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LINKING PERIODONTAL INFLAMMATION TO THE BRAIN: INSIGHTS FROM THE BRAIN–ORAL AXIS

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ABSTRACT

In developing a concept called the Brain-Oral Axis, researchers are beginning to recognize that the brain and oral cavity communicate with one another and this two-way path between oral health and the brain could lead to better understanding of how oral disease affects brain function. Chronic periodontitis, for example, is now being considered an infection with systemic effects (not just effects on the mouth) based on its well-established links to neuroinflammation and conditions such as Alzheimer's disease and Parkinson's disease.

Mechanisms involved in the Brain-Oral Axis include systemic inflammation, microbial translocation, and neural pathways, with some periodontal bacteria (like Porphyromonas gingivalis) potentially entering the bloodstream and causing damage to neurons by delivering virulence factors at the brain level; in addition, cytokines (produced during inflammation from periodontal infection) are believed to have the potential to cross or disrupt the blood-brain barrier, resulting in neuroinflammation.

More recently, as researchers have begun studying the microbiome's influence on brain health, the Brain-Oral Axis has evolved into the oral-gut-brain axis where many microbes are interacting and may play a role in determining a person's risk of developing a neurological disorder. Currently, the extent of the association between periodontal disease and neurological disorders is well supported; however, research is underway to determine if these associations are the result of direct causation or other shared factors. Overall, understanding the Brain-Oral Axis will underline the role that oral health has on overall health and will help create new opportunities for preventative care and further interdisciplinary healthcare approaches.

INTRODUCTION

The presence of numerous microorganisms in saliva and deep pockets of the gingival tissue influences the immune response and systemic function. Periodontitis, which occurs as a result of changes in the oral microbiome that disrupt the ability of the body to mount an adequate immune response to pathogens in the oral cavity (microbial dysbiosis), has historically been viewed as a localized oral disease; however, emerging research demonstrates that periodontitis is a chronic inflammatory disease that can impact many parts of the body, including the central nervous system.[14,15]

The concept of the Brain–Oral Axis describes the two-way connection between the mouth and the brain through inflammatory, microbial, and neural pathways. In addition, there is a constant influx of pro-inflammatory cytokines into systemic circulation resulting from chronic periodontal inflammation, which can influence neuronal integrity by altering the blood–brain barrier and promoting neuroinflammation.[1,2,4,5,7,8,12]

PATHOPHYSIOLOGY MECHANISM

Complex pathophysiological processes involving inflammation, immune responses, and barrier dysfunction mediate the Brain–Oral Axis. Periodontitis is considered a chronic inflammatory condition resulting from disturbances in the normal oral microbiota, leading to the continuous release of pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6.[14,15] Once released into systemic circulation, these inflammatory mediators can affect distant organs, including the brain. Cytokine-mediated pathways also contribute to the disruption of the blood–brain barrier (BBB), which normally protects the brain from harmful circulating agents. Chronic systemic inflammation increases BBB permeability, allowing inflammatory cytokines and bacterial components such as lipopolysaccharide (LPS) to enter the central nervous system.[2,4,5,7,8,12]

Once in the central nervous system, inflammatory cytokines activate microglia, the resident immune cells of the brain. Activated microglia subsequently release additional inflammatory mediators and reactive oxygen species, resulting in neuronal damage and progressive neurodegeneration. Persistent neuroinflammation is considered a major contributor to the progression of neurological disorders such as Alzheimer's disease.[1,3,5,10,11] Therefore, these pathophysiological mechanisms suggest that chronic oral inflammation

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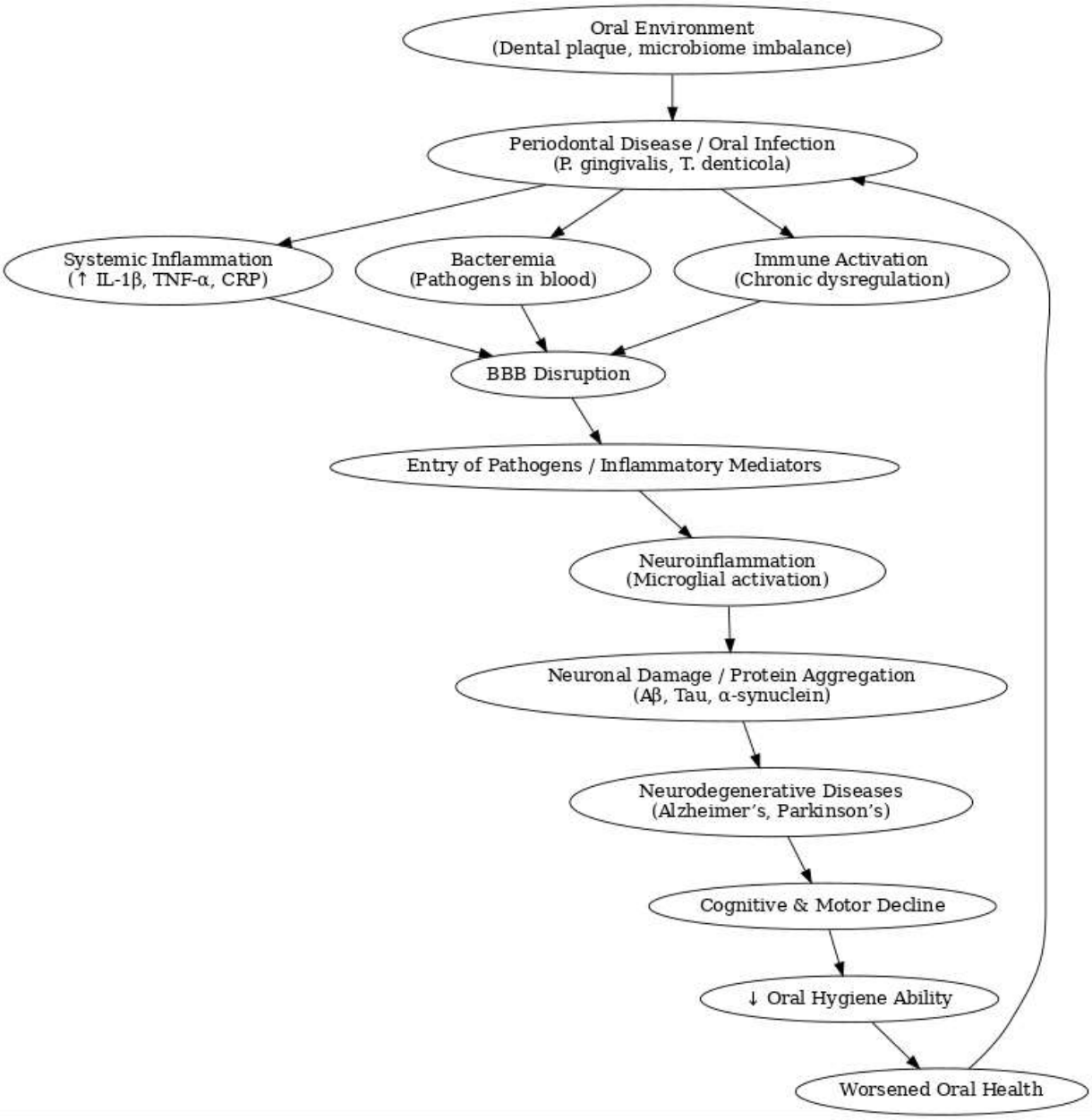
may contribute to neuronal injury through both systemic inflammatory pathways and direct cellular mechanisms.



ORAL-GUT-BRAIN AXIS :

The oral–gut–brain axis is an expanded concept of the Brain–Oral Axis that emphasizes the interconnected relationship between the oral microbiome, the gut microbiome, and the central nervous system.[11,14] The oral cavity serves as a major source of microbial entry into the gastrointestinal tract because saliva, which contains microorganisms and their metabolic products, is continuously swallowed. During active periodontitis, pathogenic oral bacteria may survive the acidic gastric environment and subsequently colonize the gut, leading to dysbiosis of the gut microbiota.[4,5,8] This microbial imbalance contributes to increased intestinal permeability ("leaky gut"), allowing microbial products and inflammatory mediators to enter systemic circulation. These circulating products can activate immune responses and promote systemic inflammation, which may adversely influence brain function and neuroinflammatory pathways.[2,6,12]

The metabolites produced by the gut microbiome, such as short-chain fatty acids and neurotransmitter precursors, help regulate brain function and behaviour. Therefore, disturbances in these metabolic activities may negatively affect cognitive function and emotional well-being.[10,11,14]

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ROLE OF ORAL MICROBIOME

The oral microbiome is a complex ecological community composed of hundreds of microbial species that coexist in a balanced state under normal conditions. When periodontitis develops, this balance is disrupted, resulting in microbial dysbiosis characterized by an increased abundance of pathogenic bacteria.[14,15] Pathogenic microorganisms within the oral cavity produce virulence factors such as lipopolysaccharides (LPS), proteolytic enzymes, and other toxins that stimulate host immune responses and contribute to periodontal tissue destruction.[4,5,14,15] The dysbiotic oral microbiome plays a central role in the development of the Brain–Oral Axis and its systemic effects. Oral pathogens, particularly Porphyromonas gingivalis, can evade host immune defenses, persist within the host, and promote chronic inflammation.[2,4,5]

These bacteria and their byproducts also can enter the systemic circulation and influence the health of distant organs such as the brain. The oral microbiome is also able to influence gut microbiota through continuous ingestion of saliva, thus contributing to the oral–gut–brain axis.

Changes in the microbial composition of the oral cavity can result in systemic immune dysregulation and increased levels of inflammation, both of which are risk factors for neurodegenerative diseases. Several studies have associated specific oral pathogens with cognitive decline as well as neuroinflammation. Consequently, maintaining an appropriate balance of the oral microbiome is essential to maintaining both oral and systemic health, particularly in preventing neurological complications.[1,3,7,8,10,11,12,13]

ROLE OF GUT MICROBIOME

The gut microbiome plays a significant role in the Brain–Oral Axis through its influence on immune regulation, inflammation, neural signaling, and microbial communication between the oral cavity, gut, and central nervous system.[11,14] The oral cavity and gastrointestinal tract harbor complex microbial communities that interact closely with one another. During periodontal disease, pathogenic oral bacteria may be transferred to the gastrointestinal tract through saliva, leading to alterations in gut microbial composition (dysbiosis).[4,5,14] This microbial imbalance can increase intestinal permeability and promote the release of inflammatory mediators into systemic circulation, contributing to systemic inflammation, neuroinflammation, and disease progression.[6,11,12] The gut microbiota also communicates with the brain through the gut–brain axis via neural, endocrine, and immune pathways. Microbial metabolites such as short-chain fatty acids, neurotransmitter-like compounds, and cytokines can influence brain function, cognition, emotional regulation, and immune responses.[11]

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Recent research highlights that maintaining a balanced gut microbiome may help regulate systemic inflammation and support both oral and neurological health. Therefore, the gut microbiome is considered an important mediator within the Brain–Oral Axis, linking periodontal disease with systemic and neurodegenerative conditions.[9,11,14]

NEURAL PATHWAYS

Direct communication between the brain and oral cavity occurs through neural pathways that function alongside systemic inflammatory and microbial routes. The trigeminal nerve plays a crucial role in transmitting sensory information and may also serve as a pathway through which pathogens or inflammatory signals reach the central nervous system.[4,5,7,8] Some periodontal pathogens have been proposed to travel along neural pathways, bypassing the bloodstream and contributing to localized neuroinflammation.[2,7,8] Oral sensory inputs can influence various brain functions, including pain perception, emotional regulation, and cognitive processing. In addition, the Brain–Oral Axis involves interactions with the autonomic nervous system, which regulates immune and inflammatory responses throughout the body.[4,5,11] Disruption of these neural and immunological pathways may contribute to diseases affecting both oral and brain health, highlighting their importance in maintaining overall health and homeostasis.[1,3,10,13]

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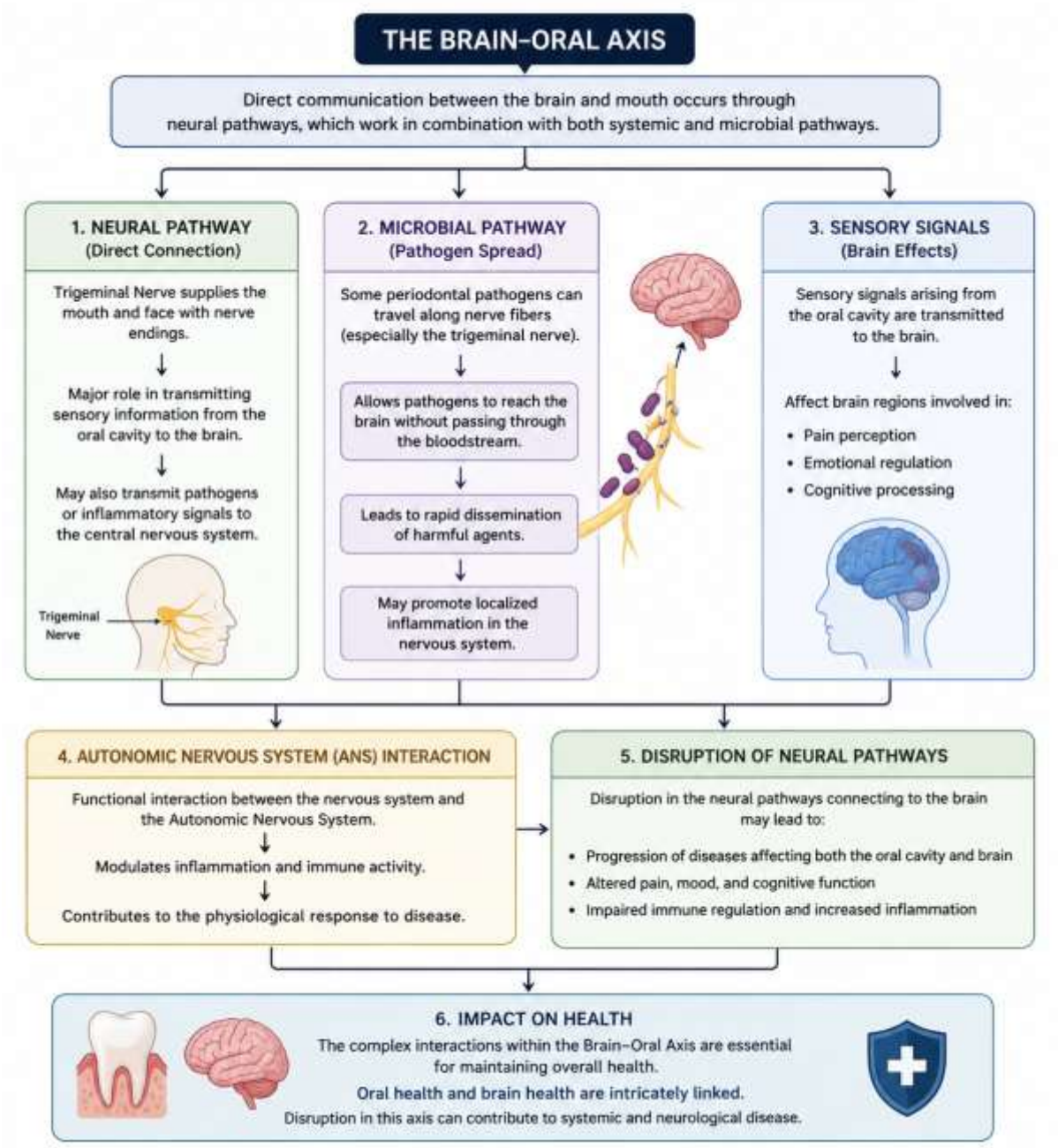

NEURODEGENERATIVE DISEASES

Emerging evidence suggests an association between periodontal disease and neurodegenerative disorders, particularly Alzheimer's disease and Parkinson's disease. Both conditions are characterized by chronic inflammation, immune dysregulation, and progressive neuronal loss.[1,3,4,5,10,11,13] In Alzheimer's disease, hallmark pathological features include the accumulation of amyloid-β plaques and abnormal tau protein deposition within the brain. Periodontal pathogens, especially Porphyromonas gingivalis, have been implicated in promoting amyloid-β production through activation of neuroinflammatory pathways. Furthermore, gingipains, the proteolytic enzymes produced by P. gingivalis, have been detected in brain tissue, suggesting a direct role for periodontal microorganisms in the pathogenesis and progression of Alzheimer's disease.[2,4,5,7,8]

Parkinson's disease is also characterised by neuronal loss as the dopaminergic neurons that are involved in the control of movement are destroyed over time. The inflammatory process and oxidative stress are believed to be contributing factors to this loss of neurons. Chronic inflammation from periodontal disease may be contributing to the progression of both Alzheimer's and Parkinson's due to the increase of systemic cytokines that are created from chronic periodontal inflammation. Patients with Parkinson's disease may

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also suffer from impaired motor function leading to poor oral hygiene, further contributing to periodontal disease and creating a bidirectional relationship between the two diseases. All of this suggests that improving periodontal disease may help to reduce the risk of developing and slowing the progression of neurodegenerative diseases.[3,9,13]

CLINICAL IMPLICATIONS AND THERAPEUTIC PERSPECTIVES

The Brain–Oral Axis highlights the important role of periodontal health in preventing systemic and neurodegenerative diseases. Effective periodontal care, including scaling, root planing, and maintenance of good oral hygiene, helps reduce pathogenic bacterial burden and systemic inflammation, thereby potentially lowering the risk of disease progression.[3,6,9,15] Salivary biomarkers offer a non-invasive approach for the early detection and monitoring of systemic and neurological disorders.[1,10] Emerging therapeutic strategies, including probiotics, prebiotics, antimicrobial agents, and host-modulation therapies, aim to restore microbial homeostasis and regulate inflammatory responses.[4,11,14] Overall, a multidisciplinary approach involving both dental and medical professionals is essential for early diagnosis, prevention, and the improvement of oral and systemic health outcomes.[5,9,13]

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DISCUSSIONS

Global discussions surrounding the Brain–Oral Axis and the role of the gut microbiome have gained significant attention in recent years due to increasing evidence linking oral health, gut dysbiosis, and neurological disorders. Researchers worldwide are exploring how periodontal pathogens and alterations in the gut microbiota contribute to systemic inflammation and neurodegeneration. Studies from countries such as the United States, Japan, China, the United Kingdom, and Germany have reported associations between chronic periodontal disease and conditions including Alzheimer's disease, Parkinson's disease, cardiovascular disease, diabetes mellitus, and inflammatory bowel disease.

One major area of discussion focuses on the ability of periodontal pathogens, particularly Porphyromonas gingivalis, to influence both gut and brain health through inflammatory and microbial pathways. Scientists are investigating whether oral bacteria can alter gut microbial balance, increase intestinal permeability, and promote neuroinflammation through the gut–brain axis. Additionally, the role of microbial metabolites and immune signaling molecules in affecting cognitive function and emotional regulation has become an important subject of research.

Another widely discussed topic is the potential use of probiotics, prebiotics, dietary interventions, and periodontal therapy to restore microbial balance and reduce systemic inflammation. Researchers are also examining salivary and gut microbial biomarkers as non-invasive tools for the early detection of neurological and systemic diseases. Despite growing evidence, many experts emphasize that the exact mechanisms linking the oral cavity, gut microbiome, and brain are still not fully understood and require further clinical and longitudinal studies.

Several authors and researchers have contributed to the growing discussion on the Brain–Oral Axis, emphasizing the relationship between periodontal disease, systemic inflammation, gut dysbiosis, and neurological disorders. Their studies suggest that chronic oral inflammation may influence brain health through microbial, immune, and neural pathways.

Sim K. Singhrao proposed that chronic periodontal infection may act as a risk factor for neurodegenerative disorders by promoting blood–brain barrier disruption, neuroinflammation, and microbial invasion of neural tissues.

Stephen Dominy and colleagues proposed that Porphyromonas gingivalis and its toxic enzymes, gingipains, may invade brain tissues and contribute to the development of Alzheimer's disease. Their work strengthened the hypothesis that chronic periodontal infection may be associated with cognitive decline and neurodegeneration.

Kamer A. R. discussed the association between periodontal inflammation and impaired cognitive function, suggesting that systemic inflammatory mediators released during chronic periodontitis may contribute to neuroinflammatory changes linked to dementia and Alzheimer's disease.

Lynch C. highlighted the importance of oral health in systemic disease progression and discussed how chronic periodontal infection may influence neurological health through inflammatory and immune pathways.

Poole S. investigated the role of periodontal pathogens and inflammatory cytokines in neurodegenerative disease progression. His work emphasized that oral bacteria and their products may contribute to chronic systemic inflammation affecting the brain.

Chen C. K. explored the virulence mechanisms of periodontal microorganisms and their role in triggering systemic immune responses, including pathways associated with neurological disorders.

Noble J. M. examined the relationship between periodontal disease, tooth loss, and cognitive impairment. His findings suggested that poor oral health may be associated with an increased risk of memory decline and neurodegenerative conditions.

Recent discussions by several researchers have strengthened the concept of the Brain–Oral Axis and its association with periodontal disease and neurological health. Kamer A. R. reported that chronic periodontal inflammation may contribute to cognitive decline through systemic inflammatory pathways. Stephen Dominy and colleagues proposed that Porphyromonas gingivalis and its toxic gingipains may invade brain tissues and play a role in Alzheimer's disease progression. Lynch C. emphasized the importance of oral health in maintaining neurological and systemic health, while Poole S. discussed how periodontal pathogens and inflammatory mediators may promote chronic neuroinflammation. Chen C. K. explored the virulence and systemic effects of periodontal microorganisms, suggesting their role in immune dysregulation and disease progression. Similarly, Noble J. M. identified associations between periodontal disease, tooth loss, and memory impairment. Collectively, these discussions support the view that periodontal inflammation, microbial dysbiosis, and systemic immune responses are closely linked to brain health, highlighting the importance of oral health in the prevention and management of neurological disorders.

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CONCLUSIONS

Understanding the correlation between oral health and brain health has been dramatically changed with the Brain-Oral Axis. Periodontitis is now considered a chronic inflammatory disease with effects on systemic health rather than a localized disease. Periodontal disease may also increase the risk of developing and/or the progression of neurodegenerative diseases such as Alzheimer's and Parkinson's through mechanisms such as microbial spread, systemic inflammation and nerve signaling.

Neurodegenerative diseases can also create negative effects on a person's oral health due to the inability to maintain proper oral hygiene; therefore, the relationship between periodontitis and neurodegenerative disease is bidirectional. There is currently evidence of an association, but more research must be conducted to determine a cause-and-effect relationship and to better understand the biological processes that exist.

Clinically, having good oral health may help to reduce systemic inflammation and improve overall health. Coordinated care between dental and medical professionals is essential for complete patient care. The Brain-Oral Axis emphasizes the significance of preventive dentistry while opening the door to integrated healthcare models of treating and managing oral and brain health.

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