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New approaches for understanding the potential role of microbes in Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) involves a complex pathological process that evolves over years, and its etiology is understood as a classic example of gene-environment interaction. The notion that exposure to microbial organisms may play some role in AD pathology has been proposed and debated for decades. New evidence from model organisms and -omic studies, as well as epidemiological data from the recent COVID-19 pandemic and widespread use of vaccines, offers new insights into the "germ hypothesis" of AD. To review new evidence and identify key research questions, the Duke/University of North Carolina (Duke/UNC) Alzheimer's Disease Research Center hosted a virtual symposium and workshop: "New Approaches for Understanding the Potential Role of Microbes in Alzheimer's disease." Discussion centered around the antimicrobial protection hypothesis of amyloid accumulation, and other mechanisms by which microbes could influence AD pathology including immune cell activation, changes in blood-brain barrier, or direct neurotoxicity. This summary of proceedings reviews the content presented in the symposium and provides a summary of major topics and key questions discussed in the workshop.

1. Introduction

This article summarizes research presented at the virtual symposium and workshop, "New Approaches for Understanding the Potential Role of Microbes in Alzheimer's Disease," hosted May 16, 2023 b y the Duke University and the University of North Carolina (Duke/UNC) Alzheimer's Disease Research Center and the Duke Aging Center. The event expanded on discussions initiated at a Duke/UNC conference covering similar themes in May 2021(Whitson et al., 2022).

The objective of these events was to review the evidence base and catalyze research to address knowledge gaps in the hypothesis that infections or microbes play some causative role in the development or progression of Alzheimer's disease. Alzheimer's disease is a complex disease; this symposium was rooted in an understanding that its pathogenesis could be triggered by both microbe-dependent and microbe-independent pathways and the two are not mutually exclusive.

The 2023 symposium was introduced with a keynote lecture describing the origins and accumulating evidence for the theory around amyloid-β (Aβ) as an antimicrobial protein that protects the brain against infection. The next session highlighted epidemiological and

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Table 1
Topics identified as gap areas and priorities for future research on the role of microbes in Alzheimer's disease (AD).

Topic areas	High priority questions
Antimicrobial role of amyloid	Which, if any, pathogen exposures stimulate amyloid production and accumulation in the live, healthy human brain? (Section 1.0) Are there genetic mutations that confer higher risk of AD, but lower risk of brain infection or encephalitis? Do such mutations play a role in amyloid production or clearance? (Section 1.0) If we had sensitive techniques to detect evidence of microbes in the brain (even from an individual's remote past), would microbial exposure be more common in brains with (vs without) amyloid?(Section 5.0)
COVID-19 and Alzheimer's risk	Does COVID-19 infection accelerate the onset or progression of Alzheimer's disease pathology? (Section 2.1) Does SARS-CoV-2 virus directly access brain tissue in most infections, or are the cognitive sequalae of COVID-19 primarily due to inflammatory responses? If so, what immune mediators drive neuronal consequences? (Section 2.2) What role might astrocytes play in long-term brain disruptions brought about by COVID-19 infection? (Section 1.0) What actions could be taken at the time of COVID-19 infection to protect against subsequent neuronal damage or cognitive decline? Do COVID-19 vaccinations lower risk of dementia? (Section 4.0)
Microbe – immune system interactions in the pathology of AD	When is the activation of innate immunity helpful in containing or avoiding AD pathology, and when does it drive neuropathology? (Section 1.0) Are there features of microglia or astrocytes that indicate this? (Sections 1.0 and 6.0) Are there some pathogens outside the brain that stimulate the expansion of T cells which gain entry to the brain? How do these T cells then interact with neurodegenerative processes? (Section 1.0) By what blood-borne mediators (e.g., lipopolysaccharide [LPS] toxin or metabolites) does the gut's microbiome alter the blood-brain barrier or brain immune cells, and how do these interactions drive AD? (Section 7.0) Could targeted immune modulation interrupt the mechanism(s) by which immune activation may drive AD pathology, without conferring the risks of nonspecific immunosuppression?
Gene expression	Could pathogenic gene variants associated with AD risk have helped our ancestors survive endemic or epidemic brain infections? (Section 1.0) How might epigenetic changes acquired in a person's lifetime alter immune or vascular responses to common infections (e.g., cytomegalovirus), potentially accounting for AD's presentation in late life, despite obvious heritability? (Section 3.0) Could age-related decline in efficient DNA repair result in poor neuronal response to microbes or inflammation? (Section 3.0) How does tauopathy in neurons lead to activation of retrovirus genes (retrotransposons) that were previously silent within human chromatin? Does this drive a vicious cycle whereby the endogenous retroviruses stimulate an immune response that causes further toxicity? (Section 6.0)
Treatment opportunities	Using large-scale, controlled trials of vaccines or antimicrobial therapy, can we develop more definitive evidence as to whether microbes play a direct role in AD or dementia? (Section 4.0) Do antibiotics, antivirals, anti-fungals, or anti-inflammatory medications confer benefit for AD prevention? In designing studies to test this, should we target acute or chronic (indolent) infections? (Section 4.0, 5.0) In people with early AD, is it possible to interrupt the toxicity caused by endogenous retrovirus activation with transcriptase inhibitors? (Section 6.0)

mechanistic data for a potential link between Covid-19 and Alzheimer's disease. The program then featured brief (10-min) lectures that explored these topics: single-cell genomic studies in Alzheimer's disease that may suggest immune response to microbes, a potential role for antiviral vaccines in Alzheimer's disease, investigations into which microbes could cause Alzheimer's, activation of endogenous retroviruses in tauopathy, and gut-microbe brain communications. The event closed with a panel discussion and presentation of the Alzheimer's Pathobiome Initiative(Lathe et al., 2023), which aims to establish guidelines and protocols for detection of infectious agents in patients with mild cognitive impairment or Alzheimer's disease (AD). The main topics covered in each session are summarized in the text below. Table 1 presents overarching topic areas and key questions for future research that were raised in large group discussions throughout the workshop.

2. Rudolph Tanzi: introductory lecture: the antimicrobial protection hypothesis of Alzheimer's disease

Much of Alzheimer's disease (AD) research has centered around the notion that accumulation of Aβ pathology prompts a decades-long series of events leading to neurofibrillary tau tangles, synaptic dysfunction, neuroinflammation, neuronal cell loss and ultimately cognitive dysfunction and dementia.

This concept — the so-called "amyloid hypothesis" of AD, was first proposed by George Glenner (Glenner and Wong 1984) and Colin Masters and Heidelberg Beyreuther (Masters et al., 1985) and later modified into the "amyloid cascade hypothesis" (Hardy and Higgins 1992). After amyloid deposits were observed in postmortem brains, Glenner isolated the Aβ protein in 1984, and later in 1987, three groups identified the amyloid precursor protein (APP) gene encoding a transmembrane receptor that gets cleaved by secretases to form Aβ peptides. They also showed that early-onset familial Alzheimer's disease results from mutations in APP or in the genes for the presenilins PSEN1 and PSEN2, which encode g-secretase, an enzyme needed to release Aβ from APP. These findings, including experiments in transgenic mice modeling the disease, pointed to Aβ as the etiologic factor in Alzheimer's (Tanzi and Bertram 2005).

Studies of genetically engineered mice complicated efforts to understand the role of amyloid-β in Alzheimer's neuropathology, especially its relationship to tangles. Initial experiments in AD mice suggested that amyloid pathology did not lead to tau tangles, raising questions as to whether amyloid was the true cause of Alzheimer's. This led to a major debate about whether amyloid triggers AD, as the human genetic studies originally suggested. However, researchers later discovered that those mice lacked the 50:50 ratio of 3 R:4 R tau isoforms needed to form tangles. In other words, it wasn't that the amyloid had failed to induce tangle formation but rather, the biology of the mouse models was not conducive to the formation of tangles.

A three-dimensional human cell culture model finally settled the decades-long debate in 2014. Created from embryonic stem cell-derived neural progenitors expressing familiar Alzheimer's mutations, this system, using a 3D gel matrix, shows the expected sequence of events — formation of Aβ oligomers and fibrils, plaques, and then tau tangles (Choi et al., 2014). When Aβ generation was blocked, tangles do not

form, suggesting Aβ was indeed the trigger. Tangle formation is mainly induced by oligomers of Ab42 (Kwak et al., 2020).

Furthermore, when neurons make plaques and tangles, it seems to set off a vicious cycle: The Aβ, tangles, and dying neurons attract and activate microglia, which accelerate tangle formation and neuroinflammation, dramatically exacerbating cell death (Joseph Park and Doo Yeon Kim, unpublished). Immunotherapies that clear Aβ have recently been approved for AD, and small molecules, such as g-secretase modulators, to reduce Aβ production are being clinically developed by Dr. Tanzi and colleagues.

Since 2008, genome-wide association studies (GWAS) have identified about 100 loci that are associated with AD risk. About two thirds of these gene loci play roles in innate immunity, microglial function or neuroinflammation (Jorfi et al. 2023a,b), beginning with the first of this class of genes to be identified by GWAS, CD33 (Bertram et al., 2008). The impact on AD pathogenesis can be complicated. The second AD-associated innate immune gene, TREM2, for example, promotes microglial clearance of amyloid and other debris, and when TREM2 levels are decreased, microglia are more likely to be inflammatory (Jonsson et al., 2013). Another AD risk variant, CD33, has the opposite effect: Increased CD33 levels induce inflammation while lower levels boost Aβ clearance (Bertram et al., 2008).

Other research suggests a role for adaptive immunity, as well. In a 2020 study, mass cytometry and single-cell T cell receptor (TCR) sequencing revealed clonal expansion of CD8 memory T cells in the cerebrospinal fluid of patients with AD to several Epstein-Barr virus antigens (Gate et al., 2020). More recently, experiments in model mice showed that T cell infiltration markedly increased in brain areas with tau pathology and that numbers of T cells correlated with the extent of neuron loss (Chen et al., 2023).

These findings prompted a new 3D human neuroimmune model of Alzheimer's that includes peripheral chambers where T cells, B cells, neutrophils and other immune cells can be added to gauge their impact on AD pathogenesis. According to a study using this 3D system, induction of amyloid and tangle pathology triggers astrocytes to release the chemokine CXCL10, which then binds to the CXCR3 receptor on CD8 T cells and recruits them into the central AD pathology chamber from the peripheral chambers. Once T cells enter, they release IFNγ, which further exacerbates microglial activation, inflammation and cell death (Jorfi et al., 2023a,b).

Experiments such as these lend plausibility to an alternative theory in which Alzheimer's pathologies first evolved as part of an orchestrated defense to protect the brain against infection. According to this hypothesis, known as the "antimicrobial protection hypothesis" of AD (Moir et al. 2018), microbes seed the formation of b-amyloid, which traps the microbe, as part of a host defense mechanism. Thus, Aβ serves as an antimicrobial peptide. This process triggers neuroinflammation and activates microglia and astrocytes in a similar manner as might occur in response to an infection, which greatly amplifies neuronal cell death. Microbe-induced b-amyloid drives the formation of tangles, leading to neuronal cell death and pro-inflammatory activation of microglia and astrocytes, which work to destroy what they sense to be an infected part of the brain, to limit the spread of infection.

In AD mouse and 3D neural cell culture model studies overexpressing Aβ, following viral (HSV-1) or bacterial infection (Salmonella or LPS), Aβ42 shows increased binding to the microbes leading to b-amyloid and tangle formation, exacerbating neuronal cell death (Kumar et al., 2016; Eimer et al., 2018). And in more recent multi-chamber neuronal 3D microfluidic models, experiments show that HSV1 directly induces tangle formation subsequent to the phospho-tau binding to the caps of the herpes virus inside neurons. This leads to tangle formation, further amplified by microbe-induced Ab oligomer formation, and prevents neurotropic spread of the virus from one neuron to another (Eimer et al., unpublished).

The framing of b-amyloid and tau pathologies as having evolved to protect against microbial infection in the brain, calls for a rethink of AD genetics. Risk variants that predispose individuals to Aβ oligomerization and tau tangle formation hold an advantage in the gene pool, because according to the microbial protection hypothesis, during evolution, these pathogenic gene variants helped people survive epidemics of encephalitis and other types of brain infection. In other words, mutations that predispose to AD pathology have been evolutionarily conserved owing to their protective effects on brain infection, e.g. encephalitis. In this manner, both pathogenic gene variants, e.g. in APP, PSEN1/2 and APOE, or the presence of microbes in the brain, can trigger AD pathology.

Metagenomic analyses of human postmortem brain aimed at identifying microbial pathogens that may trigger some cases of AD, are ongoing (Nanda Kumar, unpublished). However, it may be difficult to uncover solid evidence for infections that occurred decades before the appearance of symptoms. Thus, laser-captured plaques from postmortem AD brain are now being analyzed for the presence of microbial DNA and RNA. Recently, researchers have established a consensus protocol to explore the brain pathobiome in patients with AD and mild cognitive impairment (Lathe et al., 2023).

3. Emerging evidence on COVID-19 and Alzheimer's disease

The COVID-19 global pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), spread worldwide in early 2020. Pandemic emergency declarations were lifted in May 2023 (Silk et al., 2023), the same month that this symposium was held. At the time of this writing, there have been over 770 million cases recorded worldwide, and data on the long-term consequences of COVID-19 infection are rapidly emerging.

3.1. Monica M. Diaz: Covid-19 and Alzheimer's disease - clinical and epidemiological

Numerous studies have documented neurologic symptoms after recovery from acute COVID-19. Among 70 adult patients in a December 2020 analysis in France, 54 (77.1%) reported neurological symptoms — including anosmia, headaches and neuro-cognitive disorders (Salmon-Ceron et al., 2021). In a June 2022 meta-analysis of 83 global studies characterizing 1979 COVID-19 patients hospitalized with neurological disease (Singh et al., 2022), encephalopathy and delirium were common (978 [49%] patients), as were cerebrovascular events (506 [26%] patients). One-third of these patients developed neurological disease after hospital admission. Those with a pre-existing dementia diagnosis had a higher risk of poorer outcomes, including death.

To address whether COVID-19 influences the risk of developing AD, a large retrospective cohort study compared ~1.5 million patients who developed COVID-19 over a two-year period (Jan 20, 2020 thru April 13, 2022) against a matched cohort with other respiratory infections prior to the COVID-19 pandemic. Patients who recovered from COVID-19 had an increased probability of developing a mood disorder (Taquet et al., 2022) but the risk of depression and anxiety declined over time to equal levels of the comparison group. In contrast, the COVID-19 patients' risk of cognitive deficit and incident dementia diagnosis remained elevated, compared to the comparison group, at the end of the two-year study period. Among older adults, COVID infection was associated with a 40% higher hazard rate for dementia at 6 months(Taquet et al., 2022). Studies in Paris and Amsterdam found that declines in memory and cognition during lockdown persisted a year later (Custodio et al., 2021; Bakker et al., 2023).

As for mechanisms underlying these COVID-related cognitive changes, some evidence points to changes in brain structure. An analysis of 785 participants from the UK Biobank found greater reduction in whole brain volumes and in gray matter thickness of the left orbitofrontal cortex and parahippocampal gyrus, in people who were infected with SARS-CoV-2 compared with control patients who never had COVID-19 (Douaud et al., 2022). Other studies found higher baseline

serum levels of neurofilament light-chain (NfL), a marker of neurodegeneration, in COVID-19 patients (Kanberg et al., 2021). Longitudinal NfL levels also correlated with serum C-reactive protein and plasma D-dimer (Verde et al., 2022).

Addressing other modifiable risk factors for dementia — such as hearing loss, hypertension, alcohol use, and depression — could help reduce dementia risk that may be accelerated by COVID-19 (Livingston et al., 2020).

3.2. Serena spudich: COVID-19 and Alzheimer's - neuropathogenesis

With continued research on mechanisms underlying COVID-19 neuropathogenesis — such as neuroinflammation, vascular injury, autoimmunity, and neuronal injury — speculation intensifies as to whether these phenomena trigger processes that could initiate, unmask or worsen neurodegenerative disease.

Detailed clinical data from a study of UK adults hospitalized for COVID-19 during the first wave show different timing patterns for a spectrum of symptoms. For example, whereas some problems predated the onset of COVID-19 symptoms, other neuroinflammatory or psychiatric symptoms tended to show up several weeks after the initial respiratory symptoms (Ross Russell et al., 2021). This timing of onset suggests some sort of peri-infectious susceptibility, rather than a direct response to SARS-CoV-2 infection.

These observations raised questions about whether inflammation could be driving the neurologic symptoms. In a small study, people with neurologic symptoms during acute COVID-19 had elevated cerebrospinal fluid (CSF) markers of intracellular inflammation, compared to healthy controls, despite having undetectable SARS-CoV-2 virus in their CSF, by quantitative reverse transcription polymerase chain reaction (RT-qPCR) and metagenomic sequencing (Normandin et al., 2021).

Another study of COVID-19 patients with neurologic symptoms also failed to detect SARS-CoV-2 by PCR or metagenomic sequencing. Yet this analysis revealed different cytokine patterns, which reflect altered immune responses, in CSF compared to healthy control patients and compared to blood cytokine patterns (Song et al., 2021). That suggests a compartmentalized immune response rather than mere overflow of inflammation into the CNS. Furthermore, single-cell sequencing showed an increased frequency of B cells in the CSF of COVID-19 patients. In addition, these patients had detectable CSF anti-SARS-CoV-2 antibodies, some of which reacted to brain tissue when placed into a mouse model — suggesting the presence of autoimmune syndromes.

On a similar vein, analyses of brain tissue from COVID-19 patients have uncovered high levels of neuroinflammation — i.e. widespread microgliosis, astrogliosis and CD8 T cell infiltration — as well as microvascular injury and perivascular macrophage infiltration (Lee et al., 2021). Patients hospitalized for COVID-19 also have blood markers of neuronal injury (Frontera et al., 2022)— eg elevated NfL (biomarker of active axonal/neuronal injury) and GFAP (biomarker of astrocyte/glial injury) — and CSF evidence of amyloid processing alterations (ie changes in APP and Aβ protein levels) (Ziff et al., 2022).

The ongoing COVID Mind Study at Yale School of Medicine is analyzing a variety of CSF and blood measures in PASC (post-acute sequelae of SARS-CoV-2 infection) patients with neurologic symptoms. Preliminary data from 38 individuals about one year after acute COVID-19 infection finds no significant differences in levels of cytokines, NfL or microglial activation. However, the analyses showed a mild elevation of GFAP in both CSF and blood, suggesting that astrocyte abnormalities persist a year after acute COVID-19.

It's still unclear whether patients who survive COVID-19 infection face an increased risk for Alzheimer's, but the idea seems plausible. Potential intervention targets to prevent Alzheimer's after COVID-19 include antivirals to reduce CNS injury during acute COVID-19 infection; anti-inflammatory agents to reduce neuroinflammation and systemic perturbations; immune modulators (eg corticosteroids, IVIG) to reduce autoimmune and neuroimmune responses; antiplatelet or immune therapies to address vascular inflammation, microvascular compromise and impact on regional blood flow; and targeted therapies to counteract possible persistence of viral antigens in the CNS.

4. Manolis Kellis: single-cell genomic studies in Alzheimer's disease

Some researchers are taking a large-scale data integration approach to study AD. They are conducting single-cell genomic studies in large numbers of patients, across transcriptomic and epigenomic information, and using the resulting datasets to predict genes, pathways, regulatory regions, and upstream regulators. They validate their predictions to infer causal drivers of pathogenesis by manipulating these genes and pathways in animal and organoid models, to propose specific therapeutic intervention targets.

One set of experiments suggested an immune basis of AD by showing that common genetic variants associated with late-onset Alzheimer's from Genome-Wide Association Studies (GWAS) enrich specifically in immune cells, rather than neuronal or microglial cells, and that epigenetic changes occurred in immune cells early on and showed up in neuronal cells later in a mouse model of Alzheimer's (Gjoneska et al., 2015). Another key study revealed that neuronal activity induces double-strand DNA breaks in the promoters of early-response genes (Madabhushi et al., 2015). That suggests that the systems that repair these breaks may falter with age and thereby contribute to the onset of neurodegeneration in late life.

In the context of pathogen-associated changes in Alzheimer's, data from three cohort studies in ethnically diverse donors indicates that cytomegalovirus infection is associated with an increased risk of AD and faster cognitive decline in diverse older adults (Barnes et al., 2015). Single-cell profiling of post-mortem brains for these individuals showed immune and vascular changes associated with infections, suggesting potential pathways through which viral infections might contribute to AD.

5. Kenneth schmader: potential role of antiviral vaccines in Alzheimer's disease

By now, there's solid rationale for the idea that vaccines could reduce the risk of Alzheimer's disease and related dementias. Infections can lead to systemic inflammatory neurotoxicity, and thus vaccination could conceivably help in two ways: (1) by reducing neurotoxic inflammation or microbial damage induced by infection with a specific pathogen, and (2) exerting non-specific protection against infectious diseases more broadly by influencing microglia and oxidative stress.

Research in APP/PS1 transgenic mice offers support for these hypotheses. Influenza vaccination increased microglial clearance of Aβ and seemed to improve memory (Xing et al., 2021; Yang et al., 2020). Immunizing this mouse model with Bacillus Calmette-Guérin (BCG) also reduced amyloid pathology and seemed to help with cognitive defects (Zuo et al. 2017, 2021).

Human studies also suggest that vaccinations could reduce the incidence of Alzheimer's and other dementias. Large retrospective cohort studies in the US and a nested case-control study in the UK found 19%–35% reductions in dementia risk with herpes zoster vaccination (J. F. Scherrer et al., 2021; J. Scherrer et al., 2022; Lophatananon et al., 2021). Studies of influenza vaccine in US and Taiwan populations came to a similar conclusion: Compared to unvaccinated patients, those who received vaccinations had a significantly lower risk of dementia, with adjusted hazard ratios from 0.60 to 0.86 (Bukhbinder et al., 2022; Wiemken et al., 2021; Amran 2020; Luo et al., 2020).

A meta-analysis of 17 studies examining the impact of various vaccines on incident dementia pooled results from immunizations with influenza, zoster, Tdap, BCG, pneumonia, etc. And found that vaccinated individuals had a 35% reduced risk of dementia, compared with unvaccinated people (Wu et al., 2022). However, a more recent nested

case-control study that did not make it into the meta-analysis found that use of one or more common vaccines was associated with an increased risk of dementia (odds ratio 1.38) in a cohort of more than 13 million dementia-free seniors in the UK Clinical Practice Research Datalink (Douros et al., 2023).

While the evidence for dementia protection from the human vaccine studies is remarkable, the research has limitations. One key consideration is healthy vaccinee bias. That is, people who seek vaccinations may differ in health behavior, environment, education and other factors that influence Alzheimer's risk, compared to unvaccinated individuals. Another possibility is residual confounding — some non-measured factor, such as functional status, that is associated with both exposure and outcome. Plus, dementia and vaccine measurement biases are also possible, given that these data were obtained from administrative ICD codes. Prospective cohort studies of newer, enhanced vaccines should help shed light on the intriguing findings. The widespread use and robust tracking of COVID-19 vaccination globally presents an unprecedented opportunity to examine the relationship between inactivated virus vaccines and dementia. However, long-term treatment vs. placebo-controlled trials, which could provide the clearest evidence of protection against dementia, are not ethical with most vaccines because of their known health benefits.

6. Richard Lathe: do microbes cause Alzheimer's, and which ones?

It is plausible that infections could trigger AD. Age-related decline in stem cell renewal is thought to most seriously affect the immune system (Lathe and St Clair 2023), and infections are the most common cause of death across all metazoan species examined. Furthermore, infections increase with age, and AD is an age-related disease.

The idea that microbes enter the brain, however, does garner speculation. Nevertheless, there are robust data, at least in mice, that orally or nasally administered bacteria and fungi do reach the brain (Ilievski et al., 2018; Coelho et al., 2019). In addition, studies have found a variety of microbes — including fungi (Alonso et al., 2018), bacteria (Balin et al., 2018; Fülöp et al., 2018; Emery et al., 2017) and herpes simplex virus (Itzhaki, 2021a, 2021b) — in brains of people with Alzheimer's.

Detecting microbes in the brain is not easy. Direct culture can be difficult because some organisms do not grow easily on agar. Immunohistochemistry and PCR require specific antibodies and probes, and thus only allow analyses of known organisms. Metagenomics is comprehensive, but because there is only one genome per cell, the technique is insensitive. In addition, it produces terabytes of data and takes months to complete.

Transcriptomic studies primarily use two techniques. One is the k-mer approach, which is fast but risks false positive signals. A new method, called the electronic tree of life (eToL), uses 64-mer sequences designed from ribosomal RNA (rRNA) sequences to identify exogenous microbial and viral sequences in human tissue RNA-seq data. Performing eToL across different species (*Drosophila*, octopus, lobster, zebrafish, *Xenopus*, chicken, mouse, rat, sheep, human) showed that these brains do contain microbes — about 1 bacterium per 10 host neurons, and 1 fungal cell per 20 host neurons (X. Hu et al. 2022).

Data from the Edinburgh Brain Bank, as well as further data from the Mount Sinai Brain Bank, now show that some microbes appear to be overabundant in Alzheimer's brains, sometimes by large margins. These microbes are species typically encountered in human infections — for example, *Streptococcus* and *Staphylococcus*, as well as several *Aspergillus*-like, *Candida*-like, and *Cryptococcus*-like fungi (Hu et al., 2023), of interest because *Cryptococcus* in particular is a known cause of dementia 'masquerading' as Alzheimer's disease (reviewed in (Lathe et al., 2023). Infections appeared to be locally restricted – some samples with a heavy microbial burden were adjacent to tissues largely lacking microbes. Conversely, some atypical microbes were seen in more than one brain region, indicative of *in vivo* spreading.

However, whether microbes cause Alzheimer's remains an open question. One way to evaluate this would be to determine which brain microbes are present in each individual (perhaps through analysis of cerebrospinal fluid or olfactory neuroepithelium), and then to explore whether appropriate therapy might mitigate or slow Alzheimer's disease.

7. Bess Frost: activation of endogenous retroviruses in tauopathy

A canonical function of the microtubule-associated protein tau is to bind and stabilize microtubules. In Alzheimer's and other tauopathies, however, tau detaches from microtubules and forms toxic soluble multimeric species that accumulate into larger insoluble fibrils (Sexton et al., 2022).

Studies have shown that pathogenic forms of tau drive overstimulation of the actin cytoskeleton that destabilizes the lamin nucleoskeleton (Frost et al. 2016). Nucleoskeletal destabilization then causes decondensation of heterochromatin, leading to aberrant expression of genes that typically are transcriptionally silent (Frost et al., 2014; Mansuroglu et al., 2016; Chanu and Sarkar 2017; Klein et al., 2019), including retrotransposons (W. Sun et al., 2018).

Heterochromatic regions of the genome are highly enriched for transposable elements, which account for roughly 45% of the human genome. Transposable elements are classified into two major families: DNA transposons (2% of genome), which can "jump" to new locations in the genome but are transcriptionally inactive in humans due to the accumulation of truncations and mutations over the course of evolution; and retrotransposons (40% of genome), which can copy and paste themselves into different genomic locations by reverse transcribing their RNA into a new DNA copy. While most retrotransposons have lost the ability to retrotranspose in humans, some elements retain mobilization potential. The RNA, protein, and episomal DNA that are produced from retrotransposons can also drive toxicity via innate immune activation.

The "endogenous retroviruses" are retrotransposons that are structurally similar to viruses. Endogenous retroviruses are thought to have integrated into the human genome due to viral infections that occurred over the course of evolution (Ochoa Thomas et al., 2020). Retrotransposons, particularly endogenous retroviruses, are activated at the RNA level across *Drosophila,* mouse, and human tauopathy, including AD (W. Sun et al., 2018; Guo et al., 2018; Ramirez et al., 2022; Wahl et al., 2023). Studies in tau transgenic *Drosophila* indicate that transposable elements actively mobilize and are neurotoxic (W. Sun et al., 2018). Multiple retrotransposons were found to have an age-dependent increase in DNA copy number in tau transgenic mice (Ramirez et al., 2022) and in human AD and progressive supranuclear palsy (Frost lab, unpublished data), suggesting that these elements are actively reverse transcribed into new DNA copies in mammalian tauopathies. Nanopore long read sequencing further suggests that somatic retrotransposition is significantly elevated in human brain affected by AD (Frost lab, unpublished data).

Similar to viruses, retrotransposons can activate the innate immune system through the production of double stranded RNA (dsRNA), viral-like protein, and episomal DNA. dsRNAs are elevated in brains of tau transgenic *Drosophila* and mice, and in human AD and progressive supranuclear palsy. Tau-induced dsRNA are elevated in astrocytes that also feature upregulation of MDA-5, a pattern recognition receptor that typically functions to detect viral-derived dsRNA. Studies in tau transgenic *Drosophila* indicate that retrotransposons contribute to the dsRNA burden and that dsRNAs drive neuroinflammation (Ochoa et al., 2023).

Electron microscopy of brains of tau transgenic *Drosophila* reveal highly ordered structures that resemble paracrystalline viral arrays (Frost lab, unpublished data), suggesting that tau-induced activation of endogenous retroviruses may lead to the production of viral-like particles. In line with these findings, capsid protein produced from the mouse intracisternal A particle (IAP) endogenous retrovirus are elevated in

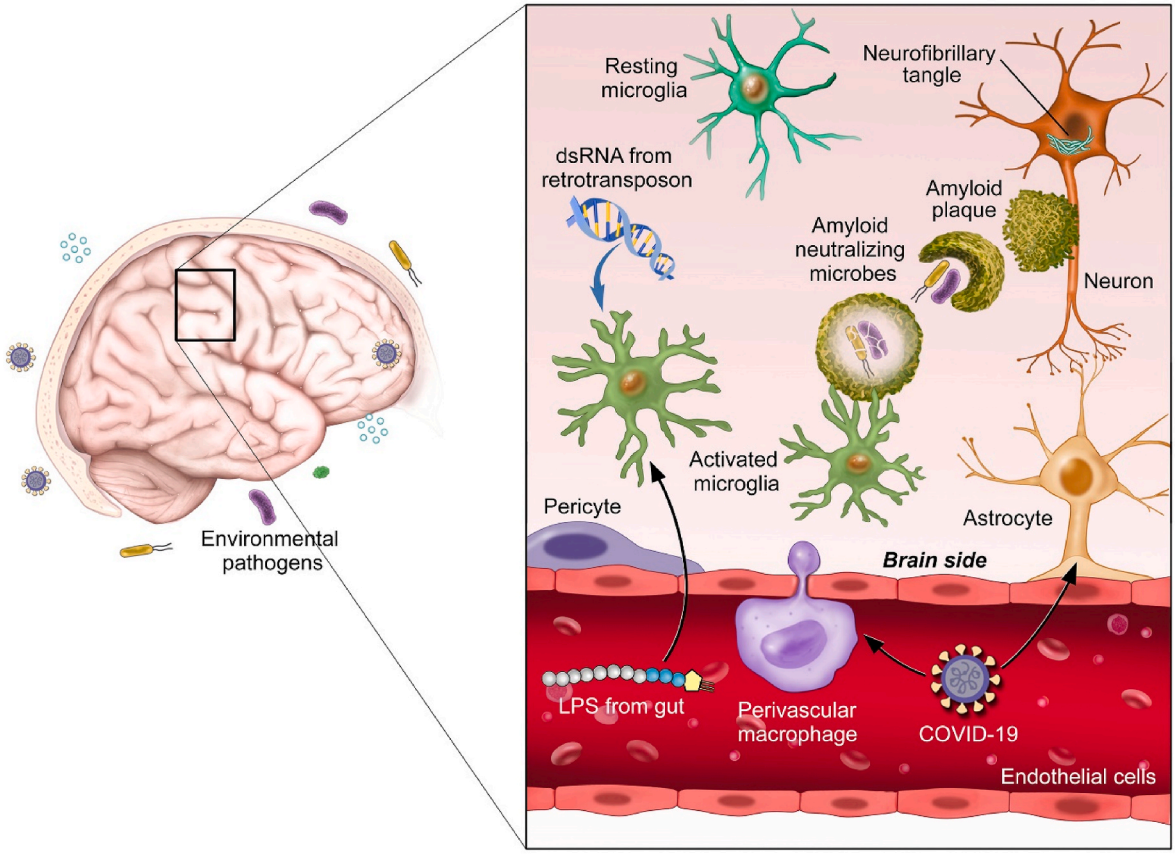

Fig. 1. Legend. Every human brain is potentially exposed to an array of microbial organisms (e.g. bacteria, fungi, viruses), which includes infectious agents from the environment or normal flora within the human microbiome. This figure illustrates a number of plausible mechanisms, at the cellular level, by which microbes could influence brain health and/or drive specific Alzheimer's disease pathology. In the center are amyloid plaques which are encasing and neutralizing pathogens that have gained entry to the brain parenchyma (as discussed in Section 1.0). Amyloid plaques are associated with a neuron that exhibits perinuclear tauopathy and with an activated microglial cell, demonstrating that the amyloid cascade of AD pathology has been initiated. The microglia and astrocytes are further activated by other microbes or microbe-derived particles (Section 5.0). The double-stranded RNA (dsRNA) from a retrotransposon (reactivated retrovirus), which was presumably released from the destabilized nucleus of a tau-damaged neuron, is activating a microglial cell (Section 6.0). A lipopolysaccharide (LPS) toxin released by gut microflora is on the blood side of the blood brain barrier, but it is activating brain-side microglia via pericytes or activated macrophages that cross the barrier (Section 7.0). Similarly, pathogenic microbes (Section 5.0) such as COVID-19 viruses (Sections 2.0-2.2), could stimulate brain immune cells and cause neuroinflammation, whether or not they cross the blood-brain barrier.

brains of tau transgenic mice (Ramirez et al., 2022).

Recent studies suggest that pharmaceuticals could mitigate the toxic activation of retrotransposons in tauopathy. 3 TC, a nucleotide analog reverse transcriptase inhibitor that is FDA approved for HIV and hepatitis B, significantly reduces neurodegeneration in tau transgenic flies (W. Sun et al., 2018), tau transgenic mice (Wahl et al., 2023), brain spheroids reprogrammed from patients with late onset AD (Z. Sun et al., 2023), and in cerebral organoids generated from patients carrying the frontotemporal dementia-associated *IVS10 + 16 MAPT* (tau) mutation (Frost lab, unpublished data). A 6-month, open-label Phase 2a pilot study (NCT04552795) is testing if 3 TC can be repurposed to treat patients with early AD.

8. Bill banks: gut microbe-brain communications

At first, it seems unlikely that gut microbes might infect the central nervous system. They must make it across the epithelial barrier and avoid destruction by various enzymes and cells in the bloodstream before reaching the biggest obstacle — the blood-brain barrier (BBB). Unlike almost all other tissues, the capillary bed of the brain is not leaky. Instead, it lacks the vesicular mechanisms and pores that account for leakage across the cells (transcellular leakage) that form other capillary beds, whereas tight junction formations prevent leakage between cells (paracellular leakage). The result is the formation of the vascular BBB. However, the BBB has many mechanisms other than leakage by which it can transfer both substances and information between the CNS and blood stream. Thus, the BBB is involved in supplying the CNS with its nutritional needs (glucose, amino acids, free fatty acids, vitamins), with homeostatic processes (regulation of electrolyte levels, removal of toxins from the brain), with brain-body communication (transport of informational molecules between brain and blood), and with immunosurveillance. Thus, the BBB is really a brain-blood interface and any of its functions are potentially affected by the microbiome.

One model that has been extensively investigated that has direct relevance to CNS/microbiome interactions are the effects of lipopolysaccharide (LPS) on BBB functions. LPS is derived from gram negative bacteria and is a powerful activator of the innate immune system. LPS's actions either directly on BBB functions or indirectly through the induction of the release of cytokines and other immune-related substances affect the CNS. For example, LPS derived from the microbiome can bind to toll-like receptors on brain endothelial cells, activating loss of function mutations responsible for cerebral cavernous malformations, resulting in pericyte loss and BBB disruption (Schulz et al., 2015; Tang et al., 2017)).

Much of sickness behavior is mediated through the actions of LPS or LPS-induced cytokines on the BBB. These include the cognitive effects, mediated through the transport of interleukin-1 across the BBB, and malaise, thought to be mediated by prostaglandin release from the brain

endothelial cells that comprise the BBB (Erickson and Banks 2018). The inflammation that it induces can disrupt the BBB and acts through several mechanisms to drive up Aβ levels in the brain (Erickson et al., 2023). LPS has many effects mediated through the BBB that results in increased CNS levels of amyloid beta protein, including decreasing activity of its efflux transporters (LRP-1 and P-glycoprotein), reducing clearance by way of CSF reabsorption, and increase blood-to-brain transport by way of receptors for advanced glycation endproduct (RAGE). LPS also increases blood-to-brain insulin transport through a prostaglandin-independent, nitric oxide-dependent mechanism.

Finally, LPS-induced inflammation has long been known to disrupt the BBB through a prostaglandin-dependent mechanism. Recently, perhaps the first ultrastructural study ever done on the effects of inflammation on the BBB showed that tight junctions are relatively preserved. Instead, BBB disruption was mainly mediated through the reintroduction of vesicular pathways across the BBB (Erickson et al., 2023).

These experiments demonstrate how microbes in the gut can act indirectly through various means to affect BBB functions, without the microbes themselves crossing the GI or blood-brain barriers. These alterations in BBB function provide mechanisms by which the microbiome can influence a host of CNS functions, including those related to cognition, appetite, and well-being.

9. Conclusions

This symposium considered recent evidence pointing to several mechanisms by which microbial organisms could play a causative role in AD. The keynote talk outlined the "antimicrobial protection hypothesis," which posits that, at least in some instances of AD, the classic amyloid-initiated cascade of AD pathology (i.e., amyloid plaque formation, tau tangles, synaptic loss, immune activation, neurotoxicity) may be initiated when Aβ accumulation is seeded by microbes as part of a host defense mechanism against infection. Other speakers presented emerging evidence that COVID-19 infection confers increased risk of dementia and discussed how COVID-19 may promote AD pathology. Although no definitive evidence exists to prove or disprove the direct involvement of any specific microbe in human AD, speakers agreed that there are multiple plausible ways that microbes could be implicated. Fig. 1 illustrates various potential mechanisms by which microbes – ranging from environmental pathogens to gastrointestinal flora to reactivated retrotransposon DNA from human genome - could influence the development or progression of AD pathology in the brain. Participants and field experts articulated key questions, which should motivate future research on the potential role of microbes in AD, with particular emphasis on opportunities to test interventions.

CRediT authorship contribution statement

Heather E. Whitson: Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization. **William A. Banks:** Writing – review & editing, Data curation, Conceptualization. **Monica M. Diaz:** Writing – review & editing, Data curation, Conceptualization. **Bess Frost:** Writing – review & editing, Data curation, Conceptualization. **Manolis Kellis:** Writing – review & editing, Data curation, Conceptualization. **Richard Lathe:** Writing – review & editing, Data curation, Conceptualization. **Kenneth E. Schmader:** Writing – review & editing, Data curation, Conceptualization. **Serena S. Spudich:** Data curation, Conceptualization. **Rudolph Tanzi:** Writing – review & editing, Data curation, Conceptualization. **Gwenn Garden:** Supervision, Project administration, Data curation, Conceptualization.

Declaration of competing interest

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Data availability

No data was used for the research described in the article.

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