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SUPPLEMENT ARTICLE

Sensory Dysfunction, Microbial Infections, and Host Responses in Alzheimer's Disease

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Sensory functions of organs of the head and neck allow humans to interact with the environment and establish social bonds. With aging, smell, taste, vision, and hearing decline. Evidence suggests that accelerated impairment in sensory abilities can reflect a shift from healthy to pathological aging, including the development of Alzheimer's disease (AD) and other neurological disorders. While the drivers of early sensory alteration in AD are not elucidated, insults such as trauma and infections can affect sensory function. Herein, we review the involvement of the major head and neck sensory systems in AD, with emphasis on microbes exploiting sensory pathways to enter the brain (the "gateway" hypothesis) and the potential feedback loop by which sensory function may be impacted by central nervous system infection. We emphasize detection of sensory changes as first-line surveillance in senior adults to identify and remove potential insults, like microbial infections, that could precipitate brain pathology.

Keywords. sensory dysfunction; host-pathogen interaction; Alzheimer's disease; microbes; parasites.

Alzheimer's disease (AD), the most prevalent form of dementia, is a progressive neurodegenerative disorder that affects millions of individuals worldwide [1]. Late-onset or sporadic AD is primarily linked to aging and partially penetrant genetic factors, representing the majority of AD cases. Among the most common AD-related symptoms there are memory loss, altered behavior, and personality changes, but diagnosis of cognitive and executive symptoms often occurs in later stages when irreversible processes commence [2]. Numerous works have shown the presence of amyloid β (Aβ) and tau pathology in the peripheral and central sensory-motor domains (smell, vision, hearing, balance) of AD patients. During their exploratory workshop, the National Institute of Aging emphasized the necessity for interventions aimed at addressing sensory-motor deficits to improve patient function in the context of aging and AD [3]. Despite studies indicating that sensory dysfunction precedes cognitive decline, the mechanistic relationship between sensory and cognitive deficits is primarily observational and correlative. While research on the clinical relevance of vision and hearing in AD is still emerging, chemosensory impairment, particularly loss of smell, is well-established in the progression of AD [4].

We posit here that one potential contributor to AD pathobiology is microbial infection. Neurotropic pathogens, including bacteria, amoebae, fungi, and viruses, can invade the central nervous system (CNS) and may exploit these sensory nerves as a route of infection. For instance, *Treponema pallidum*, the agent of syphilis, as well as *Cryptococcus neoformans*, measles virus, and human immunodeficiency virus (HIV) have been associated with dementing illnesses, including "reversible

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dementias" that remit with tailored antimicrobial therapy [5]. Evidence for direct brain infection in AD has been demonstrated for herpes simplex virus 1 (HSV-1) [6, 7], *Borrelia burgdorferi* [8], and *Chlamydia pneumoniae* [9]. Systemic analysis indicates that parasitic infections such as *Toxoplasma gondii* may impact neurodevelopment, immune response, and endocrine networks, providing insights into potential connections with epilepsy, movement disorders, and Alzheimer's dementia [10]. *Helicobacter pylori*, the agent of gastric ulcers, and periodontal pathogens in the oral cavity like *Porphyromonas gingivalis*, an agent of periodontitis, have been studied in late-onset AD [11, 12]. Both Alzheimer's and Parkinson's diseases (PD) have been associated with changes in microbial composition. Such dysbiosis has been implicated in the nasal, oral, and gut microbiome. For example in PD, the deep nasal sinus cavity microbiome revealed an increased relative abundance of proinflammatory bacteria like *Moraxella catarrhalis* with a positive correlation for an increase in clinical features [13]. The study from Bathini et al revealed stage-specific changes in the salivary microbial composition, with a decrease in periodontal pathogens like *Filifactor villosus* with the progression of dementia and an increase in oral opportunistic pathogen like *Leptotrichia wadei*, in patients with mild cognitive impairment [14].

Considering causes that may drive the accumulation of amyloid and tau in AD, infectious insults are significant and logical choices. Organisms likely to be involved in AD are those that can evade host defenses, gain entry to specific selectively vulnerable brain regions (such as through chemosensory systems), and establish chronic, persistent, latent, or relapsing infection. Infection may be the central hub that connects AD risk factors to the pathogenesis of the disease. Microbial linkage to AD risk factors has been established with *APOE-ε4* genotype, chronic neuroinflammation, autoimmune mechanisms, oxidative and mitochondrial damage, cardiovascular disease, diabetes with insulin resistance, trauma to the blood-brain barrier (BBB), and selectively vulnerable brain insult [15]. Chronic infections and persistent reactivation may be an overarching unifying hypothesis for sporadic late-onset AD. Host immune defenses against common microbial infections vary, thus impacting infectivity. This may explain why certain ubiquitous microbes cause disease in certain individuals but merely colonize others [16].

While the central nervous system is safeguarded from many circulating microorganisms by barriers, like the BBB, specific peripheral sensory systems, such as the nose and olfactory bulb are directly vulnerable to external agents, including microbes. The sensory organ for hearing, the ear, is equipped with a barrier known as the blood-labyrinthine barrier, but it also has resident immune cells and can be susceptible to infections that may affect the CNS [17]. The eye, a unique sensory organ with its own immune system, has direct contact with the external environment with the cornea and the conjunctiva acting as barriers. Regardless, certain infections can impair the eye and have the potential to impact the CNS under specific circumstances. Ongoing research aims to understand the extent to which these sensory organs may serve as portals for microbes to enter the brain and any relevance to neurodegenerative diseases like AD. Despite the brain being protected by the BBB, microbes may enter through the bloodstream, neural pathways, intranasal route, sinuses, the oral cavity, and gut-brain axis. This review highlights the potential role of selected sensory organs as gateways for entry of infections relevant to AD development (Figure 1), the so-called gateway hypothesis.

THE SENSORY PATHWAYS IN ALZHEIMER'S DISEASE

Olfactory Dysfunction in AD

The olfactory bulb, critical for odor processing, is characterized by pathological protein accumulation and volume changes contributing to olfactory dysfunction in neurodegenerative dementia [18, 19]. Early onset of olfactory dysfunction is a prominent feature in various dementia types, characterized by remarkably high prevalence rates, such as nearly 100% in AD, 90% in PD dementia, 96% in frontotemporal lobar dementia, and 15% in vascular dementia [20]. Recognized as an early marker for various neurological conditions, olfactory impairment collectively underscores the initial involvement of olfactory structures in PD, AD, Lewy body dementia, Huntington's disease, and, to some extent, Creutzfeldt-Jakob disease [21]. In contrast, frontotemporal dementia manifests later in olfactory network engagement [22]. Postmortem studies reveal early pathological changes in AD, impacting olfactory processing regions like the entorhinal and transentorhinal areas, anterior olfactory nucleus, and olfactory bulb [23]. In normal aging after 70 years old, olfactory deficits are accelerated with a reduction of the olfactory bulb volume. In AD, olfactory bulb atrophy occurs independently of age, inversely correlating with disease duration, with accumulation of amyloid and tau protein in olfactory regions. In synucleinopathies, abnormal α-synuclein or Lewy bodies accumulate in the olfactory bulb and projection areas, progressing along the olfactory pathway to other brain regions [24]. Importantly, significant correlations exist between odor identification test scores obtained before death in nondemented older persons and postmortem measures of plaques and tangles in multiple brain regions implicated in AD, including the entorhinal cortex. This, along with similar associations between test scores and volume losses in the amygdala, entorhinal cortex, and perirhinal cortices, strongly suggests olfactory dysfunction as a sign of incipient AD.

The nose serves both respiratory and olfactory functions and the nasal cavity contains specialized regions for each activity. The olfactory epithelium is crucial for our sense of smell and

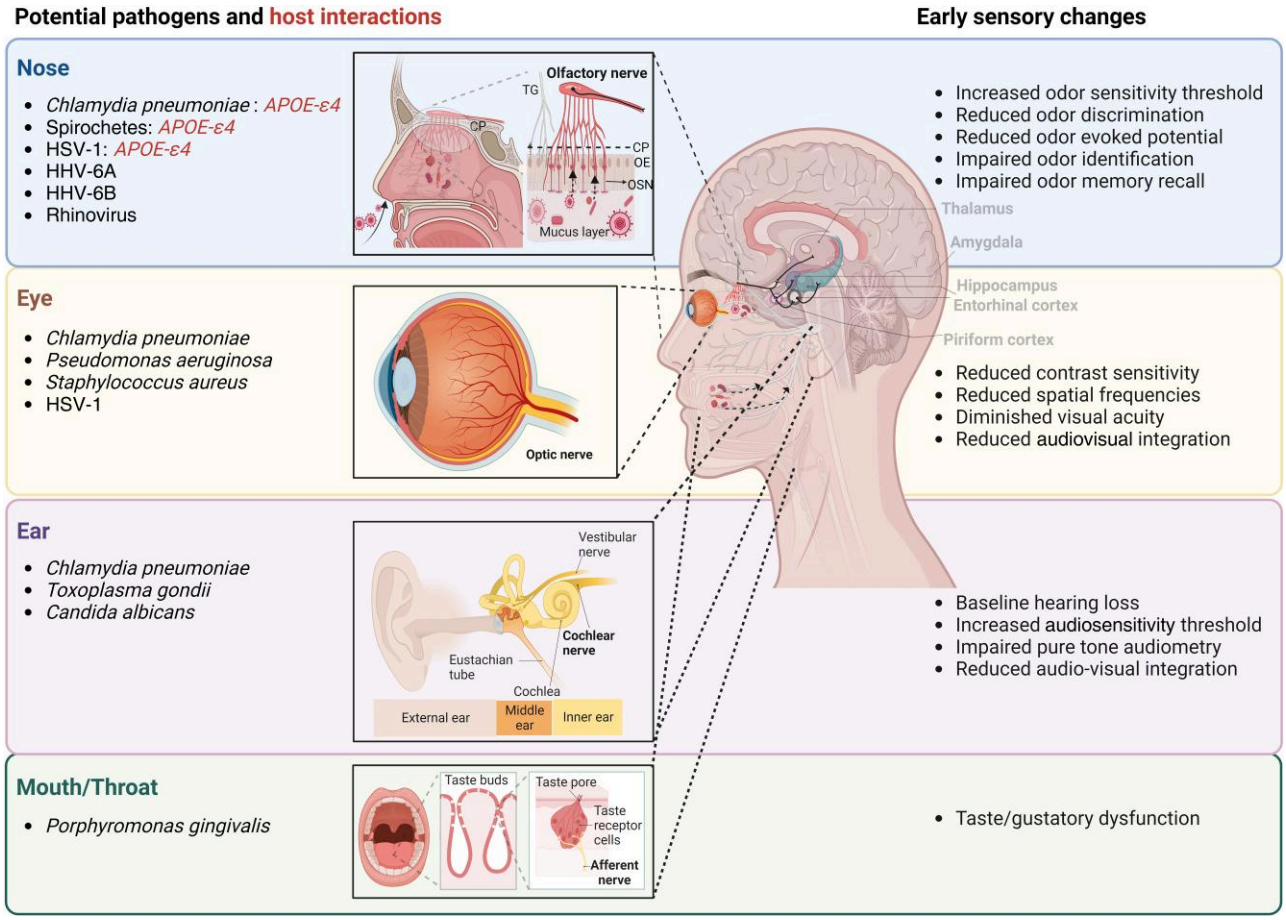

Figure 1. Sensory changes early on in dementia. Known pathogenic risk factors, genetics of the host (red), route of pathogen escape (black dotted arrows) into the central nervous system, and types of deficits manifested in the early phases of Alzheimer's disease. Abbreviations: CP, cribriform plate; HHV, human herpesvirus; HSV-1, herpes simplex virus 1; OE, olfactory epithelium; OSN, olfactory sensory neuron; TG, trigeminal nerve. Created on BioRender.

is vulnerable to various factors that can affect its integrity. The olfactory epithelium receives sensory input from the olfactory sensory neurons, the trigeminal nerve, and nervus terminalis, creating a potential route for microbial species to reach the brain and drive neuroinflammatory responses associated with dementia [25]. Additionally, the olfactory epithelium's sustentacular cells protect the olfactory sensory neurons, and their renewal can be affected by factors like head trauma or microbial infection [26]. Olfactory receptor cells play an important role in facilitating the transneuronal entry of viral species (retrograde transport of viruses to the brain), metals, and other xenobiotics into the olfactory bulb and interconnected brain regions [27, 28]. Imbalances in excitatory-inhibitory networks can further impact olfactory function in AD [29, 30]. The olfactory tract, which connects the olfactory bulb to higher olfactory areas, can undergo structural changes with age or neurodegenerative conditions [19, 31]. In humans, the regenerative capacity of the olfactory neuroepithelium decreases with age; this scenario is common in patients with chronic rhinosinusitis, who often exhibit structural and functional alterations in their neuroepithelium [32]. Chronic rhinosinusitis has been identified as a potential risk factor for the development of AD [33]. In summary, the complexity and integrity of the olfactory system can be influenced by various causes, especially microbial infections, that contribute to changes in smell perception and potentially play a role in neurodegenerative diseases.

Microbes in the Olfactory Route and Brain

The nasal cavity harbors a diverse microbiome, and some of these microorganisms can reach the CNS via the olfactory pathway or act directly (Figure 1). The colonization of the olfactory neuroepithelium by microorganisms appears to be instrumental in the development and the function of the olfactory circuit as demonstrated by the altered kinetics of odorant responses and odorant signal transduction in germ-free mice [34]. The olfactory vector hypothesis [27] emphasizes the fact that the olfactory receptor cells and associated perineural spaces provide a direct pathway for the brain invasion of such microbiota, xenobiotics,

nanoparticles, and toxins. Entrance can be rapid because no intervening synapse is present and the BBB is bypassed. Certain microbial species, including Herpesviridae [6, 7], spirochetes [35], and *C. pneumoniae* [9], have been detected in the olfactory nerve and related limbic structures, probably indicating gateway of the microbes into the brain through these sensory structures. Interestingly, pathogens trigger Aβ deposition, which exerts a protective role in entrapping microbial cells, proposing a potential link between viral infection and AD pathology [36]. This suggests that pathogens infecting the respiratory tract can access the brain via the nasal cavity, causing neuroinflammation and stimulating the generation and dispersion of amyloid species for antimicrobial activity [37]. Below we present pathogens that may enter the CNS through the olfactory route.

Viruses. Herpesviridae infections are highly prevalent: HSV-1, the virus most frequently linked to AD, is detected in over 80% of the population in some countries but its prevalence is lower in countries of higher socioeconomic levels [38, 39]. After infection, HSV-1 remains chronically latent in sensory ganglia for life, periodically reactivating during conditions of stress or immune deficit, and causing symptomatic infection—cold sores (herpes labialis) in only 25%–40% of those infected. In 1991, HSV-1 was discovered in the brain (frontal and temporal cortices) at high prevalence in elderly humans—both AD patients and aged controls—using polymerase chain reaction (PCR) [40, 41]. This was the first definitive detection of a pathogen in nondiseased "sterile" human tissue. Subsequently, it was found that in some 60% of cases, HSV-1 in the brain of *APOE-ε4* carriers conferred a risk of AD, and consistently that *APOE-ε4* carriage was also a risk for cold sores [6, 7].

The presence of HSV-1 in the brain of younger people is rare, suggesting that the virus reaches the brain with aging and the decline of the immune system. This may be from the ganglia or from entry as a new infection via the olfactory route, remaining latent until reactivated. Reactivation can be caused via direct viral damage and inflammation, and repeated reactivations could lead to the development of neuropathological processes like AD. This was supported by later findings that AD-like phenotypes developed after HSV-1 infection of a 3-dimensional brain cell model [42], and in brains of HSV-1–infected mice after repeated reactivation of the virus by hyperthermia [43].

HSV-1 infection of cultured cells caused accumulation of Aβ and phosphorylated tau (pTau). In AD brains, in situ PCR showed HSV-1 to colocalize within amyloid plaques [44] and induce activation of microglia cells through Toll-like receptors (TLRs) [45]. Later studies indicated that Aβ acts by engaging the virus [37], supporting previous suggestions that it might be protective against neurotoxins [46, 47].

The possible clinical relevance of these findings was indicated by cellular studies showing that antivirals reduce Aβ and pTau accumulation [48]. Also, antiherpetic treatment of patients with severe HSV infection reduced their risk of dementia [49]. In fact, 500 studies using a variety of approaches, including genome-wide association studies and epidemiological approaches, support a major role for HSV-1 in AD. An association between HSV-1 systemic infection and cognitive decline was shown using serologic data in epidemiologic studies [50].

Many infections, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), cause the reactivation of latent herpesviruses [51]. They also increase the risk of AD, while vaccination against shingles and other infections lessens the risk [52]. In the 3-dimensional brain model, varicella-zoster virus infection reactivates quiescent HSV-1 [53], supporting the suggestion that repeated HSV-1 reactivation in the brain, caused by infections and other insults such as inflammation, stress, axonal damage, and immunosuppression, may lead to AD.

Human herpesvirus 6 (HHV-6) infects almost 100% of humans in infancy and has been detected in the same brain regions as HSV-1 [40, 54]. Infection of olfactory-ensheathing cells surrounding the olfactory nerve layer with HHV-6A or HHV-6B revealed productive infection and an inflammatory response only after HHV-6A infection [55]. However, the causative role of HHV-6A or HHV-6B in AD pathogenesis is yet to be established.

As a result of the recent pandemic, SARS-CoV-2 has been identified as one of the pathogens with distinctive tropism for the olfactory organ, causing hyposmia or dysosmia in 20%–70% of acute cases and "long-haulers" [56]. It was demonstrated that infection of sustentacular cells by SARS-CoV-2 can dampen the conduction of olfactory sensory neurons reducing olfactory acuity and perception, and likely gaining access to the brain through the olfactory bulb [57]. While brains from subjects that developed SARS-CoV-2 pneumonia showed the presence of the SARS-CoV-2 in the olfactory region [58], it is at present unclear whether this also happens in mild and long-COVID cases. However, recent research has indicated that cognitive symptoms persist 2 years following severe SARS-CoV-2 infection [59]. This could indicate that limbic and cortical regions have been invaded via the olfactory route, contributing to the memory sequelae.

Bacteria. Significant findings from various studies reveal that *C. pneumoniae* is associated with AD [9, 60]. *C. pneumoniae* was detected in 90% of postmortem AD brains (17/19) in the original 1998 report, with only 5% of non-AD brains from identical brain regions testing positive (1/19) using PCR for DNA, electron and immunoelectron microscopy, reverse transcription PCR for RNA, immunohistochemistry, and culturing. In a comparable study, *C. pneumoniae* was found by PCR in 20 of 25 AD brains and in only 3 of 27 controls [60]. *C. pneumoniae* is an obligate intracellular gram-negative bacterium. While it has been most often associated with acute respiratory infection and as an etiologic agent of community-acquired

atypical pneumonia, it has also been associated with various chronic, autoimmune diseases, although in most individuals infection with *C. pneumoniae* is a mild and self-limiting infection. This bacterium can attach to nasal- and neuroepithelium and potentially access the brain via the olfactory bulb [9]. Studies in Balb/c mice confirm the intranasal spread of *C. pneumoniae* to the brain by showing the presence of its antigens and increase in amyloid plaque load [61]. Also, injury to the nasal epithelium leads to an enhanced spread of *C. pneumoniae* bacterial load into the peripheral nerves and olfactory bulb with Aβ deposition [62]. Furthermore, the load of *C. pneumoniae* in the AD brain varies with the *APOE* genotype, with *APOE-ϵ4* carriers having higher *C. pneumoniae* copy numbers than either *APOE-ϵ2* or *APOE-ϵ3* [16]. Chlamydial lipopolysaccharides and membrane proteins can induce the secretion of proinflammatory cytokines and reactive oxygen species from astrocytes, contributing to neurotoxicity [63].

Spirochetes like *B. burgdorferi* and *T. pallidum* are also implicated in AD. They can trigger latent or persistent infections and have neurotrophic properties that enable them to reach the brain through various routes, including the olfactory tract [64, 65]. A meta-analysis suggests a significantly higher odds ratio for identifying spirochetes in AD brains or cerebrospinal fluid compared to controls [64, 65]. *B. burgdorferi* has been cultivated from postmortem AD brains [66] and DNA traces have been detected in brains, blood serum, and cerebrospinal fluid of AD patients [65]. Borrelia antigens are associated with neuritic plaques, especially in the olfactory tract, and appear to trigger amyloidogenesis and neuroinflammation [35]. In Lyme disease, *B. burgdorferi* frequently coinfects with other pathogens, for example, *C. pneumoniae* and herpes viruses [67, 68]. Spirochetes, via their surface lipoproteins, activate TLR signaling. In AD, there is an increased expression of pattern recognition receptors in the brain. Notably, polymorphisms in the *TLR2* and *TLR4* genes play a role in influencing the pathology of the disease. This underscores the impact of TLR polymorphisms on the susceptibility to the progression of sporadic AD [64, 65].

Fungi. Using antibodies developed against fungi, postmortem immunohistochemical studies of human AD brains have indicated that a variety of filamentous or irregular structures found intra- and extracellularly are fungal [69–71]. Additional analyses of brain and blood using metagenomic approaches and more sophisticated histology supported a possible link between disseminated fungal infection, AD, and cerebral mycosis, while also revealing that both bacteria and fungi were coinfecting AD brains [72–75]. *Candida albicans* is uniquely capable of infiltrating and disrupting key CNS-based sensory pathways. The nasal passages and paranasal sinuses are frequently infected with *C. albicans* [76], where proximal olfactory neurons could provide a route for the migration of fungal cells across the BBB directly into the olfactory bulbs and nearby entorhinal cortex and hippocampus.

Parallel analyses of human and mouse brains and experimental models of cerebral mycosis further support these neuropathological investigations. More recently, *C. albicans* was shown to cross the BBB of mice readily, induce senile-plaque-like Aβ aggregates that are generated from the cleavage of the amyloid precursor protein by fungal proteinases and induce transient memory loss during the time of infection [77–79]. The nearly ubiquitous presence of *C. albicans* within human populations points to this singularly common and pathogenic fungus as a potentially common microbial contributor to AD-related neurodegeneration and memory loss [80]. Further investigation is warranted to clarify mechanistic interactions between associated fungi, the sensory organs, and the development of AD pathology.

Protozoa. *T. gondii* is present in the brain of over 2 billion people worldwide across their lifetimes, as an incurable, chronic potentially active infection. There is considerable evidence that *T. gondii* infection can contribute to the initiation and progression of neurodegeneration [81]. Whether and when this occurs is influenced by human host and parasite genetics, environmental factors, and immune response. These factors determine outcomes at various times from fetal life to older ages. Mechanistically, *Toxoplasma* can modulate signature transcriptional pathways of neurodegeneration, including AD, tauopathies, amyloidosis, PD, epilepsy, and certain tumors [10]. Nuclear factor-κB (NF-κB) is central in this process [10], and this infection appears to affect the expression of genes critical for the development of AD [82]. Modulation of transcription occurred with the chronic dormant form in cultured human primary brain neuronal stem cells [83, 84], and also with the active form of the parasite and in mice [85]. In addition, STRING (search tool for recurring instances of neighbouring genes) analysis [86, 87] shows evidence for protein-protein interaction networks pertinent to smell in cultures infected with types I, II, or III parasites, identified as odorant receptor cluster 5 [10].

Interestingly, *T. gondii* modulates smell in mice and nonhuman primates [88–90]. This is beneficial for perpetuation of the parasite life cycle because attracting prey animals to predatory species such as feline definitive hosts of *Toxoplasma* leads to production of oocysts that can widely contaminate the environment.

These observations suggest another possible mechanism for odor attraction and indicate a central odorant node. There is some evidence reporting that this mechanism might occur in humans [91]. Studies of associations of *Toxoplasma* infection with human smell and AD have not been reported. The active infection is treatable and if eradication at dormant stages is successful then treatment trials investigating this potentially

curable chronic infectious cause for damage to the brain and eye could be performed.

Host-Pathogen Interaction in Olfactory Deficit

Host susceptibility to infection is influenced by genetics, age, immune status, diet, infectious agent's dose, and virulence, with pathogens employing intricate strategies such as immune evasion to reach the immune-privileged brain (Figure 2). Also, sensory neurons innervating the local mucosal barriers can sense the mucosal environment, including the nutrients and microbial products, and stimulate the recruitment of local mucosal immune cells and release of cytokines, further activating the sensory neurons. This bidirectional communication could modulate mucosal inflammation and immunity [92]. *APOE-ϵ4*, *CLU* (clusterin), *TREM2* (triggering receptor expressed on myeloid cells 2), and *CD33* (cluster of differentiation 33) play important roles in innate immunity and are genetic risks for sporadic AD. TREM2 binds to lipoproteins and apolipoproteins including clusterin and ApoE4, enabling uptake of Aβ by microglia. Genetic variants or mutations in these genes can disrupt the binding of lipoproteins and Aβ lipoproteins complex formation and therefore cause defective clearance by microglia. CD33 expressed on microglial cells modulates innate immune response by binding to the sialic acid residues on the microbes, thereby regulating microglial activation [93, 94]. Importantly, the viral life cycle is modulated differently by various apoE isoforms with apoEe4 having an increased risk for HSV-1 and HIV infection and protection for hepatitis C virus. The lethality of the APOE 133–150 peptide extends to various gram-positive bacteria, including *Staphylococcus aureus* and *Bacillus subtilis*, as well as gram-negative bacteria such as *Pseudomonas aeruginosa, Escherichia coli*, and *Klebsiella pneumoniae* [95]. Individuals with *APOE-ϵ4* allele often exhibit early olfactory identification errors and olfactory memory deficits, along with a higher risk of developing AD [96].

Together, these studies indicate that over a lifetime, during recurrent bacterial and viral infections, microbial pathogens exploit the nasal route to colonize the brain during asymptomatic phases that may contribute to neurocognitive decline later in life. This depends on the individual virulence of the pathogen as well as the host genetic vulnerability to progressive neuropathological changes of dementia. In summary, the progressive pathogenesis of AD is multifactorial, involving aging, a more permeable or disrupted BBB, a dystrophic olfactory neuroepithelium, microbial infection, and chronic inflammation [15].

Visual Dysfunction in AD

Vision is impacted in various dementias including AD, Lewy body dementia, and posterior cortical atrophy, a visual variant of AD. While in Lewy body dementia higher visual functions are affected, both lower and higher visual deficits are associated with posterior cortical atrophy [97]. In AD, early manifestation of the pathology can be observed in the pupil, lens (Aβ in the lens), retina, and optic nerve leading to visual deficiencies, including abnormalities in visual acuity, contrast sensitivity, color vision, and visual field loss [98, 99].

The eye provides a natural window to the brain for the acquisition of visual information with its retinal layer considered a

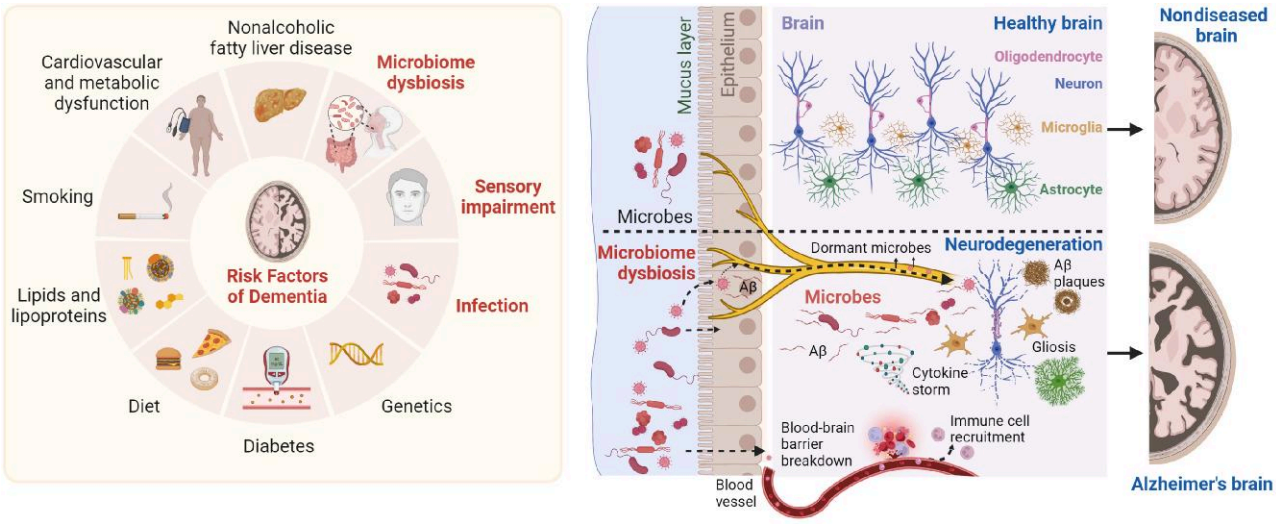

Figure 2. Risk factors for dementia with potential mechanism of microbiome entry into the brain via sensory neurons directly to the brain or through the damaged blood-brain barrier. Although many risk factors are associated, host genetics and dietary habits collectively influence microbial dysbiosis, leading to an imbalance in microbial composition and inflammatory signals promoting inflammation and a compromised barrier function. Viruses in particular are neurotrophic, can remain dormant for years, and undergo activation upon host stress. Antimicrobial peptide amyloid β (Aβ) is produced in response to microbial entry into the brain, and a phase of cytokine and immune cell recruitment leads to local inflammatory conditions and neuroinflammation followed by Alzheimer's disease pathology. Created on BioRender.

part of the central nervous system (Figure 1). Many years prior to the development of cognitive impairment and AD it is reported that there are changes in the peripheral retinal vasculature identifiable by optical coherence tomography angiography that predicts the development of AD [100]. People with dementia can experience altered vision [101] and understanding these visual deficits in early stages is of potential interest in the diagnosis of AD [102]. Imaging studies show early changes in the posterior cortical regions, including the occipital cortex, and pathological examination confirms initial changes in the medial temporal lobe with a gradual increase of pathological hallmarks in neocortical regions. Interestingly, previous reports show extracerebral accumulation of Aβ in the eye with increased accumulation of Aβ 1–40 and Aβ 1–42 peptides in the lens (supranuclear lens fiber cells) and primary aqueous humor [103] with the progression of AD. Accumulation of amyloid plaques in the retinal layer was earlier reported in human AD specimens [99]. Aβ can coaggregate with αβ-crystallin, a cytosolic lens protein that has a structural function assisting in the proper maintenance of lenticular refractive index. Irregularities and discontinuities seen in the refractive index and local light scattering in the ocular system of AD patients may be due to Aβ aggregating in the supranuclear lens fiber cells [104]. Indeed, in the early stages of the disease, accumulation of Aβ is not limited to fiber cells alone but is also observed in retinal ganglion cells and retinal nerve fiber layers [105], along with pTau protein [106] in these retinal structures. Overall, evidence of Aβ deposits in the retina supports the development of noninvasive eye biomarkers for the clinical diagnosis of AD [105].

Sensory information from the retinal layer of the eye is relayed to the higher brain structures through the cranial nerve II (optic nerve) (Figure 1). In the early stages of AD, axonal degeneration of this nerve may contribute to vision impairments. As evident in moderate and severe pathological AD stages, the optic nerve undergoes neurodegeneration (optic neuropathy) and displays a decrease in its diameter [107, 108]. In other neurodegenerative diseases, like PD, such visual disturbances also correlate with the pathology progression [109]. Optic disc analysis using blue-light high-resolution photography reveals optic nerve damage, increased pallor area to the disc area, cup-to-disc ratio, cup volume, and a reduced disc rim area. Interestingly, in a study conducted to examine the optic nerve head in AD patients, a higher AD assessment score correlates with increased pallor to disc area [110]. Assessing the optic nerve in early stages of AD could therefore be advised to study the progression of the disease.

Microbiome and Host-Pathogen Interactions in the Visual System

Similar to the nasal system, the eye can be considered a conduit to the brain. *T. gondii* infection is the most common cause of infection in the back of the eye (choroid, retina) worldwide [10]. In addition, *C. albicans*, presumably blood-borne, is one of the most common causes of endophthalmitis [111], which can include retinitis [112]. In ophthalmic disorders like diabetic retinopathy, age-related macular degeneration (AMD), and glaucoma, the eye displays AD-like pathological features, including Aβ deposition, neurodegeneration, and vascular damage, comparable to the CNS [113]. Recent evidence document the increased risk of dementia associated with ocular disorders, as highlighted by a longitudinal study involving 3877 *APOE-ϵ4*–positive patients with AMD, diabetic retinopathy, and recent glaucoma, which reported a 40% to 50% higher likelihood of developing AD compared to subjects without these pathologies; notably, cataract did not represent a risk factor for AD [114].

AMD has also been associated with *C. pneumoniae* in both past systemic and current chronic eye infections. Kalayoglu et al were the first to report, in a case-control study, a serological association between *C. pneumoniae* and AMD [115]. An association of AMD and *C. pneumoniae* serology was confirmed in a second case-control study [116] and a cohort series of 233 individuals followed for AMD progression over a mean period of 7 years. The risk of progression was greatly increased to almost 12-fold (odds ratio, 11.8; 95% confidence interval, 2.1–65.8) when, in addition to having an AMD risk allele, subjects also were in the upper tertile of *C. pneumoniae* antibody level [117]. In a mouse model, early-life peripheral *C. pneumoniae* infection reprogrammed retinal microglia and aggravated neovascular AMD in later life [118]. The human serological and mouse model evidence cited here cannot directly address the gateway hypothesis, as the associations, if causal, could be mediated by infection outside the brain proper or by organism entry into the central nervous system via the vascular bed. Thus it is notable that, in humans with AMD, *C. pneumoniae*-positive staining was detected in 68% of paraffin sections from 26 surgically removed choroidal neovascular membranes of patients with AMD [119], raising the possibility of entry via the optic nerve. No direct evidence linking the ocular microbiome and its role in AD has been reported to our knowledge.

An infection in or trauma to the eye could recruit innate immune cells promoting inflammation as in bacterial keratitis caused by *P. aeruginosa* [120] and *S. aureus* [121]. In animal keratitis models, ocular administration of HSV-1 caused accumulation of corneal intracellular glutathione levels thereby altering the redox state potential of the corneal environment [122]. The ocular surface has the presence of bacteria, viruses, and fungi, with composition of antimicrobial peptides such as lactoferrin and β-lysin in human tears suggesting microbiome-host interaction at the ocular surface [123]. Interestingly, recent studies showed the role of Aβ as an antimicrobial peptide [40] and the presence of these peptides in the lens, retina, and primary aqueous humor [103] may indicate active infections in the eye. Further studies are needed to explore the role of the ocular microbiome in targeting the visual sensory structures as a gateway for entry and their engagement, if any, in the pathogenesis of AD.

Auditory Dysfunction in AD

Several studies suggest a connection between age-related hearing loss and risk of dementia [124, 125], raising questions about shared risk factors or a potential cause-and-effect relationship. Early autopsy studies showed AD hallmarks in the auditory midbrain, forebrain, central nucleus of the inferior colliculus, ventral division of the medial geniculate body, and primary and secondary auditory cortical areas, but with minimal AD pathology in peripheral processing regions like cochlea and cochlear nucleus [126]. Animal studies demonstrated that induced hearing loss through noise exposure leads to excitotoxicity in the hippocampus, leading to tau hyperphosphorylation, synaptic loss, cognitive decline, and hippocampal dysfunction, mirroring AD pathology [127]. Overall, this evidence indicates that hearing loss alone may not cause progressive degenerative dementia, emphasizing the requirement for additional components including the interaction between aging or genetic predisposition to trigger AD-like pathology.

Unlike the olfactory and visual deficits in AD, hearing impairment is not generally considered a predictor of cognitive decline and subsequent dementia. However, some studies suggest an association between hearing loss and acceleration of cognitive dysfunction or even the possibility of predicting the disease [128]. Hearing loss affects communication and contributes to social isolation and loneliness, which may further alter the integrity of cognitive processes [129] and promote cognitive deterioration. During aging, the prevalence of peripheral hearing loss is greatly increased, and it is also estimated that about 9%–14% of people aged >65 years show central auditory processing disorders [130]. The Framingham and Baltimore longitudinal aging population studies [131, 132] showed age-related hearing impairment (ARHI) with deficits in tonal frequencies, sensitivities, and frequency thresholds. Cochlear aging, noise (industrial, vibrations), ototoxicity (aminoglycosides, salicylates), head trauma, and comorbidities (diabetes, stroke, smoking) are risk factors associated with such ARHI [130, 132]. Such studies indicate a close association between ARHI, cognitive deficit, and central auditory processing disorders. However, it is still unresolved if the cognitive decline linked to hearing loss manifests with abnormalities either in peripheral or central auditory processing structures.

Microbiome and Host-Pathogen Interactions in the Auditory System

To our knowledge, there is no evidence that microbial entry via cranial nerve VIII (vestibulocochlear) plays a role in neurodegenerative disease. *C. albicans* as well as other fungal species are increasingly frequently identified as microbial causes of otitis media and hearing loss, especially in tropical and subtropical regions [133]. Parasites like *T. gondii* can also infect the ear and cause sensorineural hearing loss [134]. Other reports hypothesize that *C. pneumoniae* might be also investigated in this regard. Middle ear infections caused by a variety of viral and bacterial pathogens, including *C. pneumoniae* in a small number of cases, are prevalent in childhood. A case-control study found that *C. pneumoniae* immunoglobulin A (IgA) seropositivity, a putative biomarker for chronic infection, was associated with sudden-onset sensorineural hearing loss [135], suggesting possible direct infection of the eighth nerve. However, we found no studies investigating direct organism involvement in, or transport within, the auditory nerve, indicating limited evidence of infection and the auditory system in AD.

Gustatory Dysfunction in AD

Taste or gustatory dysfunction and changes in appetite, or altered food preferences are not common in early AD. They are, however, frequently observed in patients with frontal variant frontotemporal dementia, semantic dementia, and definite AD. These behavioral alterations reflect the network changes in the ventral frontal lobe, temporal lobe, and amygdala depending on the specific type of dementia [136–138].

Differently from AD, taste perception is markedly affected in other pathologies during their initial stages. For instance, upon SARS-CoV2 infection gustatory impairment was frequently experienced by a large segment of the affected individuals [139]. In addition, this sensory dysfunction, together with smell loss, was often the early and only sign described in otherwise asymptomatic subjects [140]. Another condition where taste sensitivity could be damaged is oral dysbiosis [141–143]. Among the factors linked to oral microbiome disruption, poor oral hygiene is a recurrent one [144]. Interestingly, the periodontal pathogen *P. gingivalis* is associated with (1) oral dysbiosis [145]; (2) multiple chronic pathologies, including AD [146–148]; and (3) taste dysfunction [149]. Altogether, the evidence on this bacterium further supports the hypothesis that, among the risk factors contributing to the onset and progression of AD and other neurodegenerative disorders, the microbial component could play a relevant role.

The Microbial Journey to Sensory Nerves

Reports examined in this review have consistently indicated the presence of diverse microorganisms, encompassing bacteria (such as *Borrelia, Chlamydia,* and *P. gingivalis*), fungi (particularly *Candida*), and viruses (including HSV-1, HSV-2, HHV-6A, HHV-6B, Epstein-Barr virus, cytomegalovirus, varicella zoster virus, and coronaviruses) within the brains of both AD patients and healthy controls. At the same time, our comprehensive analysis of the literature shows that many of these microbial species share a pathogenic link with more than one sensory organ of the head and neck area. Even if at this point speculative, a topological migration from one sensory organ to the other may occur, allowing progressive entry to the brain. Elucidating the mechanisms through which these microorganisms access the brain necessitates a refined consideration of the routes of entry, transcending the traditional perspective

centered around the BBB. While the BBB regulates the passage of small molecules, its effectiveness as a deterrent against a multitude of microbes remains variable. Microbial access into the brain involves a spectrum of strategies, encompassing receptor-mediated transcytosis, migration within host cells (eg, macrophages; known as the Trojan horse hypothesis), and exploitation of circumventricular organs. Microbes exhibit a fascinating array of adaptations to cross these barriers, shedding light on the complex interplay between pathogens and the central nervous system [150, 151]. From the examined literature, microorganisms adapted to specific species exhibit an apparent evolution of efficient strategies to circumvent the BBB and facilitate their entry into the brain. This facilitated access to the brain may happen through sensory organs microbes colonizing the oral cavity and gut, microbial species and their byproducts (Figure 2) can exert a direct impact on the brain, bypassing the BBB through the associated peripheral sensory nerves like trigeminal, olfactory, facial, optic, and cochlear nerves, or through the enteric nervous system of the gut (gut-brain axis) [152]. Furthermore, microbiome dysbiosis can influence sensory functionality locally or have an impact on the brain via systemic inflammation.

In addition to age-related decline in sensory functions, acute microbial infections in peripheral sensory systems can contribute to sensory deficits, such as the loss of smell or hearing. For instance, microbial infections causing sinus inflammation can impede odor molecules from reaching the olfactory epithelium, while viral presence within cochlear nerve fibers may result in deafness [153, 154]. Importantly, in the context of AD, which is a pathological continuum of dementia with multiple factors, sensory impairments may precede decades before the onset of cognitive decline [2]. Whether sensory dysfunction is due to microbes trafficking to the brain, or because of the old microbes (past infection) that the immune system can no longer control, causing deficits in sensory processing, are some of the questions in the field of AD pathogenesis.

In future work, it will be crucial to understand which microbes stay in the peripheral sensory nerves versus those that reach the brain. Additionally, sensory issues could arise from a 2-way communication link between microbes located in the periphery and those present in the brain, which may also underlie sensory deficits.

As discussed above, sensory impairments may precede the onset of cognitive decline by decades; it is therefore widely believed that early sensory decline in AD could mostly arise due to progressive degeneration of key brain regions responsible for sensory processing. It remains to be unraveled whether these sensory deficits result from the microbes' entry to the brain and intersect with the host vulnerability based on the genetic background, such as *APOE-ϵ4, TREM2,* and *HLA-II* (human leukocyte antigen class II), which amplify the inflammatory responses in the periphery and CNS.

CONCLUSIONS

Sensory functions decline naturally with age. Hyposmia, and visual and hearing impairment are further aggravated in dementia, and in some cases precede the onset of cognitive deficit. In light of recent studies corroborating the causal link between infection and amyloidogenesis, the sensory peripheral organs such as the nose and the eye assume particular clinical relevance for a neuroinflammatory spreading that can underlie the slow and progressive rostral to caudal neurodegeneration in AD.

While the functional anatomy of the sensory circuits is well characterized, host-pathogen mechanisms are just beginning to emerge. From an epidemiologic perspective, population-attributable risk is defined as the proportion of a disease that can theoretically be ameliorated by the elimination of a specific risk factor. If microbial mechanisms of sensory dysfunctions are identified as causally related to neurodegenerative processes, accessible and inexpensive smell, visual, or hearing testing could represent the first line of routine diagnostics. In cases of apparent deficit, a second-line determination of the causative microbial agents would allow therapeutic interventions tailored to the personal host-pathogen profile of each subject. For instance, combining the physiology with the medical history of the patients may be sufficient to categorize those with a higher risk and consequently adopt ad hoc measures, such as druggable targeting and/or sensory stimulation protocols, to prevent the occurrence or curb the progression of pathogenic mechanisms triggering neurodegenerative events.

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