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Review

Unraveling brain aging through the lens of oral microbiota

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Abstract

The oral cavity is a complex physiological community encompassing a wide range of microorganisms. Dysbiosis of oral microbiota can lead to various oral infectious diseases, such as periodontitis and tooth decay, and even affect systemic health, including brain aging and neurodegenerative diseases. Recent studies have highlighted how oral microbes might be involved in brain aging and neurodegeneration, indicating potential avenues for intervention strategies. In this review, we summarize clinical evidence demonstrating a link between oral microbes/oral infectious diseases and brain aging/neurodegenerative diseases, and dissect potential mechanisms by which oral microbes contribute to brain aging and neurodegeneration. We also highlight advances in therapeutic development grounded in the realm of oral microbes, with the goal of advancing brain health and promoting healthy aging.

Key Words: Alzheimer's disease; brain aging; multiple sclerosis; neurodegeneration; neurodegenerative diseases; oral microbiota; Parkinson's disease; periodontitis; bacteria; *Porphyromonas gingivalis*

From the Contents

Introduction

Brain aging refers to structural and functional decline in the brain associated with age (Cai et al., 2022). Brain cells, including neuronal cells and glial cells, undergo common and cell-type-specific changes during aging (Cai et al., 2022). At the cellular and molecular level, ten hallmarks of brain aging have been postulated: mitochondrial dysfunction, oxidative damage, dysregulated energy metabolism, impaired cellular "waste disposal" mechanisms, impaired adaptive stress response signaling, impaired DNA repair, aberrant neuronal network activity, dysregulated neuronal calcium homeostasis, stem cell exhaustion, and glial cell activation and inflammation (Mattson and Arumugam, 2018). These features interact and reinforce each other, forming a self-perpetuating network that drives decline in brain structure and function. At the structural level, brain atrophy, white matter hyperintensities, and cerebral microhemorrhage are proposed as imaging markers in brain aging, whereas at the functional level, brain aging entails decline in cognitive function, motor coordination, sensory perception, and emotion (Aging Biomarker Consortium et al., 2023a). All of these brain aging–related changes markedly impact an individual's quality of life, causing frailty and leading to the onset of various neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, multiple sclerosis (MS), and amyotrophic lateral sclerosis (Wilson et al., 2023). Brain aging and neurodegeneration adversely affect millions of people globally; however, therapeutic strategies that can satisfactorily mitigate disease progression are lacking. Consequently,

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exploring risk factors of brain aging and neurodegeneration and mechanisms of disease progression may provide new insights that could be harnessed for clinical prevention and treatment.

Like other organs, the rate of brain aging varies from person to person and is affected by many factors. Environmental factors (such as smoking, alcohol, stress, diet, and socioeconomic status), genetic factors (such as *APOE4*), trauma, and acute infection, are believed to accelerate the process of brain aging (Gorbunova et al., 2021; Zakusilo et al., 2021; Aging Biomarker Consortium et al., 2023b; Hahn et al., 2023). Recently, dysbiosis was proposed as a new hallmark of aging (López-Otín et al., 2013, 2023; DeJong et al., 2020; López-Otín and Kroemer, 2021; Martino et al., 2022), and the role of oral microbes in brain aging and neurodegeneration is attracting increasing attention.

The human oral cavity hosts a complex microbiome consisting of bacteria, fungi, and viruses. As bacteria are the most frequent microorganisms in the oral cavity, dysregulation of the oral flora could cause various oral infectious diseases (Gao et al., 2018). For example, periodontitis—one of the most common chronic inflammatory diseases—is triggered by bacteria, with key roles being played by *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, *Aggregatibacter actinomycetemcomitans*, *Tannerella forsythia*, *Treponema denticola*, *Prevotella intermedia*, etc. (Abusleme et al., 2021). Periodontitis is known to destroy tooth-supporting tissues such as gingiva and alveolar bone, eventually leading to tooth loss. Perhaps less well-known is that periodontitis and periodontitis-related bacteria are closely associated with the occurrence and development of a range of systemic diseases, including AD (Hajishengallis and Chavakis, 2021; Jungbauer et al., 2022). Another very common oral infectious disease is dental caries, which manifests as the destruction of teeth caused by bacteria such as *Streptococci*, *Lactobacilli*, and *Actinomyces* and has been found through epidemiological studies to be significantly associated with the incidence of AD (Sureda et al., 2020). In addition to bacteria, opportunistic fungi commonly found in the oral cavity, such as *Candida albicans*, and viruses commonly infecting the mouth, such as herpes simplex virus type 1 (HSV1), are reported to be associated with brain aging and neurodegeneration (Sureda et al., 2020). Combined with numerous preclinical and clinical studies in recent years, the crucial role of oral microbes in brain aging and neurodegeneration has been increasingly recognized (**Figure 1**). In this review, we discuss the age-related oral microbiome variations, summarize the clinical evidence supporting a correlation between oral microbes/oral infectious diseases and brain aging/neurodegenerative diseases, analyze the mechanisms by which oral microbes promote brain aging and neurodegeneration, and highlight the therapeutic strategies developed from the perspective of oral microbes.

Search Strategy

A search of the PubMed database was performed using the following keywords and MeSH (Medical Subject Headings) terms: oral microbiota, bacteria, fungi, viruses, periodontitis, dental caries, brain aging, nerve degeneration, neurodegenerative diseases, Alzheimer's disease, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis. Only articles in English were considered. No limit was given to the year of publication. The references cited in the articles were also checked and included if they were relevant to the topic of this review. The literature search was performed between May and September 2023.

Age-Related Oral Microbiome Variations

Human microbiota succession occurs throughout life and includes the oral microbiome (Martino et al., 2022). In the elderly, the α-diversity (within-sample diversity) of oral bacteria decreased and the β-diversity (between-sample diversity) increased, compared with the youngsters (Liu et al., 2020b; Schwartz et al., 2021). Moreover, the decrease in the α-diversity of oral bacteria in the elderly was associated with the occurrence of aging-related diseases, such as AD (Singh et al., 2019; Wu et al., 2021). In the process of aging, the composition of the oral bacteria altered, including a decline of the important oral commensal *Neisseria* and an increase in the opportunistic pathogens *Streptococcus anginosus* and *Gemella sanguinis* (Kazarina et al., 2023). The decrease of *Neisseria* and increases of *Streptococcus*, *Veillonella*, and *Rothia* were also observed in the elderly with aging-related diseases, compared with the healthy elderly (Singh et al., 2019). In addition to the intrinsic effects of aging, variations in the oral microbiome of the elderly may be affected by multiple factors, such as dental caries, periodontitis, using removable dentures, systemic comorbidities, and multiple medications (Schwartz et al., 2021). However, collectively, current evidence suggests that the oral microbiome in the elderly shifts from a stable state to dysbiosis, which is more likely to cause oral diseases and potentially systemic diseases.

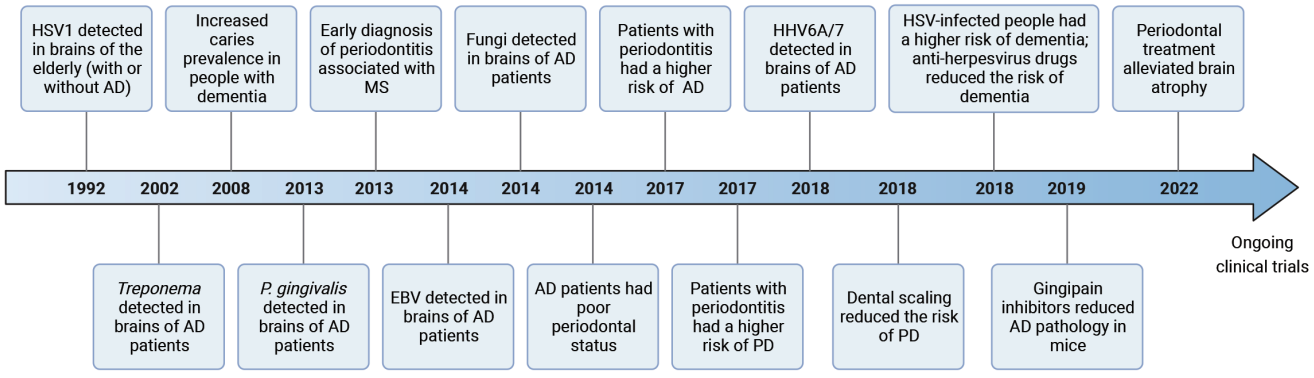

Figure 1 | **Study timeline showing the role of oral microbiota in brain aging.**
Created with BioRender.com. AD: Alzheimer's disease; EBV: Epstein–Barr virus; HHV: human herpes virus; HSV: herpes simplex virus; MS: multiple sclerosis; PD: Parkinson's disease; *P. gingivalis*: *Porphyromonas gingivalis*.

Clinical Evidence: Association Between Oral Infective Diseases and Brain Aging/ Neurodegeneration

The oral cavity hosts a complex community of diverse microorganisms. Clinical evidence shows that oral infectious diseases, such as periodontitis and dental caries, are tightly correlated with the occurrence and development of brain aging phenotypes and neurodegenerative diseases (Sureda et al., 2020). The presence of oral infectious diseases and dysbiosis of oral microbiota may promote a range of brain aging phenotypes, such as cognitive impairment. Conversely, patients with cognitive impairment usually have decreased oral motor ability, such as lip movement and swallowing function, and decreased ability to maintain oral hygiene routines, which in turn increases the oral microbial load and the risk of oral infectious diseases (Watanabe et al., 2018; **Figure 2**). The prevalence of periodontitis and dental caries increases in the elderly. The prevalence of periodontitis was 29.5%, 46.0%, and 59.8% in adults aged 30–44, 45–64, and 65–79 years, respectively (Eke et al., 2020). Similarly, the mean scores of past caries (decayed, missing, or filled teeth) for people aged 12, 35–44, and 65–74 years were 0.5, 11.2, and 17.7, respectively (Jordan et al., 2019). The high prevalence of periodontitis and dental caries in the elderly implies its correlation with aging, as well as brain aging. Since brain aging phenotypes often manifest in patients with neurodegenerative diseases, we discuss the most common neurodegenerative diseases—AD, PD, and MS—in this review. Moreover, we summarize the clinical evidence supporting an association between oral infectious diseases, represented by periodontitis and dental caries, and neurodegenerative diseases.

Periodontitis

Periodontitis and Alzheimer's disease

AD, which is the most common aging-related neurodegenerative disease, is characterized by the formation of extracellular aggregates of amyloid-β (Aβ) plaques and the intracellular accumulation of neurofibrillary tangles consisting of the hyperphosphorylated microtubule-associated protein tau (Scheltens et al., 2021; Chu et al., 2024; Ye et al., 2024). In a cross-sectional study comparing the periodontal status of patients with AD and that of healthy volunteers, multiple periodontal parameters, including gingival index, plaque index, probing depth, clinical attachment level, and percentage of bleeding sites, were substantially more severe in the patients with AD. Moreover, in patients with AD (including 22 patients with mild AD, 18 with moderate AD, and 18 with severe AD), the severity of periodontitis was significantly correlated with the extent of cognitive impairment (Martande et al., 2014). Similarly, a multicenter case-control study revealed that the patients with AD had more missing teeth and worse periodontal health compared with the control group. Furthermore, despite the older age of the AD group, after accounting for the influence of age in regression analysis, oral health was still worse in the AD group than in the control group. A lower frequency of brushing, flossing, and visiting the dentist may be related to poor oral health in the AD group (Aragón et al., 2018). Collectively, these studies support that AD is correlated with poor oral health but do not indicate a causal relationship between the two conditions.

Several cohort studies investigating relationships between oral health and AD have also been conducted. In a retrospective cohort study of 9291 patients with periodontitis and 18,672 matched individuals without periodontitis (control group; matching based on sex, age, and other factors), a marginally larger fraction of individuals in the periodontitis group relative to the control group developed AD at the end of the follow-up. Furthermore, individuals exposed to periodontitis for 10 years or more had a 1.707 times higher risk of developing AD than unexposed individuals (Chen et al., 2017b). Another cohort study showed that the presence of periodontitis at baseline in patients with AD resulted in a 6-fold increase in the rate of cognitive decline over a 6-month follow-up period (Ide et al., 2016). In addition, studies examining serum IgG against periodontal pathogens, including *Porphyromonas gingivalis*, *F. nucleatum*,

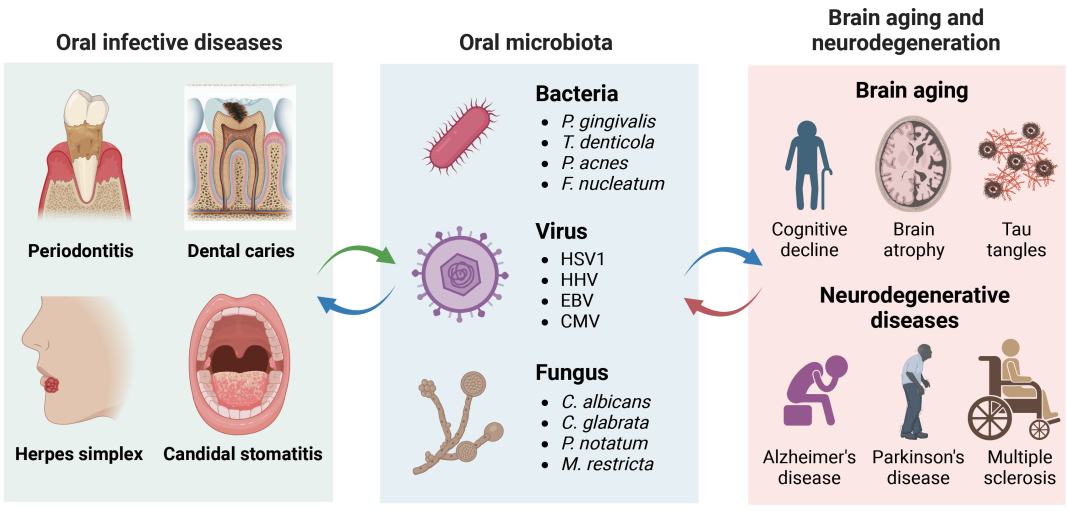

Figure 2 | The association between oral infective diseases, oral microbiota, and brain aging/neurodegeneration.
In oral infectious diseases, dysbiosis and an increased load of oral microbiota promote brain aging and neurodegeneration through multiple mechanisms, resulting in cognitive, memory, and motor impairment. In turn, in the elderly or patients with neurodegenerative diseases, there is usually a decline in oral motor capacity and oral health care ability, which increase the oral microbial load and exacerbate the risk of oral infectious diseases. Consequently, a mutually reinforcing two-way interaction is established. Created with BioRender.com. *C. albicans*: *Candida albicans*; *C. glabrata*: *Candida glabrata*; CMV: cytomegalovirus; EBV: Epstein–Barr virus; *F. nucleatum*: *Fusobacterium nucleatum*; HHV: human herpes virus; HSV: herpes simplex virus; *M. restricta*: *Malassezia restricta*; *P. acnes*: *Propionibacterium acnes*; *P. gingivalis*: *Porphyromonas gingivalis*; *P. notatum*: *Penicillium notatum*; *T. denticola*: *Treponema denticola*.

Prevotella intermedia, *Prevotella melaninogenica*, *Actinomyces naeslundii*, and *Campylobacter rectus*, found that increased IgG levels were closely related to the occurrence and pathology of AD (Kamer et al., 2009; Sparks Stein et al., 2012; Noble et al., 2014; Laugisch et al., 2018; Beydoun et al., 2020, 2021). Together, these findings suggest that periodontitis is an important risk factor for onset and progression of AD.

Periodontitis and Parkinson's disease

PD is the second-most common aging-related neurodegenerative disease after AD and is characterized by neuronal loss in the substantia nigra and abnormal accumulation of α-synuclein (Poewe et al., 2017; Balaj and Kaku, 2024; Zhang and Lingor, 2024). Numerous epidemiological studies have indicated that periodontitis is a risk factor for PD. A retrospective cohort study comparing the risk of developing PD in individuals with and without periodontitis after matching age, sex, comorbidity, and other parameters found that the risk of developing PD in the periodontitis group was 1.431 times higher than that in the control group (Chen et al., 2017a). Another large cohort study followed 6,856,180 individuals for 8 years and showed that those with periodontitis had a markedly increased risk of developing PD (Jeong et al., 2021). In addition, compared with individuals with periodontitis, individuals with both PD and periodontitis have more severe periodontal inflammation, as indicated by bleeding on probing, suggesting that the two conditions may promote each other (Yilmaz et al., 2023). The use of dental scaling (deep cleaning to remove plaque and tartar above and below the gumline) in preventing or treating periodontitis can significantly reduce the risk of PD, regardless of whether the individual has periodontitis prior to dental scaling (Chen et al., 2018). In addition, in the *LRRK2*^{R1441G} mouse model of PD, administration of the periodontal pathogen *Porphyromonas gingivalis* led to a reduction of dopaminergic neurons in the substantia nigra and an increase of activated microglial cells (Feng et al., 2020), further demonstrating the close correlation between periodontitis and PD.

Periodontitis and multiple sclerosis

MS is a common neurodegenerative disease of the central nervous system that manifests as demyelination of nerve cell fibers and infiltration of inflammatory cells and often causes severe physical and cognitive impairment (Filippi et al., 2018; Wei et al., 2023). The pathogenesis of MS is not fully understood, but includes autoimmunity and chronic inflammation, with multiple infections recognized as playing a crucial role in disease development (Wolfson and Talbot, 2002). Periodontitis, caused by various oral bacterial infections, may also be involved in the development of MS. A meta-analysis—involving 3376 people in three observational studies—systematically analyzed the epidemiological association between periodontitis and MS, and demonstrated that patients with MS were 1.93 times more likely to be diagnosed with periodontitis than the healthy controls (Tsimpiris et al., 2023). A case-control study comparing the early diagnosis of periodontitis in 316 patients with MS and 1580 control individuals found that the prevalence of early periodontitis was higher in patients with MS than in the control group, suggesting an association between periodontitis and the occurrence of MS (Sheu and Lin, 2013). A more direct relationship was demonstrated in a mouse model of MS—the experimental autoimmune encephalomyelitis model—with subcutaneous injection or gavage of the periodontal pathogen *Porphyromonas gingivalis* significantly aggravating disease severity in these mice (Polak et al., 2018). In a related study, *Porphyromonas gingivalis* lipopolysaccharide (Pg-LPS) exacerbated disease in experimental autoimmune encephalomyelitis mice by promoting glial cells to secrete the proinflammatory mediators nitric oxide and prostaglandin E2 in the central nervous system (Shapira et al., 2002).

Dental caries

Dental caries, which is one of the most common chronic infectious diseases in humans, is caused by bacteria in the biofilm formed on the dental surface and eventually leads to the demineralization and destruction of dental hard tissues (Pitts et al., 2017). Dental caries has been reported to be associated with neurodegenerative diseases. Multiple studies have found that an increase in dental caries segregates with AD or other types of dementia (Ellefsen et al., 2008; Syrjälä et al., 2012; Aragón et al., 2018). A study that analyzed 170 adults older than 75 years found that when the number of caries was greater than 3, the risk of developing AD increased by 3.47 times (Tiisanoja et al., 2019). In patients with MS, those with high levels of physical disability were more likely to have higher numbers of decayed teeth (Hatipoglu et al., 2016). Despite these findings, most of the studies are cross-sectional studies and cannot explain the causal relationship between the two conditions. Patients with neurodegenerative disease tend to have difficulty with self-oral care, which may lead to poor oral hygiene, thus exacerbating the occurrence of dental caries. Additional high-quality cohort studies are needed to clarify the relationship between dental caries and neurodegenerative disease.

Oral Microbes Exist in the Brain and Increase with Age and Neurodegeneration

Epidemiological studies have provided evidence for the link between oral infectious diseases and brain aging/neurodegeneration. For example, tooth loss or decreased tooth function caused by periodontitis or dental caries can affect food intake and nutritional status, which is linked to memory deficits and dementia (Harding et al., 2017). However, the link between dental status and dementia persisted even after adjusting for nutritional indicators (Kim et al., 2007), suggesting that other more direct mechanisms may exist, such as oral microbes. More direct and critical evidence is the numerous reports that oral microbes, including bacteria (Riviere et al., 2002; Poole et al., 2013; Emery et al., 2017; Dominy et al., 2019; Patel et al., 2021), viruses (Jamieson et al., 1992; Lin et al., 2002; Wozniak et al., 2005, 2009; Angelini et al., 2013; Carbone et al., 2014; Readhead et al., 2018; Nemergut et al., 2022), and fungi (Alonso et al., 2014b; Pisa et al., 2015), are markedly increased in the brain tissue and cerebrospinal fluid (CSF) of the elderly or in patients with neurodegeneration (**Figure 3**). The increase of microorganisms in the brain may result from multiple types of microorganisms that exist simultaneously, and not necessarily a single type (Nemergut et al., 2022). These studies provide compelling evidence in support of oral microorganisms promoting the occurrence and development of brain aging and neurodegeneration, and establish a foundation for exploring underlying mechanisms. It is worth noting that physiological barriers break down after death, providing an opportunity for rapid entry of microorganisms into the brain tissue, which may interfere with the epidemiological results. Therefore, factors such as sampling time, experimental method, and experimental control should be carefully considered when evaluating such results (Lobmaier et al., 2009). However, even after balancing factors such as time of sampling after death, the existing data demonstrate that the microbial load in the neurodegenerative brain was higher than that in the control brain (Poole et al., 2013).

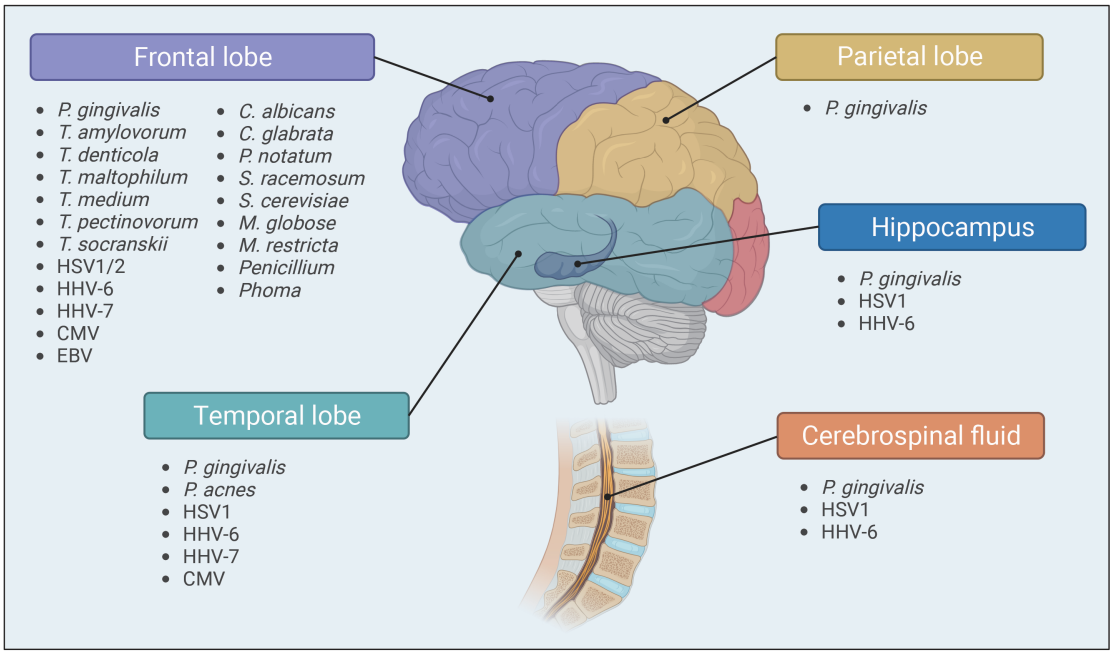

Figure 3 | **Oral microbes detected in the brain and cerebrospinal fluid.**
Oral microbes—including bacteria, viruses, and fungi—are marked at the locations in the brain or cerebrospinal fluid where they were detected (based on post-mortem studies in humans). Created with BioRender.com. *C. albicans*: *Candida albicans*; *C. glabrata*: *Candida glabrata*; CMV: cytomegalovirus; EBV: Epstein-Barr virus; HHV: human herpes virus; HSV: herpes simplex virus. *M. globose*: *Malassezia globose*; *M. restricta*: *Malassezia restricta*; *P. acnes*: *Propionibacterium acnes*; *P. notatum*: *Penicillium notatum*; *P. gingivalis*: *Porphyromonas gingivalis*; *S. cerevisiae*: *Saccharomyces cerevisiae*; *S. racemosum*: *Syncephalastrum racemosum*; *T. amylovorum*: *Treponema amylovorum*; *T. denticola*: *Treponema denticola*; *T. maltophilum*: *Treponema maltophilum*; *T. medium*: *Treponema medium*; *T. pectinovorum*: *Treponema pectinovorum*; *T. socranskii*: *Treponema socranskii*.

Bacteria

Porphyromonas gingivalis

Porphyromonas gingivalis—one of the most important periodontal pathogens and thus far most deeply studied—may play a key role in the association between periodontitis and brain aging/neurodegeneration. Among prefrontal cortex samples from 44 healthy individuals, *Porphyromonas gingivalis* sequencing reads were detected in 10 samples, whereas other important periodontitis pathogens, including *Tannerella forsythia* and *Treponema denticola*, could not be detected (Patel et al., 2021). In the brain tissues of ten AD patients analyzed after death, *Porphyromonas gingivalis* was present in four samples but undetectable in the brain tissues of ten deceased non-AD individuals (Poole et al., 2013). In another study, *Porphyromonas gingivalis* was found in the brain tissue and CSF of patients with AD (Dominy et al., 2019). Moreover, gingipain, which is the major virulence factor of *Porphyromonas gingivalis*, had a significantly higher load in the brains of patients with AD compared with the brains of non-AD individuals, and gingipain load was also positively correlated with the expression of tau protein. Further analysis revealed that gingipain was present in the hippocampus and cerebral cortex of patients with AD, and colocalized with the AD pathology hallmarks of tau tangles and intraneuronal Aβ (Dominy et al., 2019). These studies suggest that the oral bacterium *Porphyromonas gingivalis* can enter the brain and is associated with AD pathological changes. Some animal studies have provided direct evidence of *Porphyromonas gingivalis* invading the brain. Following oral colonization of *Porphyromonas gingivalis* in mice, increased levels of *Porphyromonas gingivalis* mRNA and Pg-LPS were detected in the hippocampus, confirming that *Porphyromonas gingivalis* in the mouth can reach the brain tissue (Wang et al., 2019). Several other studies confirmed the presence of *Porphyromonas gingivalis* in the brain after oral administration of this bacterium (Poole et al., 2015; Singhrao et al., 2017; Ilievski et al., 2018; Díaz-Zúñiga et al., 2020). Oral colonization of another periodontal pathogen, *F. nucleatum*, did not elicit similar changes in the brain (Poole et al., 2015; Wang et al., 2019).

Treponema

The genus *Treponema*, which belongs to the phylum *Spirochetes*, is another oral microbe strongly associated with brain aging and neurodegeneration. *Treponema* has a low detection rate in healthy periodontal tissue, but a substantially increased detection rate in chronic periodontitis. In the frontal lobe cortex of 34 individuals, many species of the genus *Treponema* were detected by PCR, including *Treponema denticola*, *Treponema amylovorum*, *Treponema maltophilum*, *Treponema medium*, *Treponema pectinovorum*, and *Treponema socranskii*. *Treponema* was also detected more frequently in the AD cortex than in the non-AD cortex, and AD cortexes harbored more species of *Treponema* compared with control cortexes (Riviere et al., 2002). In contrast, *Porphyromonas gingivalis* was detected in the brain tissue of healthy individuals and AD patients, but *Treponema denticola* was not detected in studies by Poole et al. (2013) and Patel et al. (2021). In animal experiments, oral administration of *Treponema denticola* resulted in an increase in this microbe in the brain and the accumulation of brain aging markers $A\beta_{1-40}$ and $A\beta_{1-42}$, suggesting that *Treponema denticola* can invade the brain from the mouth and contribute to pathological changes related to brain aging and neurodegeneration (Poole et al., 2015; Su et al., 2021).

Other bacteria

In 16S rRNA gene sequencing analysis of the temporal cortex of the post-mortem brain, the bacterial load in the brain of patients with AD was significantly higher than in the normal control group, and *Actinobacteria* was the dominant bacterial community component in the AD brain tissue. Further analysis showed that the bacterial species with the greatest increase in abundance in the AD group was *Propionibacterium acnes*, an opportunistic bacterium existing on human skin and in mouths (Emery et al., 2017). Although an increase of *F. nucleatum* in brain tissue could not be confirmed (Poole et al., 2015; Wang et al., 2019), periodontitis induced by *F. nucleatum* aggravated symptoms in the 5×FAD mouse model of AD, including cognitive dysfunction, Aβ accumulation, and tau phosphorylation (Wu et al., 2022). These observations suggest that *F. nucleatum* may promote the development of AD through other means than brain invasion.

Viruses

Oral viruses, such as HSV1, human herpes virus (HHV), Epstein–Barr virus (EBV), and cytomegalovirus, are also associated with brain aging and neurodegeneration. HSV1 infection is considered a potential risk factor for AD because it is neurotropic, prevalent in the general population, and can establish lifelong latency in the host (Marcocci et al., 2020). HSV1 virus DNA was initially detected in the brains of the elderly (with or without AD), but not in the brains of young people, and mainly located in the temporal cortex and hippocampus (Jamieson et al., 1992). Similarly, HSV-specific intrathecal synthesis of IgG antibody was detected in the CSF of the elderly (with or without AD) but not in the children control group (Wozniak et al., 2005). Further support that HSV1 is closely related to AD and brain aging is provided by a cohort study of 512 dementia-free elderly individuals showing that reactivation of HSV1 significant increased the risk of developing AD (Letenneur et al., 2008). Although HSV1 virus DNA was detected in frontal and temporal brain specimens of patients with AD and healthy elderly individuals, the HSV1 DNA in brain tissues of the patients with AD exhibited a higher correlation with amyloid plaques, suggesting that the virus may be instrumental in promoting the pathological changes and development of AD (Wozniak et al., 2009). In a recent study, HSV1 was detected in the brain tissue and blood of patients with AD, and HSV1 infection was markedly associated with the risk of developing AD (Tejeda et al., 2024).

HHV-6A and HHV-7, found to be enriched in multiple brain regions in patients with AD, were validated in different clinical cohorts (Readhead et al., 2018). Antibodies against HHV-6 were detected in the CSF of 22% of patients with AD, but not in healthy elderly individuals (Wozniak et al., 2005). Another study confirmed that the NDA level of HHV-6 was higher in the CSF of patients with AD than in the control group (Nemergut et al., 2022). EBV has also been detected in the brain tissue of patients with AD, and the proportion of EBV-positive peripheral blood leukocytes was significantly higher in the patients with AD than in the control group (Carbone et al., 2014). Similarly, an EBV lytic protein—BamHI fragment Z leftward open reading frame 1—was found in post-mortem MS brain samples (Angelini et al., 2013). EBV is suggested to play a role in the progression of various neurodegenerative diseases (Zhang et al., 2021b), especially MS (Soldan and Lieberman, 2023). Cytomegalovirus was detected in the brain tissues of AD patients and age-matched normal individuals, but there was no significant difference between the two groups (Lin et al., 2002).

Fungi

Oral fungal infections are opportunistic infections. In the elderly, factors such as decreased immunity and wearing removable partial dentures increased the probability of oral and even systemic fungal infection (Villar and Dongari-Bagtzoglou, 2021), which may be a risk factor for brain aging and neurodegeneration. Although absent in the brain tissue from a control group, fungi were detected in the brain tissue of AD patients using proteomic analysis, PCR analysis, and DNA sequencing. These fungi included *Saccharomyces cerevisiae*, *Malassezia globose*, *Malassezia restricta*, *Penicillium*, and *Phoma* (Alonso et al., 2014b). Consistently, serological tests showed the presence of a disseminated fungal infection in most patients with AD, with several *Candida* spp. identified (Alonso et al., 2014a). Furthermore, direct visualization of fungal infections by immunofluorescent staining in brains from patients with AD identified several fungi including *Candida glabrata*, *Candida albicans*, *Penicillium notatum*, and *Syncephalastrum racemosum*, but only about 10% of the cells contained fungi (Pisa et al., 2015). These studies provide insights for the involvement of oral fungi in brain aging and neurodegeneration.

Routes for Oral Microorganisms to Access the Brain

Given that oral microorganisms have been detected in the central nervous system, exploring how these microbes invade the brain is a vital area of research. Current understanding is that bacteria and fungi primarily enter the brain via the vasculature, whereas viruses may invade the brain via neural pathways. In addition, oral microbes can enter the brain through other routes, such as the circumventricular organs (CVOs) or perivascular spaces. **Figure 4** summarizes the possible ways by which oral microbes invade the brain.

Blood pathways

Microbes in the mouth may enter the circulatory system during brushing, chewing, and flossing, and cause bacteremia. In pathological states such as periodontitis, the gingival epithelial barrier function is impaired, the periodontal tissue is destroyed, and the oral bacterial load is substantially increased, all of which increase the probability of oral microorganisms entering the blood. Bacteremia was reported to occur after 100% of tooth extractions, 70% of periodontal scalings, 55% of bilateral tonsillectomies, and 30% of root canal therapies (Olsen, 2008). After entering the circulatory system, oral microorganisms need to penetrate the blood–brain barrier (BBB) to enter the brain. Tight junctions between vascular endothelial cells of the brain form an impermeable boundary between the brain and blood, which prevents harmful substances from entering the brain, including toxins and pathogens, and thus maintains stability of the brain environment (Sweeney et al., 2019). However, BBB damage occurs in the elderly, providing an opportunity for invasion by oral microorganisms (Yang et al., 2020). In magnetic resonance imaging analysis, BBB permeability in living human brains showed age-dependent destruction in the hippocampus (Montagne et al., 2015), and association with cognitive decline (Bowman et al., 2018). In addition, oral microorganisms and their toxins can damage the BBB. Lipopolysaccharide (LPS) significantly increased permeability of the BBB in aged mice, concomitant with degradation of the tight junction proteins occludin and claudin-5 (Wang et al., 2017). Loss of BBB integrity caused by *Candida albicans* infection was also confirmed by magnetic resonance imaging (Navarathna et al., 2013).

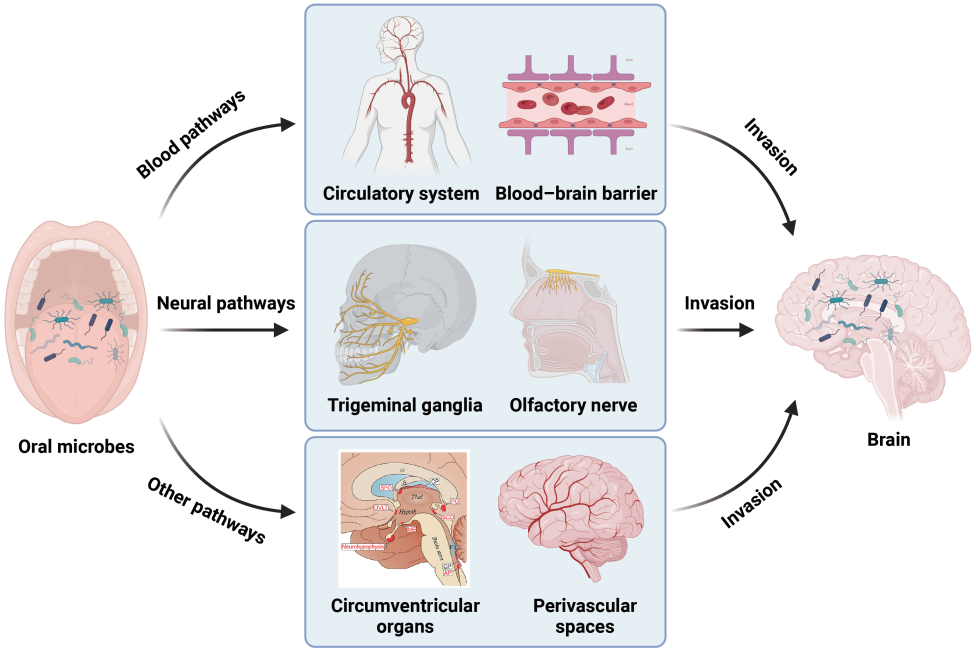

Figure 4 | Possible routes for brain invasion by oral microbes.
Oral microbes may invade the brain by entering the circulatory system and traversing the blood–brain barrier. Oral microbes may also invade the brain directly through peripheral nerves, including the trigeminal nerve and olfactory nerve. In addition, oral microbes may enter the brain through special structures, such as circumventricular organs and perivascular spaces. Created with BioRender.com.

Neural pathways

Oral microorganisms may directly invade the brain through neural pathways, such as the trigeminal nerve and olfactory nerve. Oral members of the bacterial genus *Treponema*, which are associated with periodontitis, were detected not only in the frontal lobe cortex but also in the trigeminal ganglia of AD donors, suggesting that these microbial species may enter the brain through this nerve (Riviere et al., 2002). Periodontal microorganisms or their products may also enter the central nervous system via peripheral nerves such as the glossopharyngeal nerve and the trigeminal nerve (Horowitz et al., 2004). The neural pathway may be the main way for HSV1 to enter the brain. After initial infection, HSV1 becomes latent in peripheral nervous system neurons, typically the trigeminal ganglion, and can be reactivated periodically throughout life. Various stressors or stimuli can reactivate HSV1, which predominantly affects the site of primary infection, such as the lip or corner of the mouth, but the virus can also reach the central nervous system through anterograde neural transport (Marcocci et al., 2020). The olfactory system is another route for external drugs or cells to enter the central nervous system. Intranasally administered cells can bypass the BBB and migrate from the nasal mucosa into the brain and CSF through the mesh plate along olfactory neural pathways (Danielyan et al., 2009). *Chlamydia pneumoniae* may enter the olfactory cortex and hippocampus via the olfactory bulb (Sundar et al., 2020), and *Spirochaeta* may enter the central nervous system along the olfactory filament and olfactory tract (Miklossy, 2011). The above studies demonstrate the possibility of oral microbes entering the brain through neural pathways; however, strong evidence confirming the specific role of this pathway in promoting brain aging and neurodegeneration is lacking.

Circumventricular organs and perivascular spaces

CVOs are specialized brain structures located around the third and fourth ventricles. Unlike other brain parenchyma, the vascular endothelial cells in CVOs lack tight junctions and therefore do not have a complete BBB. Consequently, CVOs are vulnerable to attack by circulating pathogens and can be an entry point for pathogens into the brain (Sisó et al., 2010). In addition, pathogens can enter the central nervous system through perivascular spaces, which are fluid-filled areas surrounding small blood vessels in the brain (Zhang et al., 2021a).

The Effects of Oral Microorganisms in Brain Aging and Neurodegeneration

On one hand, oral microorganisms can invade the brain and directly damage neural tissues, mainly through Aβ production and deposition, tau fragmentation and hyperphosphorylation, microglia activation and neuroinflammation, cerebrovascular destruction, and cathepsin B (CatB) upregulation. On the other hand, oral microorganisms can release their toxic products into the blood, induce systemic inflammatory responses, and cause damage in cerebral vessels, further promoting the entry of circulating pathogens and inflammatory substances into the brain and aggravating the damage to the nervous system (**Figure 5**).

Amyloid-β production and deposition

Imbalance between the production and clearance of Aβ, resulting in the deposition of Aβ in the brain, is a pathological characteristic of AD and a physiological sign of brain aging (Aging Biomarker Consortium et al., 2023b; Abyadeh et al., 2024). Oral microorganisms and their products can induce the production and deposition of Aβ in the brain and cause corresponding functional changes. Following *Porphyromonas gingivalis* infection in mice, significant increases in $A\beta_{1-40}$ and $A\beta_{1-42}$ were observed in the hippocampus, accompanied by memory impairment (Liu et al., 2020a). Similarly, the toxic products of *Porphyromonas gingivalis*, such as Pg-LPS (Hu et al., 2020) and gingipain (Ilievski et al., 2018), can upregulate the expression levels of Aβ and amyloid precursor protein, as well as lead to learning and memory impairment in mice. β-Site amyloid precursor protein cleaving enzyme 1, which can cleave amyloid precursor protein and cause Aβ deposition, was increased in the brain of mice after *Porphyromonas gingivalis* infection in the mouth, further suggesting that *Porphyromonas gingivalis* and its products can induce Aβ production (Ilievski et al., 2018; Liu et al., 2020a). Certain oral bacteria can produce Aβ *per se*. Oral bacteria usually exist in the form of biofilm on the tooth surface or in the periodontal pocket to resist external damage and facilitate survival. The presence of amyloid protein

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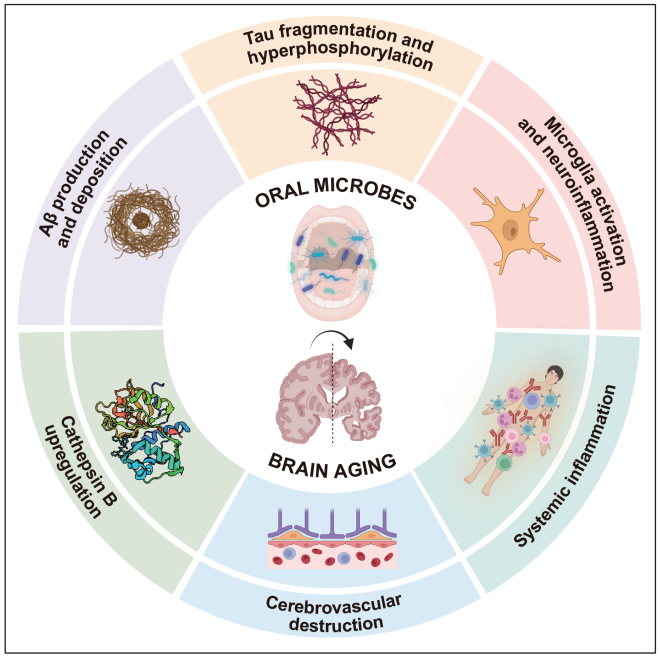

Figure 5 | The effects of oral microbes in brain aging.
Oral microbes can invade the brain and directly damage neural tissues, as manifested by Aβ production and deposition, tau fragmentation and hyperphosphorylation, microglia activation and neuroinflammation, cerebrovascular destruction, and cathepsin B upregulation. In addition, the presence of oral microbes and their toxic products in the blood can induce systemic inflammatory responses and cause cerebrovascular injury, which further promotes the entry of circulating pathogens and inflammatory substances into the brain, thereby indirectly aggravating the damage to the nervous system. Created with BioRender.com. Aβ: Amyloid-β.

as the main component of biofilm indicates that oral bacteria are likely able to produce Aβ. Sureda et al. (2020) summarized the oral microbes that can produce amyloid proteins in their review. These oral microbes include *Streptococcus mutans*, *Listeria monocytogenes*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas*, *Mycobacterium tuberculosis*, and *Staphylococcus aureus*. In addition, *Porphyromonas gingivalis* can upregulate the expression of receptor for advanced glycation end products in cerebral endothelial cells and mediate Aβ influx, thus promoting Aβ transport from the periphery into the brain (Zeng et al., 2021).

Tau fragmentation and hyperphosphorylation

Excessive phosphorylation of the tau protein resulting in the formation of neurofibrillary tangles in neurons is another hallmark of brain aging and neurodegeneration (Aging Biomarker Consortium et al., 2023b; Robbins, 2023). Infection with *Porphyromonas gingivalis*, or its toxic product Pg-LPS and its secreted protease gingipain, can induce significant upregulation of phosphorylated tau (Ilievski et al., 2018; Díaz-Zúñiga et al., 2020; Hu et al., 2020). Truncation and fragmentation of the tau protein are both thought to be important for the formation of insoluble and hyperphosphorylated tau. Gingipain cleaves tau into fragments containing hexapeptide motifs that are involved in tangle formation (Dominy et al., 2019). Consistently, gingipain colocalizes with tau tangles in the brain. Knocking out gingipain in *Porphyromonas gingivalis* significantly reduced the bacterial load in the brain of *Porphyromonas gingivalis*-infected mice and alleviated the associated pathological changes in the mice. Inhibitors of gingipain—COR271 and COR286—can also reduce the load of *Porphyromonas gingivalis* in the brain and prevent loss of hippocampal glutamate decarboxylase-67-positive interneurons (Dominy et al., 2019). These results suggest that gingipain mediates tau entanglement and subsequent neuropathological changes through its proteolytic effect and promotes the progression of brain aging and neurodegeneration.

Microglia activation and neuroinflammation

Activation of microglia is a hallmark of brain aging (Mattson and Arumugam, 2018). Under physiological conditions, microglia function as immune sentinels, monitoring pathogens or other stressors in the surrounding environment, and upon activation, releasing a series of inflammatory mediators such as cytokines and chemokines. Microglial cells are phagocytic and clear apoptotic debris or dysfunctional synapses (Leng and Edison, 2021). Accordingly, the activation of microglia and subsequent neuroinflammation are likely crucial events in brain aging and neurodegeneration induced by oral microorganisms. Oral infection with *Porphyromonas gingivalis* can activate microglia in the brain and increase pathological indicators of brain aging, including $A\beta_{42}$ and phosphorylated tau, in hippocampal neurons (Ilievski et al., 2018; Bahar et al., 2021; Tang et al., 2021). Similarly, oral topical application (Hu et al., 2020) or systemic administration (Wu et al., 2017; Gu et al., 2020) of Pg-LPS can activate microglial cells in the brain and lead to learning and memory impairments. Chronic systemic exposure to Pg-LPS increases glycogen synthase kinase-3β activity in microglia and neurons in the murine cortex, thus promoting neuroinflammation by increasing the expression of interleukin (IL)-1β and tumor necrosis factor-α while decreasing that of IL-10 and transforming growth factor-β (Jiang et al., 2021). The ability to induce neuroinflammation is not specific to Pg-LPS, as other bacterial-derived LPS also exhibit neuroinflammatory effects (Lee et al., 2008; Cunningham et al., 2009; Czerniawski et al., 2015). In an *in vitro* model with mixed microglia and hippocampal cells, stimulation with LPS from the periodontal pathogen *Aggregatibacter actinomycetemcomitans* triggered microglial secretion of proinflammatory cytokines, and thus induced neurite atrophy and increased extracellular $A\beta_{1-42}$ levels, which are cellular events linked with pathological changes in AD (Díaz-Zúñiga et al., 2019). Mechanistically, LPS from bacteria may act on Toll-like receptor 2/4 on microglia to activate the nuclear factor-κB/signal transducer and activator of transcription 3 (NF κB/STAT3) pathway, leading to the upregulation of inflammatory factors. These inflammatory factors then induce pathological changes related to brain aging and neurodegeneration (Zhang et al., 2018; Qiu et al., 2021).

Systemic inflammation

Oral microbes can also trigger systemic inflammation by entering the circulatory system and inducing the body's immune defense, resulting in the upregulation of various inflammatory factors, induction of systemic inflammatory responses, and nervous system damage. Numerous oral pathogens can cause systemic inflammation and immune responses in the body, as summarized in the review of Li et al. (2022). In the serum of patients with AD, IgG levels against a series of oral microorganisms were elevated, suggesting that the body's immune response to oral microorganisms is involved in the development of neurodegeneration (Kamer et al., 2009; Sparks Stein et al., 2012; Noble et al., 2014; Laugisch et al., 2018; Beydoun et al., 2020, 2021). Peripheral inflammatory factors can enter the brain through the BBB or CVOs, and then bind to the corresponding inflammatory factor receptors on cerebral vascular endothelial cells, neurons, and glial cells, thus aggravating neuroinflammation (Sisó et al., 2010). For example, *Porphyromonas gingivalis* infection increased serum levels of IL-17A in R1441G mice

(an animal model of PD), and upregulated expression of the IL-17A receptor in the brain, thereby triggering dopaminergic neuron damage in the substantia nigra (Feng et al., 2020). *Porphyromonas gingivalis* also aggravates disease severity in MS mice, possibly by promoting the proliferation of lymphocytes and triggering systemic proinflammatory responses (Polak et al., 2018). In addition, oral microorganisms can secrete outer membrane vesicles, which encase several key virulence factors (LPS, gingipains, and fimbriae), to promote systemic inflammatory responses and the progression of neurodegenerative diseases (Singhrao and Olsen, 2018).

Cerebrovascular destruction

Cerebrovascular injury and dysfunction are crucial factors contributing to brain aging and neurodegeneration (Sweeney et al., 2018; Yang et al., 2022). Oral microorganisms and their toxic products secreted into the blood can destroy cerebral vessels and increase permeability of the BBB, thus aggravating damage to the nervous system (Navarathna et al., 2013; Wang et al., 2017). Upregulation of matrix metalloproteinase expression in vascular endothelial cells is one mechanism through which bacterial LPS can increase BBB permeability and dysfunction (You et al., 2019). In addition, the systemic inflammatory state induced by oral microorganisms will exacerbate cerebral vessel damage. In a mouse model of periodontitis, elevated serum IL-6 was associated with BBB destruction, hippocampal neuroinflammation, and cognitive impairment (Furutama et al., 2020). Once the destruction of cerebral vessels is underway, circulating pathogens and inflammatory substances can easily enter the brain and aggravate neurodegeneration.

CatB upregulation

CatB is a lysosome-localized cysteine protease expressed in microglia and neuronal cells of the brain. The upregulation of CatB in various neurodegenerative diseases has led to its proposal as a potential therapeutic target (Hook et al., 2022). In the context of aging only, exposure to Pg-LPS significantly increased CatB expression in microglia and neurons of middle-aged WT mice, accompanied by neuronal accumulation of Aβ and learning and memory deficits. Furthermore, Pg-LPS upregulated the expression of IL-1β and Toll-like receptor 2 in hippocampal microglia in a CatB-dependent manner, thus promoting neuroinflammation and pathological changes. Conversely, deletion of *CTSB*, the gene encoding CatB, rescued these neuropathological and behavioral changes (Wu et al., 2017). *Porphyromonas gingivalis* infection may also activate the CatB/NF-κB signaling pathway and induce Aβ accumulation in inflammatory monocytes/macrophages, thus increasing the circulating pool of Aβ and promoting neurodegeneration (Nie et al., 2019). These data suggest that CatB may be instrumental in oral microbiome-promoting neurodegeneration and may be a potential intervention target (Nakanishi et al., 2020).

Intervention in Brain Aging and Neurodegenerative Diseases: from the Perspective of Oral Microbes

Antibiotics

Various oral pathogens are associated with the progression of brain aging and neurodegeneration. Therefore, the simplest therapeutic strategy would be to use antibiotics to inhibit these pathogens, so as to mitigate or delay brain aging and neurodegeneration. Relative to standard feeding regimens, pathological changes in the AD11 mouse model of AD, including Aβ deposition, tau hyperphosphorylation, microgliosis, and impaired memory function, were lessened under pathogen-free feeding conditions (Capsoni et al., 2012; Tzanoulinou et al., 2014). The effect of antibiotics was also assessed in a randomized controlled trial, where 101 patients with AD took doxycycline (200 mg/d) and rifampicin (300 mg/d) orally for 3 months. The group of AD patients that received the antibiotics was associated with less dysfunctional behavior at the third month, and less cognitive decline at the sixth month (Loeb et al., 2004). However, in another randomized controlled clinical trial with 460 AD patients treated with doxycycline (200 mg/d) and/or rifampicin (300 mg/d) orally for 12 months, there was no evidence of lessened cognitive or functional decline in patients with AD (Molloy et al., 2013). Other antibiotics, such as ceftriaxone, are being studied for their role in patients with PD dementia in clinical trials (https://clinicaltrials.gov/; **Table 1**). None of these studies examined changes in oral microbiota following antibiotic use. However, the effect of doxycycline on oral microorganisms has been reported, demonstrating that the application of doxycycline significantly reduced the periodontal pathogens *Porphyromonas gingivalis* and *Tannerella forsythia* (Shaddox et al., 2007), and affected the proportions of the genera *Streptococcus* and *Actinomyces* (Feres et al., 1999). Nevertheless, whether antibiotics affect brain aging through influencing oral microbes requires further clarification. In addition, long-term use of antibiotics has problematic side effects, such as dysbacteriosis and antibiotic resistance, which pose significant risks to patients.

Probiotics

Given drawbacks of long-term antibiotic use, probiotics have been proposed as a complementary intervention strategy to stably balance the bacterial flora. Current probiotics are predominantly aimed at regulating the intestinal flora, but also have regulatory effects on the oral flora and promotion of oral health (Chuang et al., 2011; Gruner et al., 2016; Jørgensen et al., 2017; Oliveira et al., 2017). Moreover, the effect of probiotic intervention on brain aging and neurodegeneration has been reported in animal models and clinical trials. In AD mice, oral probiotics restored glucose homeostasis, reduced the accumulation of phosphorylated tau, improved memory function, and slowed disease progression (Bonfili et al., 2020). Similarly, administration of *Bifidobacterium bifidum* BGN4 and *Bifidobacterium longum* BORI in AD mice effectively inhibited amyloidosis and apoptosis, ameliorated neuroinflammatory responses, and by upregulating brain-derived neurotrophic factor expression, improved synaptic plasticity, thereby reducing cognitive and memory impairment (Kim et al., 2021b). In a randomized controlled clinical trial, oral administration of *Bifidobacterium bifidum* BGN4 and *Bifidobacterium longum* BORI for 12 weeks significantly improved the cognitive function and mood of healthy elderly people (Kim et al., 2021a). In another randomized controlled clinical trial involving 60 patients with AD, the intervention group received a mixture of probiotics orally for 12 weeks, which included *Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifidobacterium bifidum*, and *Lactobacillus fermentum*. Administration of these probiotics improved the cognitive function and metabolic status of the patients with AD (Akbari et al., 2016). Several other clinical trials of probiotics are ongoing, but the results have not yet been reported (**Table 1**). Furthermore, although the above studies demonstrated the regulatory effect of probiotics on intestinal flora, changes in the oral flora were not explored (Bonfili et al., 2020; Kim et al., 2021a, b). Therefore, whether probiotics ameliorate brain aging by regulating oral flora still needs verifying.

Table 1 | **Clinical trials on the intervention of brain aging and neurodegenerative diseases from the perspective of oral microbes**

Interventions	Participants	Results	Reference or trial No.
Antibiotics			
Doxycycline (200 mg/d) + rifampicin (300 mg/d), for 3 mon	Patients with probable AD and mild to moderate dementia (*n* = 101)*	• Reduce dysfunctional behavior at third month • Improve cognitive decline at sixth month	Loeb et al., 2004
Doxycycline (200 mg/d) and/or rifampicin (300 mg/d), for 12 mon	Patients with mild to moderate AD (*n* = 460)	• No beneficial effects on cognition or function	Molloy et al., 2013
Doxycycline (200 mg/d) and/or rifampicin (300 mg/d), for 12 mon	Probable AD patients (*n* = 100)*	• No results posted	NCT00439166 (Phase III)
Ceftriaxone (1 g/2 d), for 2 wk	Mild to moderate PD dementia (*n* = 106)	• Ongoing, no results posted	NCT03413384 (Phase II)
Probiotics			
Bifidobacterium bifidum BGN4 + *Bifidobacterium longum* BORI, for 12 wk	Healthy elders (≥ 65 yr) (*n* = 63)	• Improve cognitive function and mood • Reduce relative abundance of inflammation-causing gut bacteria • Improvement in mental flexibility test and stress score • Increase serum BDNF level	Kim et al., 2021a
Lactobacillus acidophilus, *Lactobacillus casei*, *Bifidobacterium bifidum*, and *Lactobacillus fermentum* (2×10^9 colony forming unit/g for each), for 12 wk	AD patients (*n* = 60)	• Improvement in the MMSE score • Improvement in the metabolic related markers in blood	NCT05943925 Akbari et al., 2016
Bifidobacterium breve Bv-889, *B. longum* subsp. infantis BLI-02, *B. bifidum* VDD088, *B. animalis* subsp. lactis CP-9, and *Lactobacillus plantarum* PL-02, for 12 wk	Patients with mild to moderate AD (*n* = 40)	• Ongoing, no results posted	NCT05145881
K10 probiotic (2 mL/kg/d), for 90 d	Patients with AD (*n* = 52) or PD (*n* = 52)	• Ongoing, no results posted	NCT06019117 (Phase III)
Bifidobacterium bifidum W23, *B. lactis* W51, *B. lactis* W52, *Lactobacillus* acidophilus W22, *L. casei* W56, *L. paracasei* W20, *L. plantarum* W62, *L. salivarius* W24, and *Lactococcus lactis* W19	Patients with AD dementia (*n* = 58)	• Ongoing, no results posted	NCT03847714
Gingipain inhibitors			
COR388 (160 or 80 mg/d), for 48 wk	Mild to moderate AD dementia (*n* = 643)	• Unable to provide cognitive benefits • Liver toxicity	NCT03823404 (Phase II/III)
COR588	Healthy adult subjects (*n* = 64)	• No results posted	NCT04920903 (Phase I)
Periodontal treatment			
Periodontal treatment + extraction + topic nystatin	Mild AD (*n* = 29)	• Improvement in quality of life • Improvement in functional impairment due to cognitive compromise	Rolim Tde et al., 2014
Periodontal treatment	Mild to moderate AD dementia (*n* = 190)	• Ongoing, no results posted	NCT05183321
Anti-viral therapy			
Valaciclovir (3 g/d), for 4 wk	Patients with AD or mild cognitive impairment of AD type (*n* = 33)	• No results posted	NCT02997982 (Phase II)
Valacyclovir (4 g/d), for 18 mon	Mild AD (*n* = 120)	• Ongoing, no results posted	NCT03282916 (Phase II)

*The National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria. AD: Alzheimer's disease; BDNF: brain-derived neurotrophic factor; *B. longum*: *Bifidobacterium longum*; *B. bifidum*: *Bifidobacterium bifidum*; *B.* animalis: *Bifidobacterium animalis*; *B. lactis*: *Bifidobacterium lactis*; *L. casei*: *Lactobacillus casei*; *L. paracasei*: *Lactobacillus paracasei*; *L. plantarum*: *Lactobacillus plantarum*; *L. salivarius*: *Lactobacillus salivarius*; MMSE: Mini-mental state examination; PD: Parkinson's disease.

Targeting microbial virulence factors

Targeting bacterial virulence factors is another potential intervention strategy, with gingipain—the key virulence factor of *Porphyromonas gingivalis*—receiving the most attention. Gingipain promotes brain inflammation and neurodegeneration in animal studies (Liu et al., 2017; Ilievski et al., 2018) and has been detected in the brain tissues of more than 90% of patients with AD, exhibiting positive correlation with AD pathology, such as tau load and ubiquitin load (Dominy et al., 2019). In the same study, the authors developed gingipain inhibitors, of which COR388—an orally bioavailable, brain-penetrant small-molecule—significantly reduced intracerebral *Porphyromonas gingivalis* load, $A\beta_{1-42}$ deposition, tumor necrosis factor-α upregulation, and loss of hippocampal glutamate decarboxylase-67-positive interneurons when administered to *Porphyromonas gingivalis*-infected mice (Dominy et al., 2019). A subsequent clinical phase II/III study of COR388 in subjects with AD (**Table 1**; Detke, 2021) was discontinued due to liver toxicity and a lack of evidence of significant cognitive benefits. A second-generation version of this drug with improved safety and pharmacological characteristics, COR588, has been developed and completed phase I clinical trials (**Table 1**). The efficacy and safety of COR588 need to be further studied and confirmed.

Periodontal treatment

Periodontitis is caused by a combination of multiple oral pathogens, not by a single pathogen. Therefore, periodontal systemic therapy, including supragingival scaling, subgingival scaling and root planing, and subsequent maintenance treatment, may represent a broader and more effective approach

to ameliorating the comorbidities associated with periodontitis (compared with targeting specific bacteria or their products). In a long-term observational cross-trial comparison (median = 7.3 years), brain atrophy was significantly alleviated in a group of 177 patients with periodontitis who received periodontal treatment compared with a second group of 409 individuals who did not receive periodontal treatment (Schwahn et al., 2022). Similarly, in patients with mild AD, dental treatments (including periodontal treatments, extractions, and topic nystatin) improved periodontal indices and patient quality of life. The dental treatment was considered to reduce comorbidities associated with AD and was suggested for routine inclusion in patient management (Rolim Tde et al., 2014). In a nested case-control study, prevention and treatment of periodontitis with dental scaling reduced the risk of PD in individuals aged 40 to 69 years, regardless of whether the individual had periodontitis at the time of onset (Chen et al., 2018). A randomized controlled study to evaluate the effect of periodontal treatment in individuals with a clinical diagnosis of mild to moderate AD dementia is ongoing (**Table 1**) and should provide additional insights.

Anti-viral therapy

In addition to oral bacteria, oral viruses are involved in brain aging and neurodegeneration, with the most representative of such viruses being HSV1. HSV1 exhibited an age-related increase in brain tissue and CSF and was closely related to the deposition of amyloid plaques (Jamieson et al., 1992; Wozniak et al., 2005, 2009). These results suggest that anti-viral therapy may be a potential strategy for delaying brain aging and neurodegenerative diseases. Several clinical trials have been approved to investigate the effects of anti-viral drugs in individuals with mild AD or mild cognitive impairment (**Table 1**), but no results have been reported to date.

Limitations

This review possesses several limitations. First, the literature search was restricted to the PubMed database. In subsequent research, incorporating additional databases such as Embase and Cochrane Library would achieve a more comprehensive collection of data. Second, the inclusion of articles was limited to those published in the English language, potentially excluding pertinent international data. Finally, numerous ongoing clinical studies have not yet reported their findings, and updating these results in the future would enhance understanding of the association between oral microbes and brain aging.

Conclusions

The association between oral microbiota and brain aging and neurodegeneration is well documented in the literature, prompting new requirements for the health management of the elderly or patients with neurodegenerative diseases. Conducting oral health education and helping the elderly or patients with neurodegenerative diseases adhere to oral health management is crucial, highlighting the instrumental role of dentists in this population. Although achieving these goals in the elderly or cognitively impaired patients can be challenging, it has critical implications for preserving dental health and improving overall health, including in patients with neurological disorders.

Despite the reported research findings, some issues still need resolving. Current clinical evidence is mainly from cross-sectional studies that show an association between oral microbes and brain aging and neurodegeneration, but a causal relationship has not yet been conclusively demonstrated. Additional high-quality cohort studies and rigorously designed biological research experiments are needed to validate the existence of a causal relationship and provide a basis for exploring underlying mechanisms. Specifically, how oral microorganisms enter the brain and the mechanism(s) they use in promoting brain aging and neurodegeneration are outstanding scientific questions that need to be answered in future studies. The role and mechanism of *Porphyromonas gingivalis* have been widely studied; however, whether HSV1 and *Candida albicans*, and other common oral microorganisms, promote the progression of brain aging and neurodegeneration remains to be elucidated. Although the results of epidemiological and animal studies have provided new insights and strategies for the clinical treatment of brain aging and neurodegeneration, effective and safe results have not yet been obtained. Additional high-quality randomized controlled clinical trials are needed to demonstrate the efficacy and safety of intervention approaches.

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References

Abusleme L, Hoare A, Hong BY, Diaz PI (2021) Microbial signatures of health, gingivitis, and periodontitis. Periodontol 2000 86:57-78.
Abyadeh M, Gupta V, Paulo JA, Mahmoudabad AG, Shadfar S, Mirshahvaladi S, Gupta V, Nguyen CTO, Finkelstein DI, You Y, Haynes PA, Salekdeh GH, Graham SL, Mirzaei M (2024) Amyloid-beta and tau protein beyond Alzheimer's disease. Neural Regen Res 19:1262-1276.
Aging Biomarker Consortium, et al. (2023a) A framework of biomarkers for brain aging: a consensus statement by the aging biomarker consortium. Life Med 2:1-12.
Aging Biomarker Consortium, et al. (2023b) Biomarkers of aging. Sci China Life Sci 66:893-1066.
Akbari E, Asemi Z, Daneshvar Kakhaki R, Bahmani F, Kouchaki E, Tamtaji OR, Hamidi GA, Salami M (2016) Effect of probiotic supplementation on cognitive function and metabolic status in Alzheimer's disease: a randomized, double-blind and controlled trial. Front Aging Neurosci 8:256.
Alonso R, Pisa D, Rábano A, Carrasco L (2014a) Alzheimer's disease and disseminated mycoses. Eur J Clin Microbiol Infect Dis 33:1125-1132.
Alonso R, Pisa D, Marina AI, Morato E, Rábano A, Carrasco L (2014b) Fungal infection in patients with Alzheimer's disease. J Alzheimers Dis 41:301-311.
Angelini DF, Serafini B, Piras E, Severa M, Coccia EM, Rosicarelli B, Ruggieri S, Gasperini C, Buttari F, Centonze D, Mechelli R, Salvetti M, Borsellino G, Aloisi F, Battistini L (2013) Increased CD8+ T cell response to Epstein-Barr virus lytic antigens in the active phase of multiple sclerosis. PLoS Pathog 9:e1003220.
Aragón F, Zea-Sevilla MA, Montero J, Sancho P, Corral R, Tejedor C, Frades-Payo B, Paredes-Gallardo V, Albaladejo A (2018) Oral health in Alzheimer's disease: a multicenter case-control study. Clin Oral Investig 22:3061-3070.
Bahar B, Kanagasingam S, Tambuwala MM, Aljabali AAA, Dillon SA, Doaei S, Welbury R, Chukkapalli SS, Singhrao SK (2021) Porphyromonas gingivalis (W83) Infection induces Alzheimer's disease-like pathophysiology in obese and diabetic mice. J Alzheimers Dis 82:1259-1275.
Balaj AR, Kaku H (2024) A novel approach to Parkinson's disease treatment with a potentially dual-acting therapeutic agent that targets α-synuclein aggregation and neuron death. Neural Regen Res 19:2577-2578.
Beydoun MA, Beydoun HA, Hossain S, El-Hajj ZW, Weiss J, Zonderman AB (2020) Clinical and bacterial markers of periodontitis and their association with incident all-cause and Alzheimer's disease dementia in a large national survey. J Alzheimers Dis 75:157-172.

Beydoun MA, Beydoun HA, Weiss J, Hossain S, El-Hajj ZW, Zonderman AB (2021) Helicobacter pylori, periodontal pathogens, and their interactive association with incident all-cause and Alzheimer's disease dementia in a large national survey. Mol Psychiatry 26:6038-6053.

Bonfili L, Cecarini V, Gogoi O, Berardi S, Scarpona S, Angeletti M, Rossi G, Eleuteri AM (2020) Gut microbiota manipulation through probiotics oral administration restores glucose homeostasis in a mouse model of Alzheimer's disease. Neurobiol Aging 87:35-43.

Bowman GL, Dayon L, Kirkland R, Wojcik J, Peyratout G, Severin IC, Henry H, Oikonomidi A, Migliavacca E, Bacher M, Popp J (2018) Blood-brain barrier breakdown, neuroinflammation, and cognitive decline in older adults. Alzheimers Dement 14:1640-1650.

Cai Y, et al. (2022) The landscape of aging. Sci China Life Sci 65:2354-2454.

Capsoni S, Carucci NM, Cattaneo A (2012) Pathogen free conditions slow the onset of neurodegeneration in a mouse model of nerve growth factor deprivation. J Alzheimers Dis 31:1-6.

Carbone I, Lazzarotto T, Ianni M, Porcellini E, Forti P, Masliah E, Gabrielli L, Licastro F (2014) Herpes virus in Alzheimer's disease: relation to progression of the disease. Neurobiol Aging 35:122-129.

Chen CK, Wu YT, Chang YC (2017a) Periodontal inflammatory disease is associated with the risk of Parkinson's disease: a population-based retrospective matched-cohort study. PeerJ 5:e3647.

Chen CK, Wu YT, Chang YC (2017b) Association between chronic periodontitis and the risk of Alzheimer's disease: a retrospective, population-based, matched-cohort study. Alzheimers Res Ther 9:56.

Chen CK, Huang JY, Wu YT, Chang YC (2018) Dental scaling decreases the risk of Parkinson's disease: a nationwide population-based nested case-control study. Int J Environ Res Public Health 15:1587.

Chu D, Yang X, Wang J, Zhou Y, Gu JH, Miao J, Wu F, Liu F (2024) Tau truncation in the pathogenesis of Alzheimer's disease: a narrative review. Neural Regen Res 19:1221-1232.

Chuang LC, Huang CS, Ou-Yang LW, Lin SY (2011) Probiotic Lactobacillus paracasei effect on cariogenic bacterial flora. Clin Oral Investig 15:471-476.

Cunningham C, Campion S, Lunnon K, Murray CL, Woods JF, Deacon RM, Rawlins JN, Perry VH (2009) Systemic inflammation induces acute behavioral and cognitive changes and accelerates neurodegenerative disease. Biol Psychiatry 65:304-312.

Czerniawski J, Miyashita T, Lewandowski G, Guzowski JF (2015) Systemic lipopolysaccharide administration impairs retrieval of context-object discrimination, but not spatial, memory: evidence for selective disruption of specific hippocampus-dependent memory functions during acute neuroinflammation. Brain Behav Immun 44:159-166.

Danielyan L, Schäfer R, von Ameln-Mayerhofer A, Buadze M, Geisler J, Klopfer T, Burkhardt U, Proksch B, Verleysdonk S, Ayturan M, Buniatian GH, Gleiter CH, Frey WH, 2nd (2009) Intranasal delivery of cells to the brain. Eur J Cell Biol 88:315-324.

DeJong EN, Surette MG, Bowdish DME (2020) The gut microbiota and unhealthy aging: disentangling cause from consequence. Cell Host Microbe 28:180-189.

Detke M (2021) An update and baseline data from the phase 2/3 GAIN trial of COR388 (atuzaginstat), a novel bacterial virulence factor inhibitor for the treatment of Alzheimer's disease. Alzheimers Dement 17:e050624.

Díaz-Zúñiga J, Muñoz Y, Melgar-Rodríguez S, More J, Bruna B, Lobos P, Monasterio G, Vernal R, Paula-Lima A (2019) Serotype b of Aggregatibacter actinomycetemcomitans triggers pro-inflammatory responses and amyloid beta secretion in hippocampal cells: a novel link between periodontitis and Alzheimer´s disease? J Oral Microbiol 11:1586423.

Díaz-Zúñiga J, More J, Melgar-Rodríguez S, Jiménez-Unión M, Villalobos-Orchard F, Muñoz-Manríquez C, Monasterio G, Valdés JL, Vernal R, Paula-Lima A (2020) Alzheimer's disease-like pathology triggered by porphyromonas gingivalis in wild type rats is serotype dependent. Front Immunol 11:588036.

Dominy SS, et al. (2019) Porphyromonas gingivalis in Alzheimer's disease brains: Evidence for disease causation and treatment with small-molecule inhibitors. Sci Adv 5:eaau3333.

Eke PI, Borgnakke WS, Genco RJ (2020) Recent epidemiologic trends in periodontitis in the USA. Periodontol 2000 82:257-267.

Ellefsen B, Holm-Pedersen P, Morse DE, Schroll M, Andersen BB, Waldemar G (2008) Caries prevalence in older persons with and without dementia. J Am Geriatr Soc 56:59-67.

Emery DC, Shoemark DK, Batstone TE, Waterfall CM, Coghill JA, Cerajewska TL, Davies M, West NX, Allen SJ (2017) 16S rRNA next generation sequencing analysis shows bacteria in Alzheimer's post-mortem brain. Front Aging Neurosci 9:195.

Feng YK, Wu QL, Peng YW, Liang FY, You HJ, Feng YW, Li G, Li XJ, Liu SH, Li YC, Zhang Y, Pei Z (2020) Oral P. gingivalis impairs gut permeability and mediates immune responses associated with neurodegeneration in LRRK2 R1441G mice. J Neuroinflammation 17:347.

Feres M, Haffajee AD, Goncalves C, Allard KA, Som S, Smith C, Goodson JM, Socransky SS (1999) Systemic doxycycline administration in the treatment of periodontal infections (I). Effect on the subgingival microbiota. J Clin Periodontol 26:775-783.

Filippi M, Bar-Or A, Piehl F, Preziosa P, Solari A, Vukusic S, Rocca MA (2018) Multiple sclerosis. Nat Rev Dis Primers 4:43.

Furutama D, Matsuda S, Yamawaki Y, Hatano S, Okanobu A, Memida T, Oue H, Fujita T, Ouhara K, Kajiya M, Mizuno N, Kanematsu T, Tsuga K, Kurihara H (2020) IL-6 induced by periodontal inflammation causes neuroinflammation and disrupts the blood-brain barrier. Brain Sci 10:679.

Gao L, Xu T, Huang G, Jiang S, Gu Y, Chen F (2018) Oral microbiomes: more and more importance in oral cavity and whole body. Protein Cell 9:488-500.

Gorbunova V, Seluanov A, Mita P, McKerrow W, Fenyö D, Boeke JD, Linker SB, Gage FH, Kreiling JA, Petrashen AP, Woodham TA, Taylor JR, Helfand SL, Sedivy JM (2021) The role of retrotransposable elements in ageing and age-associated diseases. Nature 596:43-53.

Gruner D, Paris S, Schwendicke F (2016) Probiotics for managing caries and periodontitis: systematic review and meta-analysis. J Dent 48:16-25.

Gu Y, Wu Z, Zeng F, Jiang M, Teeling JL, Ni J, Takahashi I (2020) Systemic exposure to lipopolysaccharide from porphyromonas gingivalis induces bone loss-correlated Alzheimer's disease-like pathologies in middle-aged mice. J Alzheimers Dis 78:61-74.

Hahn O, Foltz AG, Atkins M, Kedir B, Moran-Losada P, Guldner IH, Munson C, Kern F, Pálovics R, Lu N, Zhang H, Kaur A, Hull J, Huguenard JR, Grönke S, Lehallier B, Partridge L, Keller A, Wyss-Coray T (2023) Atlas of the aging mouse brain reveals white matter as vulnerable foci. Cell 186:4117-4133. e22.

Hajishengallis G, Chavakis T (2021) Local and systemic mechanisms linking periodontal disease and inflammatory comorbidities. Nat Rev Immunol 21:426-440.

Harding A, Gonder U, Robinson SJ, Crean S, Singhrao SK (2017) Exploring the association between Alzheimer's disease, oral health, microbial endocrinology and nutrition. Front Aging Neurosci 9:398.

Hatipoglu H, Canbaz Kabay S, Gungor Hatipoglu M, Ozden H (2016) Expanded disability status scale-based disability and dental-periodontal conditions in patients with multiple sclerosis. Med Princ Pract 25:49-55.

Hook G, Reinheckel T, Ni J, Wu Z, Kindy M, Peters C, Hook V (2022) Cathepsin B gene knockout improves behavioral deficits and reduces pathology in models of neurologic disorders. Pharmacol Rev 74:600-629.

Horowitz M, Horowitz M, Ochs M, Carrau R, Kassam A (2004) Trigeminal neuralgia and glossopharyngeal neuralgia: two orofacial pain syndromes encountered by dentists. J Am Dent Assoc 135:1427-1433; quiz 1468.

Hu Y, Li H, Zhang J, Zhang X, Xia X, Qiu C, Liao Y, Chen H, Song Z, Zhou W (2020) Periodontitis induced by P. gingivalis-LPS is associated with neuroinflammation and learning and memory impairment in Sprague-Dawley rats. Front Neurosci 14:658.

Ide M, Harris M, Stevens A, Sussams R, Hopkins V, Culliford D, Fuller J, Ibbett P, Raybould R, Thomas R, Puenter U, Teeling J, Perry VH, Holmes C (2016) Periodontitis and cognitive decline in Alzheimer's disease. PLoS One 11:e0151081.

Ilievski V, Zuchowska PK, Green SJ, Toth PT, Ragozzino ME, Le K, Aljewari HW, O'Brien-Simpson NM, Reynolds EC, Watanabe K (2018) Chronic oral application of a periodontal pathogen results in brain inflammation, neurodegeneration and amyloid beta production in wild type mice. PLoS One 13:e0204941.

Jamieson GA, Maitland NJ, Wilcock GK, Yates CM, Itzhaki RF (1992) Herpes simplex virus type 1 DNA is present in specific regions of brain from aged people with and without senile dementia of the Alzheimer type. J Pathol 167:365-368.

Jeong E, Park JB, Park YG (2021) Evaluation of the association between periodontitis and risk of Parkinson's disease: a nationwide retrospective cohort study. Sci Rep 11:16594.

Jiang M, Zhang X, Yan X, Mizutani S, Kashiwazaki H, Ni J, Wu Z (2021) GSK3β is involved in promoting Alzheimer's disease pathologies following chronic systemic exposure to Porphyromonas gingivalis lipopolysaccharide in amyloid precursor protein(NL-F/NL-F) knock-in mice. Brain Behav Immun 98:1-12.

Jordan RA, Krois J, Schiffner U, Micheelis W, Schwendicke F (2019) Trends in caries experience in the permanent dentition in Germany 1997-2014, and projection to 2030: Morbidity shifts in an aging society. Sci Rep 9:5534.

Jørgensen MR, Kragelund C, Jensen P, Keller MK, Twetman S (2017) Probiotic Lactobacillus reuteri has antifungal effects on oral Candida species in vitro. J Oral Microbiol 9:1274582.

Jungbauer G, Stähli A, Zhu X, Auber Alberi L, Sculean A, Eick S (2022) Periodontal microorganisms and Alzheimer disease- A causative relationship? Periodontol 2000 89:59-82.

Kamer AR, Craig RG, Pirraglia E, Dasanayake AP, Norman RG, Boylan RJ, Nehorayoff A, Glodzik L, Brys M, de Leon MJ (2009) TNF-alpha and antibodies to periodontal bacteria discriminate between Alzheimer's disease patients and normal subjects. J Neuroimmunol 216:92-97.

Kazarina A, Kuzmicka J, Bortkevica S, Zayakin P, Kimsis J, Igumnova V, Sadovska D, Freimane L, Kivrane A, Namina A, Capligina V, Poksane A, Ranka R (2023) Oral microbiome variations related to ageing: possible implications beyond oral health. Arch Microbiol 205:116.

Kim CS, Cha L, Sim M, Jung S, Chun WY, Baik HW, Shin DM (2021a) Probiotic supplementation improves cognitive function and mood with changes in gut microbiota in community-dwelling older adults: a randomized, double-blind, placebo-controlled, multicenter trial. J Gerontol A Biol Sci Med Sci 76:32-40.

Kim H, Kim S, Park SJ, Park G, Shin H, Park MS, Kim J (2021b) Administration of Bifidobacterium bifidum BGN4 and Bifidobacterium longum BORI improves cognitive and memory function in the mouse model of Alzheimer's disease. Front Aging Neurosci 13:709091.

Kim JM, Stewart R, Prince M, Kim SW, Yang SJ, Shin IS, Yoon JS (2007) Dental health, nutritional status and recent-onset dementia in a Korean community population. Int J Geriatr Psychiatry 22:850-855.

Laugisch O, Johnen A, Maldonado A, Ehmke B, Bürgin W, Olsen I, Potempa J, Sculean A, Duning T, Eick S (2018) Periodontal pathogens and associated intrathecal antibodies in early stages of Alzheimer's disease. J Alzheimers Dis 66:105-114.

Lee JW, Lee YK, Yuk DY, Choi DY, Ban SB, Oh KW, Hong JT (2008) Neuro-inflammation induced by lipopolysaccharide causes cognitive impairment through enhancement of beta-amyloid generation. J Neuroinflammation 5:37.

Leng F, Edison P (2021) Neuroinflammation and microglial activation in Alzheimer disease: where do we go from here? Nat Rev Neurol 17:157-172.

Letenneur L, Pérès K, Fleury H, Garrigue I, Barberger-Gateau P, Helmer C, Orgogozo JM, Gauthier S, Dartigues JF (2008) Seropositivity to herpes simplex virus antibodies and risk of Alzheimer's disease: a population-based cohort study. PLoS One 3:e3637.

Li X, Kiprowska M, Kansara T, Kansara P, Li P (2022) Neuroinflammation: a distal consequence of periodontitis. J Dent Res 101:1441-1449.

Lin WR, Wozniak MA, Cooper RJ, Wilcock GK, Itzhaki RF (2002) Herpesviruses in brain and Alzheimer's disease. J Pathol 197:395-402.

Liu J, Wang Y, Guo J, Sun J, Sun Q (2020a) Salvianolic Acid B improves cognitive impairment by inhibiting neuroinflammation and decreasing Aβ level in Porphyromonas gingivalis-infected mice. Aging (Albany NY) 12:10117-10128.

Liu S, Wang Y, Zhao L, Sun X, Feng Q (2020b) Microbiome succession with increasing age in three oral sites. Aging (Albany NY) 12:7874-7907.

Liu Y, Wu Z, Nakanishi Y, Ni J, Hayashi Y, Takayama F, Zhou Y, Kadowaki T, Nakanishi H (2017) Infection of microglia with Porphyromonas gingivalis promotes cell migration and an inflammatory response through the gingipain-mediated activation of protease-activated receptor-2 in mice. Sci Rep 7:11759.

Lobmaier IV, Vege A, Gaustad P, Rognum TO (2009) Bacteriological investigation--significance of time lapse after death. Eur J Clin Microbiol Infect Dis 28:1191-1198.

Loeb MB, Molloy DW, Smieja M, Standish T, Goldsmith CH, Mahony J, Smith S, Borrie M, Decoteau E, Davidson W, McDougall A, Gnarpe J, O'D OM, Chernesky M (2004) A randomized, controlled trial of doxycycline and rifampin for patients with Alzheimer's disease. J Am Geriatr Soc 52:381-387.

López-Otín C, Kroemer G (2021) Hallmarks of Health. Cell 184:33-63.

López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G (2013) The hallmarks of aging. Cell 153:1194-1217.

López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G (2023) Hallmarks of aging: an expanding universe. Cell 186:243-278.

Marcocci ME, Napoletani G, Protto V, Kolesova O, Piacentini R, Li Puma DD, Lomonte P, Grassi C, Palamara AT, De Chiara G (2020) Herpes simplex virus-1 in the brain: the dark side of a sneaky infection. Trends Microbiol 28:808-820.

Martande SS, Pradeep AR, Singh SP, Kumari M, Suke DK, Raju AP, Naik SB, Singh P, Guruprasad CN, Chatterji A (2014) Periodontal health condition in patients with Alzheimer's disease. Am J Alzheimers Dis Other Demen 29:498-502.

Martino C, Dilmore AH, Burcham ZM, Metcalf JL, Jeste D, Knight R (2022) Microbiota succession throughout life from the cradle to the grave. Nat Rev Microbiol 20:707-720.

Mattson MP, Arumugam TV (2018) Hallmarks of brain aging: adaptive and pathological modification by metabolic states. Cell Metab 27:1176-1199.

Miklossy J (2011) Alzheimer's disease- a neurospirochetosis. Analysis of the evidence following Koch's and Hill's criteria. J Neuroinflammation 8:90.

Molloy DW, Standish TI, Zhou Q, Guyatt G (2013) A multicenter, blinded, randomized, factorial controlled trial of doxycycline and rifampin for treatment of Alzheimer's disease: the DARAD trial. Int J Geriatr Psychiatry 28:463-470.

Montagne A, Barnes SR, Sweeney MD, Halliday MR, Sagare AP, Zhao Z, Toga AW, Jacobs RE, Liu CY, Amezcua L, Harrington MG, Chui HC, Law M, Zlokovic BV (2015) Blood-brain barrier breakdown in the aging human hippocampus. Neuron 85:296-302.

Nakanishi H, Nonaka S, Wu Z (2020) Microglial Cathepsin B and Porphyromonas gingivalis gingipains as potential therapeutic targets for Sporadic Alzheimer's disease. CNS Neurol Disord Drug Targets 19:495-502.

Navarathna DH, Munasinghe J, Lizak MJ, Nayak D, McGavern DB, Roberts DD (2013) MRI confirms loss of blood-brain barrier integrity in a mouse model of disseminated candidiasis. NMR Biomed 26:1125-1134.

Nemergut M, Batkova T, Vigasova D, Bartos M, Hlozankova M, Schenkmayerova A, Liskova B, Sheardova K, Vyhnalek M, Hort J, Laczó J, Kovacova I, Sitina M, Matej R, Jancalek R, Marek M, Damborsky J (2022) Increased occurrence of Treponema spp. and double-species infections in patients with Alzheimer's disease. Sci Total Environ 844:157114.

Nie R, Wu Z, Ni J, Zeng F, Yu W, Zhang Y, Kadowaki T, Kashiwazaki H, Teeling JL, Zhou Y (2019) Porphyromonas gingivalis infection induces amyloid-β accumulation in monocytes/macrophages. J Alzheimers Dis 72:479-494.

Noble JM, Scarmeas N, Celenti RS, Elkind MS, Wright CB, Schupf N, Papapanou PN (2014) Serum IgG antibody levels to periodontal microbiota are associated with incident Alzheimer disease. PLoS One 9:e114959.

Oliveira LF, Salvador SL, Silva PH, Furlaneto FA, Figueiredo L, Casarin R, Ervolino E, Palioto DB, Souza SL, Taba M, Jr., Novaes AB, Jr., Messora MR (2017) Benefits of Bifidobacterium animalis subsp. lactis Probiotic in Experimental Periodontitis. J Periodontol 88:197-208.

Olsen I (2008) Update on bacteraemia related to dental procedures. Transfus Apher Sci 39:173-178.

Patel S, Howard D, Chowdhury N, Derieux C, Wellslager B, Yilmaz Ö, French L (2021) Characterization of human genes modulated by porphyromonas gingivalis highlights the ribosome, hypothalamus, and cholinergic neurons. Front Immunol 12:646259.

Pisa D, Alonso R, Juarranz A, Rábano A, Carrasco L (2015) Direct visualization of fungal infection in brains from patients with Alzheimer's disease. J Alzheimers Dis 43:613-624.

Pitts NB, Zero DT, Marsh PD, Ekstrand K, Weintraub JA, Ramos-Gomez F, Tagami J, Twetman S, Tsakos G, Ismail A (2017) Dental caries. Nat Rev Dis Primers 3:17030.

Poewe W, Seppi K, Tanner CM, Halliday GM, Brundin P, Volkmann J, Schrag AE, Lang AE (2017) Parkinson disease. Nat Rev Dis Primers 3:17013.

Polak D, Shmueli A, Brenner T, Shapira L (2018) Oral infection with P. gingivalis exacerbates autoimmune encephalomyelitis. J Periodontol 89:1461-1466.

Poole S, Singhrao SK, Kesavalu L, Curtis MA, Crean S (2013) Determining the presence of periodontopathic virulence factors in short-term postmortem Alzheimer's disease brain tissue. J Alzheimers Dis 36:665-677.

Poole S, Singhrao SK, Chukkapalli S, Rivera M, Velsko I, Kesavalu L, Crean S (2015) Active invasion of Porphyromonas gingivalis and infection-induced complement activation in ApoE-/- mice brains. J Alzheimers Dis 43:67-80.

Qiu C, Yuan Z, He Z, Chen H, Liao Y, Li S, Zhou W, Song Z (2021) Lipopolysaccharide preparation derived from porphyromonas gingivalis induces a weaker immuno-inflammatory response in BV-2 microglial cells than escherichia coli by differentially activating TLR2/4-mediated NF-κB/STAT3 signaling pathways. Front Cell Infect Microbiol 11:606986.

Readhead B, Haure-Mirande JV, Funk CC, Richards MA, Shannon P, Haroutunian V, Sano M, Liang WS, Beckmann ND, Price ND, Reiman EM, Schadt EE, Ehrlich ME, Gandy S, Dudley JT (2018) Multiscale analysis of independent Alzheimer's cohorts finds disruption of molecular, genetic, and clinical networks by human herpesvirus. Neuron 99:64-82.e7.

Riviere GR, Riviere KH, Smith KS (2002) Molecular and immunological evidence of oral Treponema in the human brain and their association with Alzheimer's disease. Oral Microbiol Immunol 17:113-118.
Robbins M (2023) Therapies for Tau-associated neurodegenerative disorders: targeting molecules, synapses, and cells. Neural Regen Res 18:2633-2637.
Rolim Tde S, Fabri GM, Nitrini R, Anghinah R, Teixeira MJ, Siqueira JT, Cesari JA, Siqueira SR (2014) Evaluation of patients with Alzheimer's disease before and after dental treatment. Arq Neuropsiquiatr 72:919-924.
Scheltens P, De Strooper B, Kivipelto M, Holstege H, Chételat G, Teunissen CE, Cummings J, van der Flier WM (2021) Alzheimer's disease. Lancet 397:1577-1590.
Schwahn C, Frenzel S, Holtfreter B, Van der Auwera S, Pink C, Bülow R, Friedrich N, Völzke H, Biffar R, Kocher T, Grabe HJ, Alzheimer's Disease Neuroimaging Initiative (2022) Effect of periodontal treatment on preclinical Alzheimer's disease-Results of a trial emulation approach. Alzheimers Dement 18:127-141.
Schwartz JL, Peña N, Kawar N, Zhang A, Callahan N, Robles SJ, Griebel A, Adami GR (2021) Old age and other factors associated with salivary microbiome variation. BMC Oral Health 21:490.
Shaddox LM, Andia DC, Casati MZ, Nociti FH, Jr., Sallum EA, Gollwitzer J, Walker CB (2007) Microbiologic changes following administration of locally delivered doxycycline in smokers: a 15-month follow-up. J Periodontol 78:2143-2149.
Shapira L, Ayalon S, Brenner T (2002) Effects of Porphyromonas gingivalis on the central nervous system: activation of glial cells and exacerbation of experimental autoimmune encephalomyelitis. J Periodontol 73:511-516.
Sheu JJ, Lin HC (2013) Association between multiple sclerosis and chronic periodontitis: a population-based pilot study. Eur J Neurol 20:1053-1059.
Singh H, Torralba MG, Moncera KJ, DiLello L, Petrini J, Nelson KE, Pieper R (2019) Gastro-intestinal and oral microbiome signatures associated with healthy aging. Geroscience 41:907-921.
Singhrao SK, Olsen I (2018) Are porphyromonas gingivalis outer membrane vesicles microbullets for sporadic Alzheimer's disease manifestation? J Alzheimers Dis Rep 2:219-228.
Singhrao SK, Chukkapalli S, Poole S, Velsko I, Crean SJ, Kesavalu L (2017) Chronic Porphyromonas gingivalis infection accelerates the occurrence of age-related granules in ApoE(-)(/)(-) mice brains. J Oral Microbiol 9:1270602.
Sisó S, Jeffrey M, González L (2010) Sensory circumventricular organs in health and disease. Acta Neuropathol 120:689-705.
Soldan SS, Lieberman PM (2023) Epstein-Barr virus and multiple sclerosis. Nat Rev Microbiol 21:51-64.
Sparks Stein P, Steffen MJ, Smith C, Jicha G, Ebersole JL, Abner E, Dawson D, 3rd (2012) Serum antibodies to periodontal pathogens are a risk factor for Alzheimer's disease. Alzheimers Dement 8:196-203.
Su X, Tang Z, Lu Z, Liu Y, He W, Jiang J, Zhang Y, Wu H (2021) Oral treponema denticola infection induces Aβ(1-40) and Aβ(1-42) accumulation in the hippocampus of C57BL/6 mice. J Mol Neurosci 71:1506-1514.
Sundar S, Battistoni C, McNulty R, Morales F, Gorky J, Foley H, Dhurjati P (2020) An agent-based model to investigate microbial initiation of Alzheimer's via the olfactory system. Theor Biol Med Model 17:5.
Sureda A, Daglia M, Argüelles Castilla S, Sanadgol N, Fazel Nabavi S, Khan H, Belwal T, Jeandet P, Marchese A, Pistollato F, Forbes-Hernandez T, Battino M, Berindan-Neagoe I, D'Onofrio G, Nabavi SM (2020) Oral microbiota and Alzheimer's disease: Do all roads lead to Rome? Pharmacol Res 151:104582.
Sweeney MD, Sagare AP, Zlokovic BV (2018) Blood-brain barrier breakdown in Alzheimer disease and other neurodegenerative disorders. Nat Rev Neurol 14:133-150.
Sweeney MD, Zhao Z, Montagne A, Nelson AR, Zlokovic BV (2019) Blood-brain barrier: from physiology to disease and back. Physiol Rev 99:21-78.
Syrjälä AM, Ylöstalo P, Ruoppi P, Komulainen K, Hartikainen S, Sulkava R, Knuuttila M (2012) Dementia and oral health among subjects aged 75 years or older. Gerodontology 29:36-42.
Tang Z, Liang D, Cheng M, Su X, Liu R, Zhang Y, Wu H (2021) Effects of Porphyromonas gingivalis and Its Underlying Mechanisms on Alzheimer-Like Tau Hyperphosphorylation in Sprague-Dawley Rats. J Mol Neurosci 71:89-100.
Tejeda M, Farrell J, Zhu C, Wetzler L, Lunetta KL, Bush WS, Martin ER, Wang LS, Schellenberg GD, Pericak-Vance MA, Haines JL, Farrer LA, Sherva R (2024) DNA from multiple viral species is associated with Alzheimer's disease risk. Alzheimers Dement 20:253-265.
Tiisanoja A, Syrjälä AM, Tertsonen M, Komulainen K, Pesonen P, Knuuttila M, Hartikainen S, Ylöstalo P (2019) Oral diseases and inflammatory burden and Alzheimer's disease among subjects aged 75 years or older. Spec Care Dentist 39:158-165.
Tsimpiris A, Tsolianos I, Grigoriadis A, Tsimtsiou Z, Goulis DG, Grigoriadis N (2023) Association of chronic periodontitis with multiple sclerosis: A systematic review and meta-analysis. Mult Scler Relat Disord 77:104874.
Tzanoulinou S, Brandi R, Arisi I, D'Onofrio M, Urfer SM, Sandi C, Constam D, Capsoni S (2014) Pathogen-free husbandry conditions alleviate behavioral deficits and neurodegeneration in AD10 anti-NGF mice. J Alzheimers Dis 38:951-964.
Villar CC, Dongari-Bagtzoglou A (2021) Fungal diseases: oral dysbiosis in susceptible hosts. Periodontol 2000 87:166-180.
Wang X, Xue GX, Liu WC, Shu H, Wang M, Sun Y, Liu X, Sun YE, Liu CF, Liu J, Liu W, Jin X (2017) Melatonin alleviates lipopolysaccharide-compromised integrity of blood-brain barrier through activating AMP-activated protein kinase in old mice. Aging Cell 16:414-421.
Wang YX, Kang XN, Cao Y, Zheng DX, Lu YM, Pang CF, Wang Z, Cheng B, Peng Y (2019) Porphyromonas gingivalis induces depression via downregulating p75NTR-mediated BDNF maturation in astrocytes. Brain Behav Immun 81:523-534.
Watanabe Y, Arai H, Hirano H, Morishita S, Ohara Y, Edahiro A, Murakami M, Shimada H, Kikutani T, Suzuki T (2018) Oral function as an indexing parameter for mild cognitive impairment in older adults. Geriatr Gerontol Int 18:790-798.
Wei SS, Chen L, Yang FY, Wang SQ, Wang P (2023) The role of fibronectin in multiple sclerosis and the effect of drug delivery across the blood-brain barrier. Neural Regen Res 18:2147-2155.
Wilson DM, 3rd, Cookson MR, Van Den Bosch L, Zetterberg H, Holtzman DM, Dewachter I (2023) Hallmarks of neurodegenerative diseases. Cell 186:693-714.
Wolfson C, Talbot P (2002) Bacterial infection as a cause of multiple sclerosis. Lancet 360:352-353.
Wozniak MA, Shipley SJ, Combrinck M, Wilcock GK, Itzhaki RF (2005) Productive herpes simplex virus in brain of elderly normal subjects and Alzheimer's disease patients. J Med Virol 75:300-306.
Wozniak MA, Mee AP, Itzhaki RF (2009) Herpes simplex virus type 1 DNA is located within Alzheimer's disease amyloid plaques. J Pathol 217:131-138.
Wu H, Qiu W, Zhu X, Li X, Xie Z, Carreras I, Dedeoglu A, Van Dyke T, Han YW, Karimbux N, Tu Q, Cheng L, Chen J (2022) The periodontal pathogen fusobacterium nucleatum exacerbates Alzheimer's pathogenesis via specific pathways. Front Aging Neurosci 14:912709.
Wu YF, Lee WF, Salamanca E, Yao WL, Su JN, Wang SY, Hu CJ, Chang WJ (2021) Oral microbiota changes in elderly patients, an indicator of Alzheimer's disease. Int J Environ Res Public Health 18:4211.
Wu Z, Ni J, Liu Y, Teeling JL, Takayama F, Collcutt A, Ibbett P, Nakanishi H (2017) Cathepsin B plays a critical role in inducing Alzheimer's disease-like phenotypes following chronic systemic exposure to lipopolysaccharide from Porphyromonas gingivalis in mice. Brain Behav Immun 65:350-361.
Yang AC, et al. (2020) Physiological blood-brain transport is impaired with age by a shift in transcytosis. Nature 583:425-430.
Yang AC, et al. (2022) A human brain vascular atlas reveals diverse mediators of Alzheimer's risk. Nature 603:885-892.
Ye J, Wan H, Chen S, Liu GP (2024) Targeting tau in Alzheimer's disease: from mechanisms to clinical therapy. Neural Regen Res 19:1489-1498.
Yilmaz M, Yay E, Balci N, Toygar H, Kılıc BB, Zirh A, Rivas CA, Kantarci A (2023) Parkinson's disease is positively associated with periodontal inflammation. J Periodontol 94:1425-1435.
You M, Miao Z, Pan Y, Hu F (2019) Trans-10-hydroxy-2-decenoic acid alleviates LPS-induced blood-brain barrier dysfunction by activating the AMPK/PI3K/AKT pathway. Eur J Pharmacol 865:172736.
Zakusilo FT, Kerry O'Banion M, Gelbard HA, Seluanov A, Gorbunova V (2021) Matters of size: roles of hyaluronan in CNS aging and disease. Ageing Res Rev 72:101485.
Zeng F, Liu Y, Huang W, Qing H, Kadowaki T, Kashiwazaki H, Ni J, Wu Z (2021) Receptor for advanced glycation end products up-regulation in cerebral endothelial cells mediates cerebrovascular-related amyloid β accumulation after Porphyromonas gingivalis infection. J Neurochem 158:724-736.
Zhang J, Yu C, Zhang X, Chen H, Dong J, Lu W, Song Z, Zhou W (2018) Porphyromonas gingivalis lipopolysaccharide induces cognitive dysfunction, mediated by neuronal inflammation via activation of the TLR4 signaling pathway in C57BL/6 mice. J Neuroinflammation 15:37.
Zhang L, et al. (2021a) SARS-CoV-2 crosses the blood-brain barrier accompanied with basement membrane disruption without tight junctions alteration. Signal Transduct Target Ther 6:337.
Zhang N, Zuo Y, Jiang L, Peng Y, Huang X, Zuo L (2021b) Epstein-Barr virus and neurological diseases. Front Mol Biosci 8:816098.
Zhang S, Lingor P (2024) Strain-dependent alpha-synuclein spreading in Parkinson's disease and multiple system atrophy. Neural Regen Res 19:2581-2582.

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