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The Oral Microbiome and Its Role in Mental Health: Exploring the Oral-Brain Axis

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Abstract

The human oral cavity hosts a complex and dynamic microbial ecosystem, second only to the gut in microbial diversity. While the gut-brain axis has been extensively studied, the potential influence of the oral microbiome on mental health remains underexplored. Evidence has emerged suggesting a significant link between the oral microbiome and mental health. Recent studies indicate that oral microbial dysbiosis may contribute to neuroinflammatory processes, thereby affecting mental health outcomes. This review explores the current findings on how dysbiosis in the oral microbiota may influence neuropsychiatric outcomes through systemic inflammation, microbial translocation, and neural pathways. Understanding the oral-brain axis could pave the way for novel diagnostic and therapeutic strategies in mental health care.

Key Words: Microbiome,Neuroinflammatory,Neuropsychiatric,oral microbial dysbiosis

Introduction

The human oral cavity hosts a complex and dynamic microbial ecosystem, comprising over 700 bacterial species, as well as fungi, viruses, and protozoa [1]. It is second only to the gut in

microbial diversity. This complex ecosystem has a significant influence on overall health through its interactions with the digestive system, immune system and metabolic pathways [2]. Recent research has highlighted the significance of the oral microbiome in systemic diseases, including cardiovascular disease, diabetes, and neurodegenerative disorders.

While the gut-brain axis has been extensively studied, the potential influence of the oral microbiome on mental health remains underexplored [3]. The concept of the oral-brain axis has emerged to describe the bidirectional communication between the oral microbiome and the central nervous system. This axis suggests that oral microbial dysbiosis can influence brain function and behaviour through various mechanisms, including systemic inflammation, microbial translocation, and neural pathways. Recent studies suggest a strong link between oral microbial dysbiosis and neuroinflammatory processes that affect mental health outcomes significantly [4].

The Oral-Gut-Brain Axis

The oral and gut microbiomes, though distinct, are interconnected systems that influence immune regulation, metabolism, and disease susceptibility [2]. The gut microbiome aids in nutrient absorption, immune development, and produces biomolecules like neurotransmitters [5]. Both microbiomes collectively modulate systemic inflammation and neurological health [6].

While the gut-brain link is well-studied, the oral microbiome, despite its role in systemic inflammation, remains underexplored [7]. Emerging evidence implicates oral pathogens like *Porphyromonas gingivalis* in Alzheimer's disease (AD), suggesting communication between oral microbes and the brain via inflammatory, neural, and immune pathways (e.g., vagus and trigeminal nerves) [8]. These findings highlight the need for integrated approaches to support both oral and gut microbial health in preserving brain function.

Oral Microbiome Composition, Complexity and Its Systemic Implications

The oral microbiome constitutes a highly diverse and dynamic microbial community, second only to the gut in terms of population and functional complexity. Estimates suggest the presence of over 700 microbial species within the oral cavity, although individual adults typically harbour about 200 predominant bacterial species at any given time [7]. Despite significant advancements in microbiome research, fewer than one-third of the oral microbial

taxa have been successfully cultured in vitro, underscoring the challenges of fully elucidating this ecosystem's complexity [9].

The environment of the oral cavity is uniquely suited for microbial survival and diversity, maintained at an average temperature of 37 °C and a mildly acidic to neutral pH range (typically between 6.2 and 7.6) [10]. Oxygen availability within oral biofilms is also highly variable and supports a diverse microbial community, including aerobic, facultative anaerobic, and obligate anaerobic organisms [11,12]. Disruption of this symbiotic balance, termed dysbiosis, can lead to the proliferation of pathogenic microbes such as *Porphyromonas gingivalis* and *Fusobacterium nucleatum*, both of which have been linked not only to periodontal disease but also to systemic illnesses. These microorganisms often exist within biofilms, which provide protection from external stressors and contribute to the microbial community's resilience. When dysbiosis occurs, these pathogens may enter systemic circulation, either directly or through inflammatory mediators, initiating a cascade of systemic immune responses [13].

Notably, the systemic spread of oral microbes and their metabolic byproducts has been increasingly associated with chronic inflammatory diseases, including diabetes, cardiovascular disorders, preterm birth, inflammatory bowel disease, and, notably, AD [14]. Several mechanisms have been proposed to explain these links.

Mechanisms of Neuroinflammation Induced by Oral Microbiota

The oral microbiome may contribute to neuroinflammation through multiple interconnected pathways. Gram-negative bacteria commonly found in the oral cavity, such as *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, and *Aggregatibacter actinomycetemcomitans*, produce lipopolysaccharides (LPS), potent endotoxins capable of initiating strong inflammatory responses [15, 16]. These LPS molecules bind to Toll-like receptor 4 (TLR4), triggering the activation of immune cells, including neutrophils, macrophages, and monocytes. This immune activation leads to the release of key pro-inflammatory cytokines such as interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), and interleukin-1β (IL-1β) [17].

Once released, these cytokines not only heighten systemic inflammation but also contribute to insulin resistance and vascular dysfunction, both of which are established risk factors for neurodegenerative diseases. Critically, LPS can cross the blood-brain barrier (BBB), where it may activate microglia, the brain's resident immune cells, leading to sustained

neuroinflammatory responses, a hallmark of AD pathology [18]. Moreover, these endotoxins and inflammatory mediators can compromise the integrity of the BBB, facilitating the infiltration of peripheral immune cells and microbial components into the central nervous system [19]. Chronic exposure to oral pathogens thus has the potential to drive ongoing microglial activation and neuronal damage, underscoring the oral microbiome's influence on brain health.

Oral Microbiota & Its Role in Depression and Anxiety

While growing evidence links poor oral health to neurological conditions like Alzheimer's disease (AD) and depression, it remains unclear whether oral health issues are a cause or a consequence of these conditions. Research on the gut microbiome's impact on mental health has gained traction in recent years, but only recently has attention turned toward the oral microbiome as a potential contributor to psychiatric disorders.

Two recent studies have identified changes in the salivary microbiome associated with symptoms of depression, particularly in adolescents. Certain bacterial genera, such as *Spirochaetaceae*, *Actinomyces*, *Treponema*, *Fusobacterium*, and *Leptotrichia*, were linked to the severity of depressive and anxiety symptoms [20]. These patterns are not limited to adolescents; similar trends have been observed in adults as well. In a non-clinical adult population, both the overall composition and the daily fluctuations of oral microbial communities were influenced by psychological stress and emotional well-being [21].

Wingfield et al. (2021) examined the salivary microbiome in adults with and without depression and found subtle but meaningful distinctions [22]. Although alpha diversity (the overall variety of bacteria) remained relatively unchanged between the groups, there were clear differences in beta diversity (the types and proportions of bacteria), allowing researchers to distinguish between the microbiomes of depressed and non-depressed individuals. Notably, 21 bacterial variants (amplicon sequence variants, or ASVs) differed significantly; 19 of these were reduced in depressed individuals, while two increased. Signs of oral dysbiosis, an imbalance in the microbial community, were observed, including a rise in *Prevotella nigrescens*, a pro-inflammatory species linked to periodontal disease.

These findings echo results from gut microbiome studies, which similarly show reduced bacterial diversity and abundance in individuals with depression [23–25]. Although the gut and

oral microbiomes differ in composition, oral bacteria have been detected in the gut of patients with inflammatory bowel conditions like Crohn's disease, suggesting potential microbial translocation. It is hypothesised that bacteria or their byproducts may also enter the brain through a weakened blood-brain barrier, triggering inflammation, a key mechanism underlying depression [26].

Importantly, many of the same risk factors, such as age, low income, smoking, alcohol use, sleep disturbances, and chronic stress, are common to both periodontitis and depression. Genetic links between gum disease and depression have also been identified [27], reinforcing the idea of a shared inflammatory pathway. In this context, oral pathogens may contribute to systemic inflammation that affects brain function, possibly explaining why anti-inflammatory treatments, including antidepressants, often show therapeutic benefits [28].

A major finding from these studies is the reduction of beneficial, protective bacteria in individuals with depression. *Haemophilus parainfluenzae*, a species known for anti-cancer effects (but which can become pathogenic), was significantly decreased [29,30]. Similarly, *Rothia mucilaginosa*, which helps suppress harmful bacteria, and *Schaalia lingnae*, associated with a healthy oral environment, were also reduced [31,32]. This depletion of protective microbes may create ecological space for more harmful species to thrive, promoting inflammation. Previous research has linked lower levels of *Actinomyces* with high cortisol levels and anxiety in adolescents, possibly reflecting overactivation of the hypothalamic-pituitary-adrenal (HPA) axis, a hallmark of chronic stress and depression [21].

Other bacterial genera, including *Prevotella*, *Haemophilus*, and *Neisseria*, have been negatively associated with depression and various inflammatory conditions, further supporting the idea of an immune-mediated connection [33]. Interestingly, some species often considered harmful, such as *Solobacter moorei*, *Alloprevotella tannerae*, and *Porphyromonas endodontalis*, were also found in higher abundance in healthy individuals. This highlights the importance of strain-level specificity: not all members of a bacterial species behave identically, and their interactions with co-residing microbes and host factors can significantly influence health outcomes [10].

Other Influencing Factors

Both smoking and depression influence the oral microbiome, but findings from the Wingfield study [22] showed that microbiome changes associated with depression persisted even after adjusting for smoking, suggesting independent effects. Limited data on oral hygiene—an important factor shaping the oral microbiome—complicates interpretations [34]. Since depression is linked to poor oral health, some microbial shifts might stem from hygiene habits rather than depression itself [35]. However, it's also possible that poor oral health drives inflammation, contributing to depression—a theory explored in cardiovascular studies but not yet in mental health. Dietary changes common in depression may further alter the oral microbiome.

Clinical Implications and Future Directions

Identifying specific oral microbial signatures associated with mental health disorders could aid in early diagnosis and intervention. Targeting oral dysbiosis through probiotics, antimicrobial therapies, or improved oral hygiene practices may alleviate neuroinflammatory conditions. Further interdisciplinary research is essential to unravel the complex relationships between oral microbiota and mental health, paving the way for innovative diagnostic and therapeutic approaches.

Conclusion

The oral microbiome influences systemic health in ways that extend well beyond the mouth. Emerging research links oral dysbiosis to mental health conditions like depression and anxiety through pathways involving systemic inflammation, microbial translocation, and neural signalling. These findings underscore the importance of the oral-brain axis and suggest that maintaining oral microbial balance may be crucial for protecting cognitive and emotional well-being. As such, the oral microbiome holds promise both as a biomarker and a potential therapeutic target in the prevention and management of mood disorders and neurodegenerative diseases.

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