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Reviewing the Role of Oral Microbiota in Cognitive Impairment from Microbiota Homeostasis and Pathogenic Bacteria

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Abstract: Cognitive impairment is a common symptom of various neurodegenerative diseases. In recent years, an increasing body of research has focused on the relationship between oral microbiota and cognitive impairment. This review aims to explore the microbial homeostasis of oral microbiota and its interactions and mechanisms with the host, as well as the impact of specific pathogenic bacteria on cognitive function. By summarizing existing studies, this review aims to provide a theoretical basis for the pathogenesis, risk assessment, and early intervention and treatment strategies for cognitive impairment.

Keywords: Cognitive impairment; Oral microbiota; Alzheimer's disease; neurodegenerative diseases

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1. Introduction

Cognitive impairment (CI) refers to a decline in cognitive function caused by various factors, including impairments in perception, memory, attention, and executive function, independent of normal aging processes. It encompasses multiple types, such as mild cognitive impairment (MCI), Alzheimer's disease (AD), and cerebrovascular diseases. With the intensification of global population aging, the number of CI patients worldwide is projected to reach 130 million by 2050 [1]. In recent years, a substantial body of research has demonstrated significant associations between oral health and a variety of systemic diseases [2–4]. Additionally, oral health has been linked to neurological conditions, with dental issues exhibiting a bidirectional relationship with

cognitive impairment. Poor oral health is a risk factor for cognitive dysfunction, and conversely, diminished cognitive abilities can exacerbate oral health decline [5, 6]. The correlation between oral health issues and cognitive impairment has emerged as a subject of global research interest. Therefore, this review aims to explore the relationship between oral microbiota and CI, with a particular focus on elucidating the potential impact mechanisms of specific oral pathogens on cognitive function. The goal is to provide a theoretical foundation for the development of preventive and therapeutic strategies for individuals with CI.

2. Microbial homeostasis of oral microbiota and host interactions

The oral microbiota of healthy individuals maintains microbial homeostasis through interspecies cooperation and competition, host immune modulation, and environmental adaptability. The microbiota in the oral cavity is diverse, including bacteria, archaea, fungi, viruses, and protozoa [7]. These microorganisms interact and cooperate to stabilize the biofilm, playing a crucial role in protecting host health. For instance, *Streptococcus mutans* secretes extracellular polysaccharides to enhance the structural stability of the biofilm, creating a favorable environment for the coexistence of multiple bacterial species [8]. Meanwhile, S*treptococcus sanguinis* degrades glycerol to maintain its persistence and competitiveness while producing hydrogen peroxide to inhibit the growth of competing bacterial strains [9, 10]. Furthermore, some bacteria can adjust their growth and metabolic strategies through quorum sensing to achieve coexistence in resource-limited environments [11].

The physical and chemical conditions of the oral environment, such as temperature, humidity, and pH, have a significant impact on the composition of the microbial community. Saliva in the oral cavity not only mechanically removes food debris and microorganisms but also promotes microbial balance by maintaining an optimal pH level. Saliva buffers the acidic substances from the diet and acids produced by the fermentation of carbohydrates by bacteria, maintaining its pH level within a relatively stable range of 6.5 to 7 [12, 13]. This is crucial for promoting and maintaining a healthy microbial composition in the oral cavity and helps regulate the microbial homeostasis between microbes and the host. Additionally, saliva provides essential nutrients to oral bacteria through enzymatic breakdown of dietary starches, proteins, and salivary glycoproteins [13].

The relationship between the host's immune system and the oral microbiota is also of critical importance. Under healthy conditions, the host's immune system maintains the dynamic balance of the microbiota and prevents pathogen invasion through the cooperation of innate and adaptive immunity. When immune function is normal, the oral microbiota can sense signaling molecules released by the host and adjust its growth and metabolism to minimize harm to the host [14]. For example, in the case of elevated lactate levels, the oral microbiota in periodontitis patients influences macrophage polarization and promotes osteoblast differentiation, suppressing inflammation and aiding tissue repair [15]. Of course, oral microbiota can also release inflammatory cytokines or stimulate specific immune cells, activating the host's immune system, thereby affecting the ratio and composition of immune cells to induce local or distant diseases. For example, oral microbiota promotes colitis by activating inflammatory caspases in colonic mononuclear phagocytes and inducing migratory Th17 cells [16].

The balance between oral microbiota and immune activity maintains systemic homeostasis. Disrupting this balance can lead to oral and systemic diseases, such as cognitive dysfunction, cardiovascular diseases, pneumonia, rheumatoid arthritis, and digestive system cancers [17]J. R.</author><author>Gabaldón, T.</author></authors></contributors><auth-address>Barcelona Supercomputing Centre (BCS-CNS. The metabolic products of oral microbiota not only impact oral health through local pathways but also regulate the host's immune system and

systemic inflammatory responses through distant actions. These discoveries highlight the significance of oral microbiota in overall health and offer new directions for future disease prevention and treatment.

3. Mechanisms of oral microbiota impact on CI

Oral microbiota can influence the central nervous system (CNS) through multiple mechanisms, thereby affecting cognitive function. First, the proximity of the oral cavity to the brain and the rich neural connections provide the basis for direct interaction between oral microbiota and the brain [18]. Oral microbiota can invade the brain through neural pathways, particularly the trigeminal nerve and olfactory nerve. In 2002, Riviere *et al.* first observed that the colonization rate of oral spirochetes in the cerebral cortex, brainstem, and trigeminal ganglion of AD patients was significantly higher than that of cognitively normal elderly individuals [19]. This finding suggests that oral microbiota may enter the brain through neural pathways, influencing cognitive function. In 2020, Sundar *et al.* further discovered that *Chlamydia pneumoniae* could enter the olfactory cortex and hippocampus via the olfactory bulb, providing additional evidence for the relationship between oral microbiota and cognitive function [20].

Secondly, oral microbiota may affect brain function by inducing inflammatory responses. For example, the toxic protein gingipain produced by *Porphyromonas gingivalis* (*P. gingivalis*) can trigger brain inflammation, thereby promoting the deposition of β-amyloid protein and exacerbating CI [21, 22]. In addition, the oral microbiota may exert influence on the brain via the circulatory system. On one hand, oral microbes can enter the brain by traversing the blood-brain barrier (BBB) or the circumventricular organs and choroid plexus through the bloodstream [23]. On the other hand, once these oral microbes infiltrate the cerebral blood vessels, they can induce arteriosclerosis, potentially leading to inadequate cerebral blood flow, neuronal damage, and ultimately, the onset or exacerbation of AD [24]. Furthermore, oral microbiota may influence cognitive function through the regulation of gene expression, especially the TREM-2 gene in microglial cells, which triggers neuroinflammation and accelerates neuronal apoptosis [25].

Lastly, the interaction between dysbiosis of the oral and gut microbiota is also considered an important mechanism influencing cognitive function. Research indicates that significant dysbiosis of the oral and gut microbiota is associated with progressive cognitive decline in periodontitis mice, and its mechanism is probably related to microbiota-gut-brain axis disorders [26]. Oral microbiota influence cognitive function through neural pathways, inflammatory responses, blood circulation, gene expression regulation, and interactions with the oral and gut microbiota. These mechanisms suggest a complex relationship between oral health and cognitive function, providing theoretical foundations for the prevention and treatment of related diseases in the future.

4. The role of major oral pathogenic bacteria in the formation of CI

4.1. Porphyromonas gingivalis

P. gingivalis is one of the most significant periodontal pathogens and is also one of the most extensively studied, playing a pivotal role in the association between periodontitis and brain aging/neurodegeneration. *P. gingivalis* is an anaerobic, Gram-negative bacterium with various virulence factors that can trigger persistent, nonspecific inflammatory responses by modulating the host's immune response. This inflammation not only damages periodontal tissues but can also spread to distant organs through compromised epithelial barriers [27]. Gingipains, the primary virulence factors of *P. gingivalis*, have been found to be significantly more abundant in the brains

of AD patients compared to non-AD individuals, and the gingipain load was also positively correlated with the expression of tau protein [23]. Research has discovered that gingipains are present in the hippocampus and cerebral cortex of AD patients, and colocalized with the AD pathology hallmarks of tau tangles and intraneuronal β-amyloid (Aβ) [21]. These findings suggest that the oral bacterium *P. gingivalis* can enter the brain and is associated with AD pathological changes. Several animal studies have provided direct evidence of *P. gingivalis* invading the brain. After oral colonization with *P. gingivalis* in mice, increased levels of *P. gingivalis* mRNA and Pg-LPS were detected in the hippocampus, confirming that *P. gingivalis* from the oral cavity can reach brain tissue [28].

Furthermore, *P. gingivalis* is also closely associated with neurodegenerative diseases such as Parkinson's disease (PD) and multiple sclerosis (MS). Research on PD mouse models found that *P. gingivalis* leads to a reduction of dopaminergic neurons in the substantia nigra and an increase in activated microglial cells [29]. MS is characterized by demyelination of nerve cell fibers and infiltration of inflammatory cells, often resulting in severe physical and cognitive impairments [30]. A meta-analysis indicated that individuals with MS are 1.93 times more likely to be diagnosed with periodontitis compared to healthy controls, suggesting a significant association between periodontitis and MS [31]. Interestingly, the detection rate of *P. gingivalis* in healthy individuals was also 43.33%, and in patients with moderate to severe periodontitis and those with AD complicated by periodontitis, the detection rates were 76.67% and 100%, respectively [32]. This result suggests that while *P. gingivalis* can exist in the oral cavity of healthy individuals, whether it can cause disease under normal conditions still requires further investigation.

4.2. Spirochetal

Spirochetal are highly active Gram-negative bacteria that include various pathogens related to oral and periodontal infections. Among them, *Treponema denticola* (*T. denticola*) is one of the primary pathogens of periodontitis. Spirochetal exhibit significant neurotropism and can spread through the lymphatic system along nerve fibers [33]. Studies have detected spirochetal in the trigeminal nerve and trigeminal ganglia, with *T. denticola* and *Borrelia burgdorferi* being the most frequently detected species [34]. *T. denticola* is capable of bypassing the blood-brain barrier, entering the brainstem's mesencephalic nucleus of the trigeminal nerve (Vmes) and the locus coeruleus, triggering inflammatory responses that lead to neurodegenerative changes and norepinephrine imbalance, ultimately resulting in cognitive dysfunction [35]. Multiple laboratory studies have indicated an association between spirochetal and AD [36, 37]. Moreover, spirochetal may also enter the central nervous system via the olfactory nerve fibers and olfactory tract, affecting brain function [20]. However, the specific mechanisms involved require further investigation and validation.

4.3. Candida albicans

Recent studies have indicated that *Candida albicans*, a common opportunistic fungus in the oral cavity, is associated with neurodegenerative diseases [38]. *Candida albicans* is the most commonly isolated fungal species from the oral swabs of AD patients, and its prevalence is significantly higher in AD patients compared to non-AD patients [39]. Research has shown that after causing oral ulcers, *Candida albicans* can cross the blood-brain barrier, leading to asymptomatic fungal infections in the cerebral cortex, and form granulomas similar to AD plaques, thereby causing transient memory impairment [40]. More importantly, *Candida albicans* infection may compromise the integrity of the blood-brain barrier in elderly individuals, making it easier for pathogens and virulence factors to invade the nervous system [41]. Animal experiments have also confirmed this mechanism.

Based on previous research, Wu *et al.* established a fungal encephalitis mouse model and found that the spatial memory of the mice was significantly impaired. Anatomical analysis revealed spherical lesions in the mouse brain, with *Candida albicans* at the core, surrounded by astrocytes and microglial cells. Therefore, it is hypothesized that these granulomas may activate immune-related NF-KB signaling pathways, promote the secretion of cytokines such as IL-6 and IL-18, and increase the levels of amyloid precursor protein (APP) and Aβ, thus accelerating the progression of neurodegenerative lesions [42].

4.4. Streptococcus mutans

Streptococcus mutans (*S. mutans*) is a Gram-positive bacterium commonly found in the oral cavity and is a major pathogen responsible for dental caries [43]. Although *S. mutans* is primarily associated with dental caries, it can also induce local and systemic inflammatory responses, leading to increased levels of inflammatory factors in the brain. Moreover, the acidic metabolic products and other toxins produced by *S. mutans* can cross the BBB, directly or indirectly damaging neuronal cells, thereby affecting cognitive function. In a 2016 study, Watanabe *et al.* demonstrated in a mouse model that Cnm-positive *S. mutans* is associated with cognitive impairment, accompanied by an increase in cerebral microbleeds (CMBs) [44]. Notably, previous studies have established that CMBs are an independent risk factor for cognitive decline [45]. Cnm is a collagen-binding protein, 120-kDa in size, encoded by the cnm gene on the surface of *S. mutans* cells [46]. Recent multicenter prospective studies have further revealed the longitudinal association between Cnm-positive *S. mutans* and CMBs, and comprehensive oral examinations have confirmed the relationship between Cnm-positive *S. mutans* and the development of CMBs, as well as the increased risk of cognitive decline [47].

The impact of Cnm-positive *S. mutans* on cognitive impairment may be related to the following mechanisms: First, Cnm-positive *S. mutans* strongly binds to dentin, which is composed of type I collagen, promoting the development of caries in the periodontal space and facilitating the entry of *S. mutans* into the bloodstream [48]. Second, Cnm-positive *S. mutans* attracts circulating neutrophils to the site of injury, where they activate local inflammation and secrete matrix metalloproteinase (MMP)-9, ultimately increasing the permeability of the BBB. Dysfunction of the BBB disrupts the brain's homeostasis, reducing the supply of glucose and other nutrients, and impairing the elimination of waste products and metabolic byproducts, all of which can contribute to cognitive dysfunction [49].

5. Conclusion

The oral cavity serves as a reservoir for various microorganisms, and the balance of these microorganisms is crucial for maintaining overall health. Poor oral health can significantly impact cognitive function, with a bidirectional relationship between the two. Oral microorganisms not only reside in the oral cavity but can also enter the brain, increasing with age and neurodegeneration. The relationship between oral health issues and cognitive dysfunction is invaluable for the early detection and prevention of oral risk factors associated with cognitive impairment. Therefore, it is essential to comprehensively investigate the connection between oral health and cognitive dysfunction to effectively prevent or identify potential risk factors for cognitive impairment at an early stage.

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