflammation and cognitive impairment	[143]
Cytomegalovirus (CMV)	**Virus**	CMV infection, CMV encephalitis	Increases tau phosphorylation, cognitive impairment and increased risk of AD	[110]
Varicella-zoster virus (VZV)	**Virus**	VZV encephalitis	Neuroinflammation and cognitive impairment	[144]

Table 2
Microbial molecules and their associated conditions in relation to cognition and neuroinflammation.

Microbial Molecule	Type	Associated Microbe	Cognitive/Neuroinflammatory Impact	References
Lipopolysaccharides (LPS)	Endotoxin	Gram-negative bacteria (e.g., *E. coli*)	LPS can cross the blood-brain barrier, trigger neuroinflammation, and is linked to cognitive decline in AD models	[145]
Amyloid-like proteins	Bacterial amyloid	*Curli* from *E. coli* and *Salmonella* spp.	Bacterial amyloids can induce misfolding of host amyloid proteins, contributing to AD pathology	[146,147]
Gingipains	Protease	*Porphyromonas gingivalis*	Gingipains have been found in AD brains and are linked to tau pathology and neuroinflammation	[66]
Peptidoglycan	Cell wall component	Gram-positive bacteria (e.g., *Streptococcus* spp.)	Peptidoglycan fragments can stimulate microglial activation, leading to neuroinflammation and contributing to AD	[148,153, 154]
Lipoteichoic acid (LTA)	Cell wall component	Gram-positive bacteria (e.g., *Staphylococcus aureus*)	LTA is linked to neuroinflammatory processes that are associated with cognitive decline in AD	[10]
Fungal β-glucans	Cell wall polysaccharides	*Candida* spp.	Fungal β-glucans can trigger neuroinflammation and have been detected in AD brains	[149]
Toxoplasma gondii Antigens	Parasitic antigen	*Toxoplasma gondii*	Chronic infection with *T. gondii* is linked to neuroinflammation and increased risk of AD	[104,141]
Human herpesvirus 1 (HHV-1) proteins	Viral protein	*Herpes simplex virus (HSV-1)*	HHV-1 proteins, including ICP0, can contribute to neuroinflammation and amyloid-beta accumulation in AD	[150,151]
Human herpesvirus 2 (HHV-2) proteins	Viral protein	*Herpes simplex virus (HSV-2)*	HHV-2 proteins are implicated in neuroinflammatory processes and cognitive decline	[151]
Varicella-zoster virus (VZV) proteins	Viral protein	*Varicella-zoster virus (VZV)*	VZV proteins linked o neuroinflammation and cognitive decline in AD	[144]

controls without AD (46.7 %), suggesting a potential association between *H. pylori* infection and AD [79].

Spirochetes, a phylum of Gram-negative bacteria most commonly known for causing Lyme disease, including those from the genera *Treponema* and *Borrelia*, have been linked to neurodegenerative diseases [80]:

- **Microbial DNA:** *Treponema pallidum*, the causative agent of syphilis, has been detected in postmortem brain samples from patients with a history of neurosyphilis. Studies have reported that *T. pallidum* DNA is present in the brains of individuals with syphilis, suggesting a connection between spirochetal infections and cognitive impairment [80,81].
- **Microbial Proteins:** Proteins from spirochetes, such as those from *Borrelia burgdorferi* (which causes Lyme disease), have been implicated in neuroinflammation and cognitive decline. The detection of spirochetal proteins in AD brains may indicate a role for these pathogens in exacerbating neurodegenerative processes [82–84].

Porphyromonas gingivalis, a pathogen linked to periodontitis, has garnered significant attention in AD research:

- **Microbial DNA:** Dominy et al. (2019) [66] detected *P. gingivalis* DNA in AD brains. This finding suggests that chronic oral infections could contribute to AD pathology through mechanisms involving neuroinflammation and Aβ plaque formation [66].
- **Microbial Proteins:** Proteins from *P. gingivalis*, including gingipains, have been identified in AD brains. These proteolytic enzymes can exacerbate neuroinflammation and neuronal damage, linking oral pathogens to cognitive decline [66,85].

Herpesviruses, particularly Herpes Simplex Virus 1 (HSV1) and Human Herpesvirus 6 (HHV6), have been increasingly studied in the context of AD. These neurotropic viruses can establish latent infections in the brain, where they can be reactivated under certain conditions [86]. Emerging evidence suggests that these viruses may contribute to the

development and progression of AD through mechanisms involving neuroinflammation, Aβ accumulation, and tau pathology [87].

Herpes Simplex Virus type 1 (HSV1):

- **Microbial DNA:** HSV1 DNA has been detected in postmortem brain samples of AD patients. Research by Itzhaki et al. (2016) [12] suggests that the presence of HSV1 DNA in the brain, particularly in individuals carrying the APOE-ε4 allele, is associated with a higher risk of developing AD. This connection supports the hypothesis that HSV1 infection could contribute to amyloid plaque formation and neurodegeneration [55,72,88].

Human Herpesvirus 6 (HHV6):

- **Microbial DNA:** HHV6 DNA has been found in the brains of AD patients, indicating a possible viral contribution to the disease process. Studies by Readhead et al. (2018) [55] have reported higher levels of HHV6 DNA in AD brains compared to controls, suggesting a potential role for the virus in AD pathology, possibly through mechanisms involving neuroinflammation and tau phosphorylation [55].
- **Microbial RNA:** The detection of HHV6 RNA in AD brain tissue supports the notion of an active viral presence in the disease. This ongoing viral activity could trigger chronic inflammation, thereby contributing to neurodegenerative processes associated with cognitive impairment [55].

The findings by Readhead et al. [55] regarding the presence of viral sequences in post-mortem brains have not been reproducible in recent publications, which found no association with AD. These studies reported low levels of transcripts for herpes simplex virus 1, Epstein-Barr virus, and cytomegalovirus, failing to establish any biological significance related to AD. Additionally, some sequences of HHV-6A and HHV-6B could not be matched to the viral transcriptome, contradicting earlier findings and highlighting the need for further validation of the correlation with HHV-6 or HSV-1. In another study by Hyun-Hwan Jeong, data from Readhead et al. were reanalyzed using different RNA-seq analysis methods to investigate these viral associations with AD. This analysis also found no significant differences in viral levels between AD and control groups, suggesting that the low expression levels of viral RNA and DNA in these brain samples limit detection capabilities. Consequently, this study does not support a link between AD and viral load, despite considerable public interest in the topic.

Fungal proteins

In the context of fungal presence in AD, research by Alonso et al. revealed that fungi from the genera *Alternaria*, *Botrytis*, *Candida*, and *Malassezia* are significantly more prevalent in the frontal cortices of AD patients compared to controls [89]Further supporting these findings, Pisa et al. detected fungal material, including *Candida*, *Cladosporium*, *Malassezia*, *Neosartorya hiratsukae*, *Phoma*, *Saccharomyces cerevisiae*, and *Sclerotinia borealis*, in brain samples from all AD patients in their study [90]. However, they noted that no single fungal species was consistently present across all the brain regions that was examined, in AD brains.

Microbes and Neuroinflammation

Microbial pathogens, encompassing bacteria, fungi, parasites, and viruses, are increasingly recognized for their role in inducing neuroinflammation, which can lead to cognitive deficits and various neurological impairments. However, while the current section summarizes the impact of these microbes or microbial agents on neuroinflammation and associated cognitive outcomes, it falls short of providing critical insights into the causal mechanisms linking these pathogens to AD. The existing overview primarily presents correlations between the presence of microbial components—such as DNA, RNA, or proteins—and the incidence of AD, yet it lacks a discussion on the underlying mechanisms that could establish a causal relationship. To better understand the role of microbes links to AD, it is essential to delve deeper into how specific microbial agents may trigger neuroinflammatory pathways that contribute to AD pathology. This could involve elucidating how microbial elements activate immune responses, disrupt the blood-brain barrier, or promote the aggregation of amyloid-beta, thereby offering a clearer understanding of their roles in neurodegeneration. Additionally, integrating key experimental findings that demonstrate these mechanisms would bridge the gap between correlation and causality, providing a more comprehensive perspective on the complex interplay between microbial infections and the development of AD. By incorporating these insights, it would better align with its goal of elucidating the multifaceted relationships between microbial pathogens and neurodegenerative diseases, particularly AD.

List of Microbes associated with neuroinflammation and cognition:

1. Bacteria

***Neisseria meningitidis*:** *Meningococcal meningitis, caused by Neisseria meningitidis*, is a serious infection that leads to neuroinflammation. Survivors often experience cognitive deficits, including memory and attention issues, due to the inflammatory processes affecting the central nervous system (CNS). These deficits can persist long-term, highlighting the role of neuroinflammation in post-infection cognitive impairment [91,92].

***Chlamydia pneumoniae*:** Known for causing respiratory infections, *Chlamydia* has also been linked to neuroinflammation and found in the brains of AD patients. Evidence provided by Balin et al. (1998) [78] suggests that this pathogen may influence the neuroinflammatory pathways that contribute to AD pathology [78].

***Helicobacter pylori*:** A bacterium linked to gastritis and peptic ulcers, has also been implicated in cognitive impairment, potentially through systemic inflammation that affects the brain. Kountouras et al. (2006) [79] discussed the association between *H. pylori* infection and an increased risk of cognitive decline, suggesting that neuroinflammation may be a mediating factor [79,93,94].

***Borrelia burgdorferi*:** This bacterium is responsible for Lyme disease and can cause cognitive deficits often referred to as "Lyme brain," which are linked to neuroinflammation. Fallon et al. (2008) [95] demonstrated that persistent neuroinflammation in Lyme disease patients correlates with cognitive impairment, emphasizing the need for early diagnosis and treatment to prevent long-term neurological damage [82–84,95].

***Streptococcus pneumoniae*:** *Pneumococcal meningitis* caused by *Streptococcus penumoniae*, leads to significant neuroinflammation and long-term cognitive impairment. Survivors of pneumococcal meningitis frequently experience lasting cognitive deficits due to the intense inflammatory response in the central nervous system [96,97]. Similarly, Group B Streptococcus (GBS) brain infection in adult mice impairs hippocampal neurogenesis by suppressing progenitor cell proliferation and neuron generation, leading to cognitive deficits [98].

***Mycobacterium tuberculosis*:** Based on the postmortem studies, tuberculous meningitis (TBM) begins when one of these lesions, known as a Rich focus, ruptures and releases *Mycobacterium tuberculosis* into the subarachnoid space, leading to a granulomatous infection and inflammation of the meninges. It has been reported to cause cognitive impairment, which is associated with elevated cytokine levels [99].

2. Fungi

***Candida* spp.:** Systemic candidiasis, particularly in immunocompromised patients, has been linked to neuroinflammation and cognitive dysfunction. Pisa et al. (2015) [89,90] found that *Candida* species may contribute to neuroinflammatory processes in AD, highlighting the potential role of fungal pathogens in exacerbating neurodegenerative

conditions [89,90].

***Aspergillus* spp.:** Invasive aspergillosis, particularly cerebral aspergillosis, is highly fatal in the CNS. Kourkoumpetis et al. [100] reported that mortality in CNS aspergillosis remains high, especially in patients with preexisting brain pathology [100].

***Histoplasma capsulatum*:** Infection with *Histoplasma capsulatum* infection can lead to CNS histoplasmosis, particularly in endemic regions. Wheat et al. [140] described how this infection results in neuroinflammation and cognitive impairment, underscoring the significant impact of fungal pathogens on brain health [101].

3. Parasites

***Plasmodium falciparum*:** Cerebral malaria, caused by *Plasmodium falciparum*, is a severe form of malaria that leads to significant cognitive impairment due to brain inflammation. Idro et al. (2010) [102] provided evidence of the long-term cognitive consequences of cerebral malaria, driven by the intense neuroinflammatory response [102].

***Toxoplasma gondii*:** Chronic infection with *Toxoplasma gondii* is linked to cognitive decline and psychiatric disorders, with neuroinflammation being a central pathological feature. Torrey et al. [141] discussed the association between *Toxoplasma* infection and cognitive dysfunction, highlighting the role of persistent inflammation [103–105].

***Trypanosoma brucei*:** African trypanosomiasis, or sleeping sickness, caused by *Trypanosoma brucei*, has been shown to possibly induce a neuroinflammatory response, as measured using CSF samples. The inflammatory response in the CNS may play a significant role in contributing to the neurological symptoms associated with this parasitic infection [106,107].

4. Viruses

Herpes simplex virus (HSV): HSV is the causative agent of herpes simplex encephalitis, a condition characterized by acute neuroinflammation and cognitive deficits [12,108].

Human immunodeficiency virus (HIV): HIV-associated neurocognitive disorder (HAND) results from chronic neuroinflammation driven by the virus. Antinori et al. [143] highlighted the pervasive cognitive decline seen in HIV-infected individuals, with neuroinflammation playing a central role [109].

Cytomegalovirus (CMV): Cytomegalovirus (CMV) infection increases tau levels and phosphorylation, resembling AD tau pathology. This suggests CMV as a potential model to study neurodegeneration mechanisms in AD [110]. In particularCMV, congenital CMV infectionscan cause significant cognitive impairment due to neuroinflammation. Cheeran et al. (2009) [111] detailed the cognitive consequences of CMV encephalitis, linking them to the underlying inflammatory processes [54, 110,111].

Varicella-zoster virus (VZV): VZV can cause encephalitis, leading to neuroinflammation and cognitive impairment. Gilden et al. [144] provided evidence of the significant cognitive deficits associated with VZV encephalitis [112].

Microbial pathogens, including bacteria, fungi, parasites, and viruses, are increasingly recognized for their role in driving neuroinflammation, leading to cognitive deficits and neurological impairments. Key studies highlight how different pathogens contribute to this process, emphasizing the shared pathology of intense and persistent inflammation. This inflammation is a central factor in the cognitive decline observed across various infections.

Therapeutic Implications: Targeting the Pathobiome in the Brain

Current interventions targeting the microbiome in AD, including probiotics, prebiotics, dietary interventions, antibiotic treatments, immune boosting strategies, and FMT, have shown some efficacy in ameliorating disease symptoms [113,114].

Antibiotic treatments and their effects

Antibiotic treatments have been investigated for their ability to alter the gut microbiome and reduce neuroinflammation, potentially impacting AD progression [115,116]. Studies in animal models have shown that antibiotics can reduce amyloid-beta plaques in the brains of AD mice by altering gut bacteria composition [36]. For example, a study published in 2016 demonstrated that long-term antibiotic treatment significantly reduced amyloid-beta levels and neuroinflammation in a mouse model of AD [36], which correlated with changes in the gut microbiome [117]. However, antibiotics can also disrupt beneficial gut bacteria, leading to negative health outcomes such as increased inflammation and altered gut-brain signaling.

In human studies, the effects of antibiotics on cognitive function have been less clear, with some trials showing minimal benefit and others suggesting potential risks due to microbiome disruption. The therapeutic use of antibiotics for AD remains controversial, necessitating a careful balance between beneficial and harmful effects.

Immune boosting and Alzheimer's disease

Emerging evidence suggests that immune-boosting strategies, particularly through non-specific vaccines, may delay the onset or progression of AD. The interplay between immune function and AD pathology highlights systemic inflammation, infection, and immune senescence as critical risk factors for neurodegeneration. Some of the potential vaccines reportedly showing promise as non-specific immune boosters to prevent AD are summarized below.

Bacillus Calmette-Guérin (BCG) vaccine

Research on the Bacillus Calmette-Guérin (BCG) vaccine, primarily used for tuberculosis prevention, indicates that individuals vaccinated with BCG exhibit lower incidences of neurodegenerative diseases, including AD [118]. This immune-boosting action may reduce chronic inflammation and enhance the body's immune surveillance mechanisms. That may attenuate mechanistic pathways involved in early AD progression. However, more clinical trials in human volunteers are needed before implementing these non-specific immune boosters as therapeutics in AD.

Herpes zoster vaccination

Studies on herpes zoster vaccination (shingles vaccine) further support the potential of immune-boosting to reduce dementia risk [119]. A retrospective study in two patient cohorts found that herpes zoster (HZ) vaccination was associated with a reduced risk of dementia in individuals over 65. In both veteran and commercial healthcare populations, vaccinated patients had a significantly lower incidence of dementia compared to unvaccinated individuals. The study suggests that HZ vaccination may provide neuroprotection, either by reducing inflammation or preventing viral damage. Another study found that the herpes zoster vaccine reduced dementia risk by 19.9 %, with stronger protective effects in women, suggesting a possible link between the varicella-zoster virus and dementia [120]. Stimulating the immune system with non-specific vaccines can have protective effects beyond their primary purpose, potentially by reducing systemic infections that exacerbate neuroinflammation. Additionally, immune responses triggered by vaccines may help clear pathological protein aggregates, such as amyloid-beta plaques and hyperphosphorylated tau, which are central to AD pathology.

Additionally, an anti-herpetic trial explored the use of antiviral drugs in AD patients seropositive for HSV-1. The findings indicated that long-term antiviral treatment, such as with acyclovir, may lower the risk of dementia in individuals infected with HSV-1. This highlights the potential of targeting HSV-1, a virus linked to AD pathology, as a promising

approach to delay or prevent the onset of AD [121].

Pneumococcal vaccines

A study using the IBM® MarketScan® Database found that adults aged 65 and older who received the pneumococcal vaccine had a 63 % lower risk of developing AD compared to unvaccinated individuals [122]. The analysis employed propensity-score matching and conditional logistic regression to confirm the significant protective association. Similarly, another study using a large U.S. claims database found that older adults (65+) who received influenza vaccinations had a 40 % lower risk of developing AD compared to those unvaccinated [123]. These findings highlight the potential protective effect of flu vaccination on AD risk, reinforcing the idea that long-term immune stimulation through vaccines may help maintain immune competence and reduce the risk of neurodegeneration over time.

Therapeutic strategies for P. gingivalis in Alzheimer's disease

Another significant development is the research on *P. gingivalis*, a bacterium associated with chronic periodontitis. Cortexyme, a biotechnology company, has been developing a gingipain inhibitor, COR388 (atuzaginstat), aimed at reducing the bacterial load of *P. gingivalis* in the brain [124]. Early clinical trials showed promise, but a recent phase 2/3 trial did not meet its primary endpoint of improving cognitive function, although it did show some positive effects in secondary outcomes and in patients with specific biomarkers. The challenges of targeting *P. gingivalis* in the brain, including drug delivery across the blood-brain barrier and the complexity of AD pathology, underscore the difficulties in developing effective anti-infective treatments for AD.

Probiotics, prebiotics, and dietary interventions

Probiotics, which consist of live beneficial bacteria, and prebiotics, which are non-digestible fibers that promote the growth of beneficial gut bacteria, have been explored for their potential to influence the gut microbiome in a way that may benefit brain health [23,125–127]. As discussed previously, the gut microbiome can modulate the production of SCFAs, modulating their anti-inflammatory properties and neuroprotective effects. Studies have shown that specific strains of probiotics, such as *Lactobacillus* and *Bifidobacterium*, can reduce systemic inflammation and improve cognitive function in animal models of AD [128–130].

Dietary interventions, particularly the Mediterranean diet, rich in fruits, vegetables, whole grains, and healthy fats, have been associated with a lower risk of developing cognitive decline [131]. This diet is believed to support a healthy gut microbiome, enhance SCFA production, and reduce neuroinflammation. Although human studies are still in the early stages, findings in animal models suggest these interventions could be effective for AD prevention and management [132].

Fecal microbiota transplantation

Fecal Microbiota Transplantation (FMT) has emerged as a potential therapeutic strategy for AD, as it aims to transfer a healthy microbiome to restore gut-brain axis function. Although FMT is well-established for treating conditions like Clostridioides difficile infection, its application in neurodegenerative diseases is still experimental. Preclinical studies have shown promising results; for instance, FMT from healthy mice to AD mouse models has been reported to improve cognitive function and reduce amyloid-beta deposition.

In human studies, FMT remains in the early stages of investigation. A recent pilot study involving cognitively impaired patients demonstrated that FMT led to improvements in gut microbiome diversity and some cognitive measures, though larger and more controlled trials are needed to confirm these findings [114,133]. The potential of FMT in AD treatment lies in its ability to restore microbial diversity and reduce neuroinflammation. Despite this, patient aversion, lack of procedure standardization, long screening processes, and lack of data on the long-term effects and safety of this approach hamper its widespread use and highlight the need for further research.

Challenges and Controversies

Diverse pathogen involvement

Despite the breadth of evidence implicating microbes in neurodegeneration, recent studies have raised skepticism about the presence of low biomass microbiomes in organs previously thought to be sterile, such as the placenta and the brain. In AD research, the variability in detecting microbes and establishing causality highlights the complexity of the issue. Detecting microbes in various organs, including the brain, lung, and blood, challenges the belief that these tissues are sterile. In AD patients, where the blood-brain barrier is compromised, microbial infiltration into brain tissue is possible. Given the significant variability in findings across studies, rigorous testing and validation are essential.

These variable results highlight potential artifact-related issues, including collection and host contamination, sequencing and analytical errors, and problematic reference databases. To address these concerns, research teams are seeking to establish the robustness and clarity of preliminary data while rigorously examining and mitigating the risks of contamination and methodological errors [134]. If we were to observe any statistically significant differences in microbial species between the control and AD subjects that do not typically infect the human brain, it is essential to emphasize that further validation of the data is imperative before drawing any conclusions about disease pathogenesis.

Methodological limitations in brain microbiome research

Detecting and analyzing the brain microbiome presents significant challenges, particularly when using postmortem tissue samples and bioinformatic tools to analyze microbial signatures. This section outlines the complexities and potential confounding factors researchers must navigate to ensure accuracy and reliability in their findings. Addressing these limitations requires a multifaceted approach. Below are several strategies to overcome these challenges:

1. **Improving sample integrity and Addressing Postmortem Tissue and Contamination**: Addressing the limitations associated with postmortem brain tissue in AD research, particularly concerning the identification of infection etiology or microbial involvement, requires careful consideration of several factors. First, the potential for contamination and artifacts during the post-mortem interval (PMI) highlights the need for standardized protocols for tissue collection, preservation, and storage. Utilizing rapid cooling methods and optimizing the time between death and tissue processing can help maintain sample integrity. Second, implementing stringent aseptic techniques by using sterile equipment during sample collection can reduce the risk of microbial contamination from external sources. Third, the use of advanced preservation techniques, such as flash freezing or chemical fixation, may aid in preserving the original microbial profiles, thereby minimizing changes due to post-mortem artifacts and environmental contamination. Finally, integrating clinical data and pre-mortem health information from patients can help contextualize findings, allowing for a better understanding of how microbial signatures correlate with the disease state prior to death. By addressing these factors, researchers can enhance the reliability of post-mortem studies in understanding the role of infection in AD.
2. **Analytical Rigor in Bioinformatics**: In brain microbiome research, various bioinformatic tools like Kraken, Metaphlan, Diamond, Kaiju, and Etol have unique strengths and limitations. Using multiple

algorithms on the same datasets helps cross-validate findings and reduces analytical errors.

- **Kraken, Metaphlan, and Diamond:** These tools are effective at identifying a broad range of microbes, but they often have lower sensitivity, particularly for low-abundance species and highly complex samples. They are also less adept at identifying viral sequences, which can limit their utility in virome analysis [135,136].
- **Kaiju and Etol:** Both offer improved accuracy in sequence classification—Kaiju through versatile taxonomic classification and Etol with its 64-mer based long probes. However, despite their enhanced accuracy, they can still struggle with specificity and may require cross-validation with other tools to ensure reliable results [137,138].
- **Virome Analysis:** Identifying viral components in the brain microbiome is particularly challenging due to the limited representation of viral sequences in reference databases and the complexities of viral genome diversity. Tools like Diamond can assist in virome analysis by translating DNA sequences into proteins and aligning them with protein databases, but this process can still lead to discrepancies and lower reproducibility across studies.

3. **Use of Negative Controls**: Incorporating negative controls at every stage—from DNA extraction to sequencing—helps identify and eliminate environmental contaminants that could be misinterpreted as part of the brain microbiome.
4. **Complementary Methods**: Employing a combination of metagenomic sequencing, 16S rRNA gene sequencing, and fluorescence in situ hybridization (FISH) improves the robustness of microbial identification. Additionally, using brain organoids to validate host-pathogen interactions offers another layer of cross-validation for microbial presence and activity.
5. **Longitudinal Studies**: Future research should focus on longitudinal analysis of cerebrospinal fluid (CSF) or less invasive biomarkers to track microbiome changes over time, offering insights into the dynamic nature of the brain microbiome and its connection to neurodegenerative diseases.
6. **Collaborative Data Sharing**: Establishing large, multi-institutional consortia to pool brain microbiome data enhances statistical power and validates findings across different populations and disease models. Standardizing protocols ensures that results are consistent and reproducible.
7. **Advanced Statistical Models**: Using sophisticated statistical models and machine learning algorithms can help distinguish true microbial signals from background noise or postmortem changes. These models can adjust for confounding factors such as age, cause of death, and medical history.
8. **Regional Variability and Sample Consistency**: Analyzing different brain regions and subjects can introduce variability that obscures true microbial patterns. Standardizing sampling protocols and conducting repeated analyses on the same samples from the same subjects improves consistency and helps account for regional differences.
9. **Comprehensive Multi-Omics Approaches:** To further elucidate the role of the microbiome in neuroinflammation and cognitive function, it is crucial to perform multi-omics analyses. Integrating data from blood, stool, and brain samples can provide a holistic view of the microbiome's influence on the central nervous system. Researchers can uncover potential links between systemic microbial changes and brain pathology by correlating microbial profiles across different biological matrices.

In conclusion, addressing these methodological limitations requires a multi-faceted approach that includes meticulous sample handling, diverse analytical tools, consistent sampling protocols, and comprehensive multi-omics analyses [134]. Establishing a consensus protocol for collecting and analyzing samples will allow for accurate and consistent identification of microbes, thereby overcoming these challenges and advancing our understanding of the brain microbiome's role in neuroinflammation and cognitive disorders.

Future Directions

Neuroimaging for detecting microbial involvement

Neuroimaging holds significant potential for detecting microbial involvement in AD by offering insights into how microbial presence and activity might influence brain pathology. Advanced imaging techniques, such as positron emission tomography (PET) and magnetic resonance imaging (MRI), can be leveraged to visualize and quantify brain inflammation, amyloid-beta plaques, and other markers associated with microbial infections. For example, PET scans using radiolabeled tracers can detect specific inflammatory responses or the presence of microbial components in the brain. Additionally, MRI techniques can identify structural changes and lesions associated with neuroinflammation driven by microbial activity. By combining neuroimaging with molecular and microbiological analyses, researchers can better understand how microbes contribute to AD pathology and potentially identify biomarkers for early disease progression detection and monitoring [139].

Personalized medicine approaches

Microbiome profiling for individualized treatment

Microbiome profiling involves analyzing the composition and functionality of an individual's microbiota to tailor treatments based on their unique microbial profile. In AD research, this approach can help identify specific microbial communities or biomarkers associated with disease progression or response to therapy. Personalized treatment strategies may include targeted probiotics, prebiotics, or dietary modifications designed to balance the gut microbiota and potentially mitigate AD symptoms. By considering the individual variations in microbiome composition, personalized medicine aims to optimize therapeutic outcomes and minimize adverse effects.

Implications for early diagnosis and prevention

Microbiome profiling can also be leveraged for early diagnosis of AD. Identifying microbial signatures associated with early disease stages or preclinical microbial markers. This can facilitate early intervention and the implementation of preventative strategies or treatments before significant neurodegenerative changes occur. Additionally, understanding the relationship between microbiome alterations and AD risk factors can lead to the development of novel preventive measures and interventions tailored to individual risk profiles.

The pathobiome concept of AD represents a significant challenge to the research community in understanding the disease's development and progression. Historically considered a sterile environment, the brain has been found to harbor various microorganisms, both commensal and pathogenic. Many of these microbes are increasingly recognized as potential contributors to AD, potentially initiating and exacerbating neuroinflammation and neurodegeneration.

Recent research suggests that microbial infections—whether bacterial, viral, or fungal—can drive neuroinflammation, a key factor in AD pathology. Supporting this approach, amyloid-beta (Aβ) has been identified as an antimicrobial peptide that, when interacting with microbes, can form plaques that contribute to neuroinflammation and cognitive decline. Pathogens such as *Porphyromonas gingivalis* and *Chlamydia pneumoniae* among others, have been detected in AD brains [54,66,78], reinforcing the idea that chronic infections may play a role in disease progression.

Dysbiosis in the gut microbiota has been linked to systemic inflammation and immune system alterations that may impact brain function and contribute to AD [26]. Although the exact mechanisms by which these microbes influence β-amyloidosis and other AD pathologies remain unclear, the presence of gut microbial components and pathogens in AD brains supports their involvement in the disease.

Grounded in the growing evidence of microbial involvement in AD, therapeutic strategies targeting the microbiome presents potential avenues for intervention. Antibiotics, probiotics, prebiotics, and FMT are being explored for their ability to alter the microbiome and reduce neuroinflammation. However, the effects of antibiotics on human cognitive function have been inconsistent, and more research is needed to fully understand their benefits and risks. The research linking AD and microorganisms is relatively new to the field of neurodegenerative diseases. Furthermore, Microbiology is vastly multifurcated into myriad facets comprising bacteria, viruses, fungi, protozoa, cyanobacteria etc,. Although limited studies are available on the role of protozoa and cyanobacteria, more recent investigations have begun to acknowledge their relevance and role in many CNS disorders. Future investigations would shed more light on the associations with AD and other nervous disorders.

In summary, our understanding of the pathobiome is reshaping AD research by highlighting the role of microorganisms in disease onset and progression. Further examination is essential to unravel the complex interactions between the microbiome and neuroinflammation and to develop targeted therapies that address these interactions effectively.

Authorship Contributions

Nanda K. Navalpur Shanmugam – Conceptualizing, Writing, Editing.
William A. Eimer – Writing, Editing.
Deepak K. Vijaya Kumar – Writing, Editing.
Rudolph E. Tanzi – Conceptualizing, Editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] DeTure MA, Dickson DW. The neuropathological diagnosis of Alzheimer's disease. Mol Neurodegener 2019;14(1):32.
[2] Trejo-Lopez JA, Yachnis AT, Prokop S. Neuropathology of alzheimer's disease. Neurotherapeutics 2022;19(1):173–85.
[3] McFarland KN, Chakrabarty P. Microglia in alzheimer's disease: a key player in the transition between homeostasis and pathogenesis. Neurotherapeutics 2022;19(1):186–208.
[4] Tarasoff-Conway JM, Carare RO, Osorio RS, Glodzik L, Butler T, Fieremans E, et al. Clearance systems in the brain-implications for Alzheimer disease. Nat Rev Neurol 2015;11(8):457–70.
[5] Verheggen ICM, de Jong JJA, van Boxtel MPJ, Gronenschild E, Palm WM, Postma AA, et al. Increase in blood-brain barrier leakage in healthy, older adults. Geroscience 2020;42(4):1183–93.
[6] Krezalek MA, DeFazio J, Zaborina O, Zaborin A, Alverdy JC. The shift of an intestinal "microbiome" to a "pathobiome" governs the course and outcome of sepsis following surgical injury. Shock 2016;45(5):475–82.
[7] Defazio J, Fleming ID, Shakhsheer B, Zaborina O, Alverdy JC. The opposing forces of the intestinal microbiome and the emerging pathobiome. Surg Clin 2014;94(6):1151–61.
[8] Fang P, Kazmi SA, Jameson KG, Hsiao EY. The microbiome as a modifier of neurodegenerative disease risk. Cell Host Microbe 2020;28(2):201–22.
[9] Bhattacharjee S, Lukiw WJ. Alzheimer's disease and the microbiome. Front Cell Neurosci 2013;7:153.
[10] Vogt NM, Kerby RL, Dill-McFarland KA, Harding SJ, Merluzzi AP, Johnson SC, et al. Gut microbiome alterations in Alzheimer's disease. Sci Rep 2017;7(1):13537.
[11] Chandra S, Sisodia SS, Vassar RJ. The gut microbiome in Alzheimer's disease: what we know and what remains to be explored. Mol Neurodegener 2023;18(1):9.
[12] Itzhaki RF, Lathe R, Balin BJ, Ball MJ, Bearer EL, Braak H, et al. Microbes and alzheimer's disease. J Alzheimers Dis 2016;51(4):979–84.
[13] Honjo K, van Reekum R, Verhoeff NP. Alzheimer's disease and infection: do infectious agents contribute to progression of Alzheimer's disease? Alzheimers Dement 2009;5(4):348–60.
[14] Arabi TZ, Alabdulqader AA, Sabbah BN, Ouban A. Brain-inhabiting bacteria and neurodegenerative diseases: the "brain microbiome" theory. Front Aging Neurosci 2023;15:1240945.
[15] Kinashi Y, Hase K. Partners in leaky gut syndrome: intestinal dysbiosis and autoimmunity. Front Immunol 2021;12:673708.
[16] Bonaz B, Bazin T, Pellissier S. The vagus nerve at the interface of the microbiota-gut-brain Axis. Front Neurosci 2018;12:49.
[17] Nagpal R, Mainali R, Ahmadi S, Wang S, Singh R, Kavanagh K, et al. Gut microbiome and aging: physiological and mechanistic insights. Nutr Healthy Aging 2018;4(4):267–85.
[18] Donohoe DR, Garge N, Zhang X, Sun W, O'Connell TM, Bunger MK, et al. The microbiome and butyrate regulate energy metabolism and autophagy in the mammalian colon. Cell Metabol 2011;13(5):517–26.
[19] Sharon G, Sampson TR, Geschwind DH, Mazmanian SK. The central nervous system and the gut microbiome. Cell 2016;167(4):915–32.
[20] Rehman T. Role of the gut microbiota in age-related chronic inflammation. Endocr, Metab Immune Disord: Drug Targets 2012;12(4):361–7.
[21] Wilmanski T, Diener C, Rappaport N, Patwardhan S, Wiedrick J, Lapidus J, et al. Gut microbiome pattern reflects healthy ageing and predicts survival in humans. Nat Metab 2021;3(2):274–86.
[22] Lyte M. Probiotics function mechanistically as delivery vehicles for neuroactive compounds: microbial endocrinology in the design and use of probiotics. Bioessays 2011;33(8):574–81.
[23] Sarkar A, Lehto SM, Harty S, Dinan TG, Cryan JF, Burnet PWJ. Psychobiotics and the manipulation of bacteria-gut-brain signals. Trends Neurosci 2016;39(11):763–81.
[24] Lal S, Kirkup AJ, Brunsden AM, Thompson DG, Grundy D. Vagal afferent responses to fatty acids of different chain length in the rat. Am J Physiol Gastrointest Liver Physiol 2001;281(4):G907–15.
[25] Goehler LE, Gaykema RP, Nguyen KT, Lee JE, Tilders FJ, Maier SF, et al. Interleukin-1beta in immune cells of the abdominal vagus nerve: a link between the immune and nervous systems? J Neurosci 1999;19(7):2799–806.
[26] Jiang C, Li G, Huang P, Liu Z, Zhao B. The gut microbiota and alzheimer's disease. J Alzheimers Dis 2017;58(1):1–15.
[27] Zhao Y, Cong L, Jaber V, Lukiw WJ. Microbiome-Derived lipopolysaccharide enriched in the perinuclear region of alzheimer's disease brain. Front Immunol 2017;8:1064.
[28] Godbout JP, Chen J, Abraham J, Richwine AF, Berg BM, Kelley KW, et al. Exaggerated neuroinflammation and sickness behavior in aged mice following activation of the peripheral innate immune system. Faseb J 2005;19(10):1329–31.
[29] Cryan JF, Dinan TG. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. Nat Rev Neurosci 2012;13(10):701–12.
[30] Cenit MC, Sanz Y, Codoner-Franch P. Influence of gut microbiota on neuropsychiatric disorders. World J Gastroenterol 2017;23(30):5486–98.
[31] Zhang L, Wang Y, Xiayu X, Shi C, Chen W, Song N, et al. Altered gut microbiota in a mouse model of alzheimer's disease. J Alzheimers Dis 2017;60(4):1241–57.
[32] Bauerl C, Collado MC, Diaz Cuevas A, Vina J, Perez Martinez G. Shifts in gut microbiota composition in an APP/PSS1 transgenic mouse model of Alzheimer's disease during lifespan. Lett Appl Microbiol 2018;66(6):464–71.
[33] Wu SC, Cao ZS, Chang KM, Juang JL. Intestinal microbial dysbiosis aggravates the progression of Alzheimer's disease in Drosophila. Nat Commun 2017;8(1):24.
[34] Brenner SR. Blue-green algae or cyanobacteria in the intestinal micro-flora may produce neurotoxins such as Beta-N-Methylamino-L-Alanine (BMAA) which may be related to development of amyotrophic lateral sclerosis, Alzheimer's disease and Parkinson-Dementia-Complex in humans and Equine Motor Neuron Disease in horses. Med Hypotheses 2013;80(1):103.
[35] Cattaneo A, Cattane N, Galluzzi S, Provasi S, Lopizzo N, Festari C, et al. Association of brain amyloidosis with pro-inflammatory gut bacterial taxa and peripheral inflammation markers in cognitively impaired elderly. Neurobiol Aging 2017;49:60–8.
[36] Minter MR, Zhang C, Leone V, Ringus DL, Zhang X, Oyler-Castrillo P, et al. Antibiotic-induced perturbations in gut microbial diversity influences neuro-inflammation and amyloidosis in a murine model of Alzheimer's disease. Sci Rep 2016;6:30028.
[37] Harach T, Marungruang N, Duthilleul N, Cheatham V, Mc Coy KD, Frisoni G, et al. Reduction of Abeta amyloid pathology in APPPS1 transgenic mice in the absence of gut microbiota. Sci Rep 2017;7:41802.
[38] Minter MR, Hinterleitner R, Meisel M, Zhang C, Leone V, Zhang X, et al. Antibiotic-induced perturbations in microbial diversity during post-natal development alters amyloid pathology in an aged APPSWE/PS1DeltaE 9 murine model of Alzheimer's disease. Sci Rep 2017;7(1):10411.
[39] Chu C, Murdock MH, Jing D, Won TH, Chung H, Kressel AM, et al. The microbiota regulate neuronal function and fear extinction learning. Nature 2019;574(7779):543–8.
[40] Braniste V, Al-Asmakh M, Kowal C, Anuar F, Abbaspour A, Toth M, et al. The gut microbiota influences blood-brain barrier permeability in mice. Sci Transl Med 2014;6(263):263ra158.
[41] Ramakrishna BS, Roediger WE. Bacterial short chain fatty acids: their role in gastrointestinal disease. Dig Dis 1990;8(6):337–45.
[42] Liu J, Wang F, Liu S, Du J, Hu X, Xiong J, et al. Sodium butyrate exerts protective effect against Parkinson's disease in mice via stimulation of glucagon like peptide-1. J Neurol Sci 2017;381:176–81.
[43] Ho L, Ono K, Tsuji M, Mazzola P, Singh R, Pasinetti GM. Protective roles of intestinal microbiota derived short chain fatty acids in Alzheimer's disease-type beta-amyloid neuropathological mechanisms. Expert Rev Neurother 2018;18(1):83–90.
[44] Kong Y, Jiang B, Luo X. Gut microbiota influences Alzheimer's disease pathogenesis by regulating acetate in Drosophila model. Future Microbiol 2018, Aug;13:1117–28.
[45] Sharma S, Taliyan R, Singh S. Beneficial effects of sodium butyrate in 6-OHDA induced neurotoxicity and behavioral abnormalities: modulation of histone deacetylase activity. Behav Brain Res 2015;291:306–14.

[46] Li D, Ke Y, Zhan R, Liu C, Zhao M, Zeng A, et al. Trimethylamine-N-oxide promotes brain aging and cognitive impairment in mice. Aging Cell 2018:e12768.
[47] Del Rio D, Zimetti F, Caffarra P, Tassotti M, Bernini F, Brighenti F, et al. The gut microbial metabolite trimethylamine-N-oxide is present in human cerebrospinal fluid. Nutrients 2017;9(10).
[48] Kohler CA, Maes M, Slyepchenko A, Berk M, Solmi M, Lanctot KL, et al. The gut-brain Axis, including the microbiome, leaky gut and bacterial translocation: mechanisms and pathophysiological role in alzheimer's disease. Curr Pharmaceut Des 2016;22(40):6152–66.
[49] Minter MR, Hinterleitner R, Meisel M, Zhang C, Leone V, Zhang X, et al. Antibiotic-induced perturbations in microbial diversity during post-natal development alters amyloid pathology in an aged APP(SWE)/PS1(DeltaE 9) murine model of Alzheimer's disease. Sci Rep 2017;7(1):10411.
[50] Elangovan S, Borody TJ, Holsinger RMD. Fecal microbiota transplantation reduces pathology and improves cognition in a mouse model of alzheimer's disease. Cells 2022;12(1).
[51] Pisa D, Alonso R, Fernandez-Fernandez AM, Rabano A, Carrasco L. Polymicrobial infections in brain tissue from alzheimer's disease patients. Sci Rep 2017;7(1): 5559.
[52] Yadav P, Lee YH, Panday H, Kant S, Bajwa N, Parashar R, et al. Implications of microorganisms in alzheimer's disease. Curr Issues Mol Biol 2022;44(10): 4584–615.
[53] Haas JG, Lathe R. Microbes and alzheimer's disease: new findings call for a paradigm change. Trends Neurosci 2018,Sep;41(9):570–3.
[54] Itzhaki RF, Wozniak MA, Appelt DM, Balin BJ. Infiltration of the brain by pathogens causes Alzheimer's disease. Neurobiol Aging 2004;25(5):619–27.
[55] Readhead B, Haure-Mirande JV, Funk CC, Richards MA, Shannon P, Haroutunian V, et al. Multiscale analysis of independent alzheimer's cohorts finds disruption of molecular, genetic, and clinical networks by human herpesvirus. Neuron 2018;99(1):64–82 e7.
[56] Kumar DK, Choi SH, Washicosky KJ, Eimer WA, Tucker S, Ghofrani J, et al. Amyloid-beta peptide protects against microbial infection in mouse and worm models of Alzheimer's disease. Sci Transl Med 2016;8(340):340ra72.
[57] Hill JM, Clement C, Pogue AI, Bhattacharjee S, Zhao Y, Lukiw WJ. Pathogenic microbes, the microbiome, and Alzheimer's disease (AD). Front Aging Neurosci 2014;6:127.
[58] Fulop T, Itzhaki RF, Balin BJ, Miklossy J, Barron AE. Role of microbes in the development of alzheimer's disease: state of the art - an international symposium presented at the 2017 IAGG congress in san francisco. Front Genet 2018;9:362.
[59] De Chiara G, Marcocci ME, Sgarbanti R, Civitelli L, Ripoli C, Piacentini R, et al. Infectious agents and neurodegeneration. Mol Neurobiol 2012;46(3):614–38.
[60] Soscia SJ, Kirby JE, Washicosky KJ, Tucker SM, Ingelsson M, Hyman B, et al. The Alzheimer's disease-associated amyloid beta-protein is an antimicrobial peptide. PLoS One 2010;5(3):e9505.
[61] Eimer WA, Vijaya Kumar DK, Navalpur Shanmugam NK, Rodriguez AS, Mitchell T, Washicosky KJ, et al. Alzheimer's disease-associated beta-amyloid is rapidly seeded by herpesviridae to protect against brain infection. Neuron 2018;99(1): 56–63.e3.
[62] Alkasir R, Li J, Li X, Jin M, Zhu B. Human gut microbiota: the links with dementia development. Protein Cell 2017;8(2):90–102.
[63] Diniz BS, Teixeira AL, Ojopi EB, Talib LL, Mendonca VA, Gattaz WF, et al. Higher serum sTNFR1 level predicts conversion from mild cognitive impairment to Alzheimer's disease. J Alzheimers Dis 2010;22(4):1305–11.
[64] Michan-Dona A, Vazquez-Borrego MC, Michan C. Are there any completely sterile organs or tissues in the human body? Is there any sacred place? Microb Biotechnol 2024;17(3):e14442.
[65] Gerard HC, Dreses-Werringloer U, Wildt KS, Deka S, Oszust C, Balin BJ, et al. Chlamydophila (Chlamydia) pneumoniae in the Alzheimer's brain. FEMS Immunol Med Microbiol 2006;48(3):355–66.
[66] Dominy SS, Lynch C, Ermini F, Benedyk M, Marczyk A, Konradi A, et al. Porphyromonas gingivalis in Alzheimer's disease brains: evidence for disease causation and treatment with small-molecule inhibitors. Sci Adv 2019;5(1): eaau3333.
[67] Miklossy J, Khalili K, Gern L, Ericson RL, Darekar P, Bolle L, et al. Borrelia burgdorferi persists in the brain in chronic lyme neuroborreliosis and may be associated with Alzheimer disease. J Alzheimers Dis 2004;6(6):639–49. discussion 673-81.
[68] Emery DC, Shoemark DK, Batstone TE, Waterfall CM, Coghill JA, Cerajewska TL, et al. 16S rRNA next generation sequencing analysis shows bacteria in alzheimer's post-mortem brain. Front Aging Neurosci 2017;9:195.
[69] Emery DC, Davies M, Cerajewska TL, Taylor J, Hazell M, Paterson A, et al. High resolution 16S rRNA gene Next Generation Sequencing study of brain areas associated with Alzheimer's and Parkinson's disease. Front Aging Neurosci 2022; 14:1026260.
[70] Singhrao SK, Harding A, Poole S, Kesavalu L, Crean S. Porphyromonas gingivalis periodontal infection and its putative links with alzheimer's disease. Mediat Inflamm 2015;2015:137357.
[71] Park JY, Choi J, Lee Y, Lee JE, Lee EH, Kwon HJ, et al. Metagenome analysis of bodily microbiota in a mouse model of alzheimer disease using bacteria-derived membrane vesicles in blood. Exp Neurobiol 2017;26(6):369–79.
[72] Wozniak MA, Mee AP, Itzhaki RF. Herpes simplex virus type 1 DNA is located within Alzheimer's disease amyloid plaques. J Pathol 2009;217(1):131–8.
[73] Mone Y, Earl JP, Krol JE, Ahmed A, Sen B, Ehrlich GD, et al. Evidence supportive of a bacterial component in the etiology for Alzheimer's disease and for a temporal-spatial development of a pathogenic microbiome in the brain. Front Cell Infect Microbiol 2023;13:1123228.
[74] Alonso R, Pisa D, Fernandez-Fernandez AM, Carrasco L. Infection of fungi and bacteria in brain tissue from elderly persons and patients with alzheimer's disease. Front Aging Neurosci 2018;10:159.
[75] Zhan X, Stamova B, Jin LW, DeCarli C, Phinney B, Sharp FR. Gram-negative bacterial molecules associate with Alzheimer disease pathology. Neurology 2016; 87(22):2324–32.
[76] Zhao Y, Cong L, Lukiw WJ. Lipopolysaccharide (LPS) accumulates in neocortical neurons of alzheimer's disease (AD) brain and impairs transcription in human neuronal-glial primary Co-cultures. Front Aging Neurosci 2017;9:407.
[77] Carter CJ. Genetic, transcriptome, proteomic, and epidemiological evidence for blood-brain barrier disruption and polymicrobial brain invasion as determinant factors in alzheimer's disease. J Alzheimers Dis Rep 2017;1(1):125–57.
[78] Balin BJ, Gerard HC, Arking EJ, Appelt DM, Branigan PJ, Abrams JT, et al. Identification and localization of Chlamydia pneumoniae in the Alzheimer's brain. Med Microbiol Immunol 1998;187(1):23–42.
[79] Kountouras J, Tsolaki M, Gavalas E, Boziki M, Zavos C, Karatzoglou P, et al. Relationship between Helicobacter pylori infection and Alzheimer disease. Neurology 2006;66(6):938–40.
[80] Miklossy J. Historic evidence to support a causal relationship between spirochetal infections and Alzheimer's disease. Front Aging Neurosci 2015;7:46.
[81] MacDonald AB. Transfection "Junk" DNA - a link to the pathogenesis of Alzheimer's disease? Med Hypotheses 2006;66(6):1140–1.
[82] Miklossy J. Alzheimer's disease - a neurospirochetosis. Analysis of the evidence following Koch's and Hill's criteria. J Neuroinflammation 2011;8:90.
[83] MacDonald AB. Borrelia in the brains of patients dying with dementia. JAMA 1986;256(16):2195–6.
[84] Senejani AG, Maghsoudlou J, El-Zohiry D, Gaur G, Wawrzeniak K, Caravaglia C, et al. Borrelia burgdorferi Co-localizing with amyloid markers in alzheimer's disease brain tissues. J Alzheimers Dis 2022;85(2):889–903.
[85] Poole S, Singhrao SK, Kesavalu L, Curtis MA, Crean S. Determining the presence of periodontopathic virulence factors in short-term postmortem Alzheimer's disease brain tissue. J Alzheimers Dis 2013;36(4):665–77.
[86] Itzhaki RF, Lin WR, Shang D, Wilcock GK, Faragher B, Jamieson GA. Herpes simplex virus type 1 in brain and risk of Alzheimer's disease. Lancet 1997; 349(9047):241–4.
[87] Sait A, Angeli C, Doig AJ, Day PJR. Viral involvement in alzheimer's disease. ACS Chem Neurosci 2021;12(7):1049–60.
[88] Lovheim H, Gilthorpe J, Adolfsson R, Nilsson LG, Elgh F. Reactivated herpes simplex infection increases the risk of Alzheimer's disease. Alzheimers Dement 2015;11(6):593–9.
[89] Pisa D, Alonso R, Rabano A, Rodal I, Carrasco L. Different brain regions are infected with fungi in alzheimer's disease. Sci Rep 2015;5:15015.
[90] Pisa D, Alonso R, Juarranz A, Rabano A, Carrasco L. Direct visualization of fungal infection in brains from patients with Alzheimer's disease. J Alzheimers Dis 2015; 43(2):613–24.
[91] Hoogman M, van de Beek D, Weisfelt M, de Gans J, Schmand B. Cognitive outcome in adults after bacterial meningitis. J Neurol Neurosurg Psychiatry 2007; 78(10):1092–6.
[92] Merkelbach S, Sittinger H, Schweizer I, Muller M. Cognitive outcome after bacterial meningitis. Acta Neurol Scand 2000;102(2):118–23.
[93] Noori M, Mahboobi R, Nabavi-Rad A, Jamshidizadeh S, Fakharian F, Yadegar A, et al. Helicobacter pylori infection contributes to the expression of Alzheimer's disease-associated risk factors and neuroinflammation. Heliyon 2023;9(9): e19607.
[94] Kountouras J, Boziki M, Gavalas E, Zavos C, Deretzi G, Grigoriadis N, et al. Increased cerebrospinal fluid Helicobacter pylori antibody in Alzheimer's disease. Int J Neurosci 2009;119(6):765–77.
[95] Fallon BA, Keilp JG, Corbera KM, Petkova E, Britton CB, Dwyer E, et al. A randomized, placebo-controlled trial of repeated IV antibiotic therapy for Lyme encephalopathy. Neurology 2008;70(13):992–1003.
[96] Christie D, Viner RM, Knox K, Coen PG, Wang H, El Bashir H, et al. Long-term outcomes of pneumococcal meningitis in childhood and adolescence. Eur J Pediatr 2011;170(8):997–1006.
[97] Kloek AT, Brouwer MC, Schmand B, Tanck MWT, van de Beek D. Long-term neurologic and cognitive outcome and quality of life in adults after pneumococcal meningitis. Clin Microbiol Infect 2020;26(10):1361–7.
[98] Segklia K, Matsas R, Papastefanaki F. Brain infection by group B Streptococcus induces inflammation and affects neurogenesis in the adult mouse Hippocampus. Cells 2023;12(12).
[99] Ganaraja VH, Jamuna R, Nagarathna C, Saini J, Netravathi M. Long-term cognitive outcomes in tuberculous meningitis. Neurol Clin Pract 2021;11(3):e222–31.
[100] Kourkoumpetis TK, Desalermos A, Muhammed M, Mylonakis E. Central nervous system aspergillosis: a series of 14 cases from a general hospital and review of 123 cases from the literature. Medicine (Baltim) 2012;91(6):328–36.
[101] Hariri OR, Minasian T, Quadri SA, Dyurgerova A, Farr S, Miulli DE, et al. Histoplasmosis with deep CNS involvement: case presentation with discussion and literature review. J Neurol Surg Rep 2015;76(1):e167–72.
[102] Idro R, Marsh K, John CC, Newton CR. Cerebral malaria: mechanisms of brain injury and strategies for improved neurocognitive outcome. Pediatr Res 2010; 68(4):267–74.
[103] Monroe JM, Buckley PF, Miller BJ. Meta-Analysis of anti-toxoplasma gondii IgM antibodies in acute psychosis. Schizophr Bull 2015;41(4):989–98.
[104] Nayeri T, Sarvi S, Sharif M, Daryani A. Toxoplasma gondii: a possible etiologic agent for Alzheimer's disease. Heliyon 2021;7(6):e07151.
[105] Kusbeci OY, Miman O, Yaman M, Aktepe OC, Yazar S. Could Toxoplasma gondii have any role in Alzheimer disease? Alzheimer Dis Assoc Disord 2011;25(1):1–3.

[106] MacLean L, Reiber H, Kennedy PG, Sternberg JM. Stage progression and neurological symptoms in Trypanosoma brucei rhodesiense sleeping sickness: role of the CNS inflammatory response. PLoS Neglected Trop Dis 2012;6(10):e1857.
[107] Lejon V, Buscher P. Review Article: cerebrospinal fluid in human African trypanosomiasis: a key to diagnosis, therapeutic decision and post-treatment follow-up. Trop Med Int Health 2005;10(5):395–403.
[108] Itzhaki RF. Overwhelming evidence for a major role for herpes simplex virus type 1 (HSV1) in alzheimer's disease (AD); underwhelming evidence against. Vaccines (Basel) 2021;9(6).
[109] Saylor D, Dickens AM, Sacktor N, Haughey N, Slusher B, Pletnikov M, et al. HIV-associated neurocognitive disorder–pathogenesis and prospects for treatment. Nat Rev Neurol 2016;12(4):234–48.
[110] Mody PH, Marvin KN, Hynds DL, Hanson LK. Cytomegalovirus infection induces Alzheimer's disease-associated alterations in tau. J Neurovirol 2023;29(4):400–15.
[111] Cheeran MC, Lokensgard JR, Schleiss MR. Neuropathogenesis of congenital cytomegalovirus infection: disease mechanisms and prospects for intervention. Clin Microbiol Rev 2009;22(1):99–126 (Table of Contents).
[112] Gilden DH, Kleinschmidt-DeMasters BK, Wellish M, Hedley-Whyte ET, Rentier B, Mahalingam R. Varicella zoster virus, a cause of waxing and waning vasculitis: the New England Journal of Medicine case 5-1995 revisited. Neurology 1996;47(6):1441–6.
[113] Mehta RS, Lochhead P, Wang Y, Ma W, Nguyen LH, Kochar B, et al. Association of midlife antibiotic use with subsequent cognitive function in women. PLoS One 2022;17(3):e0264649.
[114] Park SH, Lee JH, Shin J, Kim JS, Cha B, Lee S, et al. Cognitive function improvement after fecal microbiota transplantation in Alzheimer's dementia patient: a case report. Curr Med Res Opin 2021;37(10):1739–44.
[115] Angelucci F, Cechova K, Amlerova J, Hort J. Antibiotics, gut microbiota, and Alzheimer's disease. J Neuroinflammation 2019;16(1):108.
[116] Ye Y, Tong HYK, Chong WH, Li Z, Tam PKH, Baptista-Hon DT, et al. A systematic review and meta-analysis of the effects of long-term antibiotic use on cognitive outcomes. Sci Rep 2024;14(1):4026.
[117] Parachikova A, Vasilevko V, Cribbs DH, LaFerla FM, Green KN. Reductions in amyloid-beta-derived neuroinflammation, with minocycline, restore cognition but do not significantly affect tau hyperphosphorylation. J Alzheimers Dis 2010;21(2):527–42.
[118] Umar TP, Jain N, Stevanny B, Javed B, Priandhana A, Siburian R, et al. Protective role of Bacillus Calmette-Guerin vaccine in Alzheimer's disease progression: a systematic review and meta-analysis. Heliyon 2024;10(5):e27425.
[119] Eyting M, Xie M, Hess S, Geldsetzer P. Causal evidence that herpes zoster vaccination prevents a proportion of dementia cases. medRxiv 2023. May 25: 2023.05.23.23290253.
[120] Scherrer JF, Salas J, Wiemken TL, Hoft DF, Jacobs C, Morley JE. Impact of herpes zoster vaccination on incident dementia: a retrospective study in two patient cohorts. PLoS One 2021;16(11):e0257405.
[121] Schnier C, Janbek J, Williams L, Wilkinson T, Laursen TM, Waldemar G, et al. Antiherpetic medication and incident dementia: observational cohort studies in four countries. Eur J Neurol 2021;28(6):1840–8.
[122] Huo X, Finkelstein J. Pneumococcal vaccination lowers the risk of alzheimer's disease: a study utilizing data from the IBM(R) MarketScan(R) database. Stud Health Technol Inform 2024;310:961–5.
[123] Bukhbinder AS, Ling Y, Hasan O, Jiang X, Kim Y, Phelps KN, et al. Risk of alzheimer's disease following influenza vaccination: a claims-based cohort study using propensity score matching. J Alzheimers Dis 2022;88(3):1061–74.
[124] Sabbagh MN, Decourt B. COR388 (atuzaginstat): an investigational gingipain inhibitor for the treatment of Alzheimer disease. Expet Opin Invest Drugs 2022;31(10):987–93.
[125] Savignac HM, Corona G, Mills H, Chen L, Spencer JP, Tzortzis G, et al. Prebiotic feeding elevates central brain derived neurotrophic factor, N-methyl-D-aspartate receptor subunits and D-serine. Neurochem Int 2013;63(8):756–64.
[126] Xin Y, Diling C, Jian Y, Ting L, Guoyan H, Hualun L, et al. Effects of oligosaccharides from Morinda officinalis on gut microbiota and metabolome of APP/PS1 transgenic mice. Front Neurol 2018;9:412.
[127] Naomi R, Embong H, Othman F, Ghazi HF, Maruthey N, Bahari H. Probiotics for alzheimer's disease: a systematic review. Nutrients 2021;14(1).
[128] Kobayashi Y, Sugahara H, Shimada K, Mitsuyama E, Kuhara T, Yasuoka A, et al. Therapeutic potential of Bifidobacterium breve strain A1 for preventing cognitive impairment in Alzheimer's disease. Sci Rep 2017;7(1):13510.
[129] Bonfili L, Cecarini V, Cuccioloni M, Angeletti M, Berardi S, Scarpona S, et al. SLAB51 probiotic formulation activates SIRT1 pathway promoting antioxidant and neuroprotective effects in an AD mouse model. Mol Neurobiol 2018;55(10):7987–8000.
[130] Kaur H, Nagamoto-Combs K, Golovko S, Golovko MY, Klug MG, Combs CK. Probiotics ameliorate intestinal pathophysiology in a mouse model of Alzheimer's disease. Neurobiol Aging 2020;92:114–34.
[131] Fu J, Tan LJ, Lee JE, Shin S. Association between the mediterranean diet and cognitive health among healthy adults: a systematic review and meta-analysis. Front Nutr 2022;9:946361.
[132] Leblhuber F, Steiner K, Schuetz B, Fuchs D, Gostner JM. Probiotic supplementation in patients with alzheimer's dementia - an explorative intervention study. Curr Alzheimer Res 2018;15(12):1106–13.
[133] Hazan S. Rapid improvement in Alzheimer's disease symptoms following fecal microbiota transplantation: a case report. J Int Med Res 2020;48(6):300060520925930.
[134] Lathe R, Schultek NM, Balin BJ, Ehrlich GD, Auber LA, Perry G, et al. Establishment of a consensus protocol to explore the brain pathobiome in patients with mild cognitive impairment and Alzheimer's disease: research outline and call for collaboration. Alzheimers Dement 2023;19(11):5209–31.
[135] Wood DE, Salzberg SL. Kraken: ultrafast metagenomic sequence classification using exact alignments. Genome Biol 2014;15(3):R46.
[136] Valenzuela-Gonzalez F, Martinez-Porchas M, Villalpando-Canchola E, Vargas-Albores F. Studying long 16S rDNA sequences with ultrafast-metagenomic sequence classification using exact alignments (Kraken). J Microbiol Methods 2016;122:38–42.
[137] Hu X, Haas JG, Lathe R. The electronic tree of life (eToL): a net of long probes to characterize the microbiome from RNA-seq data. BMC Microbiol 2022;22(1):317.
[138] Marcais G, Kingsford C. A fast, lock-free approach for efficient parallel counting of occurrences of k-mers. Bioinformatics 2011;27(6):764–70.
[139] Giron MC, Mazzi U. Molecular imaging of microbiota-gut-brain axis: searching for the right targeted probe for the right target and disease. Nucl Med Biol 2021;92:72–7.
[140] Wheat LJ, Freifeld AG, Kleiman MB, Baddley JW, McKinsey DS, Loyd JE, et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. Clin Infect Dis 2007;45(7):807–25.
[141] Torrey EF, Bartko JJ, Yolken RH. Toxoplasma gondii and other risk factors for schizophrenia: an update. Schizophr Bull 2012;38(3):642–7.
[142] Whitley RJ. Herpes simplex virus infections of the central nervous system. Continuum 2015;21(6 Neuroinfectious Disease):1704–13.
[143] Antinori A, Arendt G, Becker JT, Brew BJ, Byrd DA, Cherner M, et al. Updated research nosology for HIV-associated neurocognitive disorders. Neurology 2007;69(18):1789–99.
[144] Gilden D, Cohrs RJ, Mahalingam R, Nagel MA. Varicella zoster virus vasculopathies: diverse clinical manifestations, laboratory features, pathogenesis, and treatment. Lancet Neurol 2009;8(8):731–40.
[145] Zhan X, Stamova B, Sharp FR. Lipopolysaccharide associates with amyloid plaques, neurons and oligodendrocytes in alzheimer's disease brain: a review. Front Aging Neurosci 2018;10:42.
[146] Lundmark K, Westermark GT, Olsen A, Westermark P. Protein fibrils in nature can enhance amyloid protein A amyloidosis in mice: cross-seeding as a disease mechanism. Proc Natl Acad Sci U S A 2005;102(17):6098–102.
[147] Chen SG, Stribinskis V, Rane MJ, Demuth DR, Gozal E, Roberts AM, et al. Exposure to the functional bacterial amyloid protein curli enhances alpha-synuclein aggregation in aged fischer 344 rats and Caenorhabditis elegans. Sci Rep 2016;6:34477.
[148] Gosztyla ML, Brothers HM, Robinson SR. Alzheimer's amyloid-beta is an antimicrobial peptide: a review of the evidence. J Alzheimers Dis 2018;62(4):1495–506.
[149] Alonso R, Pisa D, Marina AI, Morato E, Rabano A, Carrasco L. Fungal infection in patients with Alzheimer's disease. J Alzheimers Dis 2014;41(1):301–11.
[150] Harrell TL, Davido DJ, Bertke AS. Herpes simplex virus 1 (HSV-1) infected cell protein 0 (ICP0) targets of ubiquitination during productive infection of primary adult sensory neurons. Int J Mol Sci 2023;24(3).
[151] Athanasiou E, Gargalionis AN, Anastassopoulou C, Tsakris A, Boufidou F. New insights into the molecular interplay between human herpesviruses and alzheimer's disease-A narrative review. Brain Sci 2022;12(8).
[152] Kennedy PG. Clinical features, diagnosis, and treatment of human African trypanosomiasis (sleeping sickness). Lancet Neurol 2013;12(2):186–94.
[153] Spielbauer J, Glotfelty EJ, Sarlus H, Harris RA, Diaz Heijtz R, Karlsson TE. Bacterial peptidoglycan signalling in microglia: activation by MDP via the NF-kappaB/MAPK pathway. Brain Behav Immun 2024;121:43–55.
[154] Laman JD, t Hart BA, Power C, Dziarski R. Bacterial peptidoglycan as a driver of chronic brain inflammation. Trends Mol Med 2020;26(7):670–82.