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From Mouth to Mind: Unraveling the Oral Microbiome's Role in Orofacial Pain and Neurodegeneration

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ABSTRACT

The human oral cavity hosts a diverse and dynamic microbiome comprising more than 700 microbial species, which plays a crucial role in maintaining oral and systemic health. Oral dysbiosis, defined as disruption of this microbial balance, has been increasingly implicated not only in periodontal disease but also in the pathogenesis of orofacial pain and neurodegenerative diseases. Key pathogens, such as *Porphyromonas gingivalis*, *Treponema denticola*, and *Fusobacterium nucleatum*, have been proposed to release virulence factors, including lipopolysaccharides and gingipains, which may activate immune pathways and nociceptors, thereby driving peripheral sensitization and neuroinflammation. These organisms have also been suggested to breach mucosal and vascular barriers, enter the systemic circulation, and, in some cases, access the central nervous system. Evidence has linked oral pathogens to Alzheimer's disease, Parkinson's disease, autism spectrum disorder, and multiple sclerosis. Notably, *P. gingivalis* and its gingipains have been identified in postmortem brain tissue from patients with Alzheimer's disease, with proposed roles in neuroinflammation and amyloid plaque formation. Salivary microbial alterations in burning mouth syndrome and temporomandibular disorders further highlight the influence of the oral microbiome on neuropathic pain. Therefore, the oral-gut-brain axis represents a novel and promising area of investigation, offering potential diagnostic biomarkers and targeted microbial therapies for the management of chronic orofacial pain and neurological disorders.

Keywords: Brain-gut axis, microbiota-gut-brain axis, neurodegenerative diseases, neuroinflammation, orofacial pain, periodontal pathogens.

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INTRODUCTION

The relationship between the gut and the brain in the context of mental health disorders has become a subject of growing scientific inquiry. Because the oral cavity is the anatomical entry point of the digestive system, researchers have increasingly focused on the potential role of oral microbial communities in mental health outcomes.[1,2]

The oral and gut microbiomes are among the most structurally diverse and microbially rich ecosystems in the human body.[1] A substantial body of research has focused on understanding the gut-brain-microbiome axis, a continuous, bidirectional communication network linking gut

microbial activity to central nervous system (CNS) function. This network operates through neural, endocrine, and immunological pathways, and disruptions within it have been implicated in a range of CNS-related conditions.[2]

The relationship between the gut and the brain extends further, intersecting meaningfully with oral cavity health. The oral environment contains a wide range of microhabitats, including the tongue, gingiva, buccal mucosa, palatal surfaces, and tooth structures, and is the body's second most densely populated microbial niche.[3] Emerging data indicate that gut microbial states may influence oral health outcomes, including the development of dental caries. Cariogenic biofilm communities drive caries initiation, and gut-derived dysbiosis may impair immune regulation in ways that reduce the host's ability to manage these oral pathogens, particularly in pediatric populations.[4]

Of particular note is the expanding body of evidence linking the oral microbiota, which serves as the microbiome's initial interface with the digestive tract, to neurological health outcomes. Because the oral cavity is readily accessible, its microbial profile may serve as a diagnostic indicator of both local and distant diseases, including conditions affecting the nervous system.[5]

The concept of an oral-gut-brain axis has now emerged in the literature. This framework proposes that microorganisms native to the mouth may translocate to the gastrointestinal environment, seeding ectopic colonies that disrupt resident microbial populations. Beyond direct colonization, metabolic products and structural components of oral bacteria may affect brain function either through neural pathways or by entering the systemic circulation. Just as the gut microbiome requires ecological stability to maintain health, the oral microbial ecosystem also depends on microbial balance. Mapping the interactions between host biology and resident microbiota is therefore essential for understanding disease mechanisms and designing microbiome-based approaches to diagnosis and treatment.

Although the oral cavity is anatomically continuous with the gastrointestinal tract, its microbial community differs substantially from that of the gut. Physical compartmentalization by the stomach and small intestine, combined with chemical defenses, including gastric acid and bile salts, limits the direct passage of microbes between the two sites.[6] Even so, oral bacteria can reach the gut, where their presence may shape both local and systemic physiology. Global metagenomic analyses of paired salivary and fecal samples have shown that certain oral bacterial taxa can establish themselves in the intestinal environment, even under conditions of gut health.

Neuropsychiatric conditions, such as depression, autism spectrum disorder (ASD), and schizophrenia, tend to follow a chronic disease course and are frequently accompanied by comorbid health conditions, complicating treatment and contributing to poor long-term outcomes.[7] Depression and anxiety have emerged as particularly pressing public health challenges, with prevalence estimates suggesting that approximately 15–20% of the global population is affected.[5]

A rapidly growing body of evidence identifies the gut microbiome as a key contributor to brain health, with possible roles in neurodevelopment, neurotransmitter modulation, and behavioral regulation. These microbial influences may be relevant to the pathogenesis and progression of neurodevelopmental, psychiatric, and neurodegenerative conditions.[8]

CLINICAL AND RESEARCH IMPLICATIONS

Oral-Gut Microbial Transmission

Neural Pathways

Recent studies have revealed a compelling link between oral microbes and gut health. Although the oral and intestinal microbiomes are generally distinct in healthy individuals.[9] Nearly one-third of oral bacteria may establish themselves in the gut under specific conditions.[10] This transmission is more pronounced in gastrointestinal disorders, in which microbial balance is already disrupted. In periodontitis, oral bacteria can disturb the gut flora, triggering inflammation and further complications.[11] Notably, *Porphyromonas gingivalis* compromises the intestinal barrier by reducing tight junction proteins, including occludin and TJP1, and increasing pro-inflammatory markers, such as IL-6 and IFN-γ.[12] Another oral bacterium, *Streptococcus salivarius*, has also been shown to weaken duodenal epithelial integrity, as demonstrated in a single observational study of patients with functional dyspepsia. However, a causal relationship has not been definitively established.

Immune Pathways

A growing body of evidence links periodontal disease to inflammatory bowel conditions, including Crohn's disease and ulcerative colitis. Oral bacteria are suggested to be capable of migrating to and establishing themselves in the gut, where they may aggravate or possibly even initiate inflammation. Multiple studies have documented shared microbial signatures, such as increased *Prevotella*, *Veillonella*, and *S. salivarius*, in both the oral cavities and intestines of individuals with Crohn's disease.[6] Many studies and meta-analyses are human-based, which strengthens the level of evidence.

Oral bacteria access the gastrointestinal system through two main routes. The first is via the bloodstream, through which microbes such as *Fusobacterium nucleatum* can travel to distant sites. This bacterium has been linked to colorectal cancer, initially identified by Kostic et al.[13] Subsequent studies have confirmed its association with worse outcomes and reduced treatment response. *F. nucleatum* appears to promote tumor development by altering the immune microenvironment and stimulating cancer cell growth. Research on *F. nucleatum* and colorectal cancer includes both human and animal studies; however, human clinical studies and observational analyses are more numerous in identifying the association and clinical significance. Animal studies, however, are crucial and predominant for establishing causation, clarifying functional mechanisms, and testing treatment efficacy.

Microbial and Metabolic Pathways

The second pathway is gastrointestinal. Disruptions, such as antibiotic use or proton pump inhibitor therapy, create opportunities for oral bacteria to thrive in the gut. In addition, Th17 cells primed in inflamed periodontal tissues may enter the systemic circulation and reactivate upon encountering familiar microbial triggers, thereby perpetuating inflammation. Notably, direct colonization may not be necessary for oral bacteria to exert systemic effects. Oral microbiome imbalances driven by poor oral hygiene, diet, medications, or reduced salivation can cause broader physiological disturbances. One affected pathway involves nitric oxide (NO) signaling, which is critical for gut motility. Periodontitis has been linked to reduced systemic levels of NO and BH4, potentially altering intestinal function through the BH4/NO/Nrf2 pathway and contributing to symptoms such as constipation.[6] Epidemiological and observational studies using large databases, such as NHANES, have shown that individuals with periodontitis have significantly higher odds, approximately 45% higher, of experiencing chronic constipation. In animal studies, scientists have established causation by using knockout mice, which are born without the Nrf2 gene, and comparing them with healthy mice. In humans, primarily strong associations have been demonstrated; however, there are not yet enough large-scale clinical trials to confirm causality. In the present scenario, evidence relies heavily on animal models to establish mechanistic causality, creating both opportunities for deeper molecular understanding and limitations in direct human translation.

Mechanism of the Oral-Gut-Brain Axis

Neural Pathways

The brain, gut, and oral cavity are interconnected through neural pathways, with the central nervous system and enteric nervous system (ENS) in constant communication. The vagus nerve serves as the primary conduit, transmitting sensory information from the gut to the brain and relaying motor commands in return. Embedded within the gastrointestinal lining, the ENS, often referred to as the "second brain," governs digestive function while also influencing mood and behavior through vagal and spinal connections.[11]

Sensory signals from the oral cavity, including pain, temperature, and tactile stimuli, travel through the trigeminal nerve (cranial nerve V) and the trigeminal ganglion to the brainstem before ascending to higher processing centers.[12] Oral microbiome dysbiosis can activate this pathway, triggering local or referred pain. Furthermore, persistent oral infections promote systemic inflammation and are increasingly implicated in neuroinflammatory and neurodegenerative conditions. Given the abundance of animal models and *in vitro* studies, this association has been proposed based on anatomical proximity; however, direct human evidence remains lacking. Human evidence is largely observational and indirect. Neither pathway has been definitively proven in humans.

Immune Pathways

Disruptions in the oral microbiota have downstream effects on gut and brain health. When oral bacteria such as *F. nucleatum* travel to the digestive tract, they can impair enteric glial cells, weaken the intestinal lining, and trigger chronic inflammation, potentially affecting cognitive function. Similarly, *P. gingivalis* can disturb gut microbial balance and alter immune responses beyond the oral environment.

The immune system plays a pivotal role in the oral-gut-brain axis. Beneficial gut microbes produce short-chain fatty acids that support brain function, but a compromised gut barrier, often referred to as "leaky gut," allows toxins and harmful molecules to enter the bloodstream, adversely affecting both physical health and emotional well-being (Fig. 1).

THE ORAL-GUT-BRAIN AXIS: IMPLICATIONS FOR NEUROLOGICAL AND MENTAL HEALTH

Mechanisms by Which Oral Microbiota Affect Brain Function

Neural Pathways

A growing body of evidence suggests that the translocation of oral microbes to the brain plays a significant role in the development of neuroinflammatory conditions. Oral microbes can translocate to the brain through neural pathways, including the trigeminal nerve and olfactory system, both of which directly link the oral cavity to the olfactory bulb.[4] When the oral mucosal barrier is compromised, as in chronic periodontitis, bacteria and their components, such as lipopolysaccharides, enter the bloodstream and activate endothelial cells through inflammatory cytokine receptors, including TNF-α and IL-1β. This

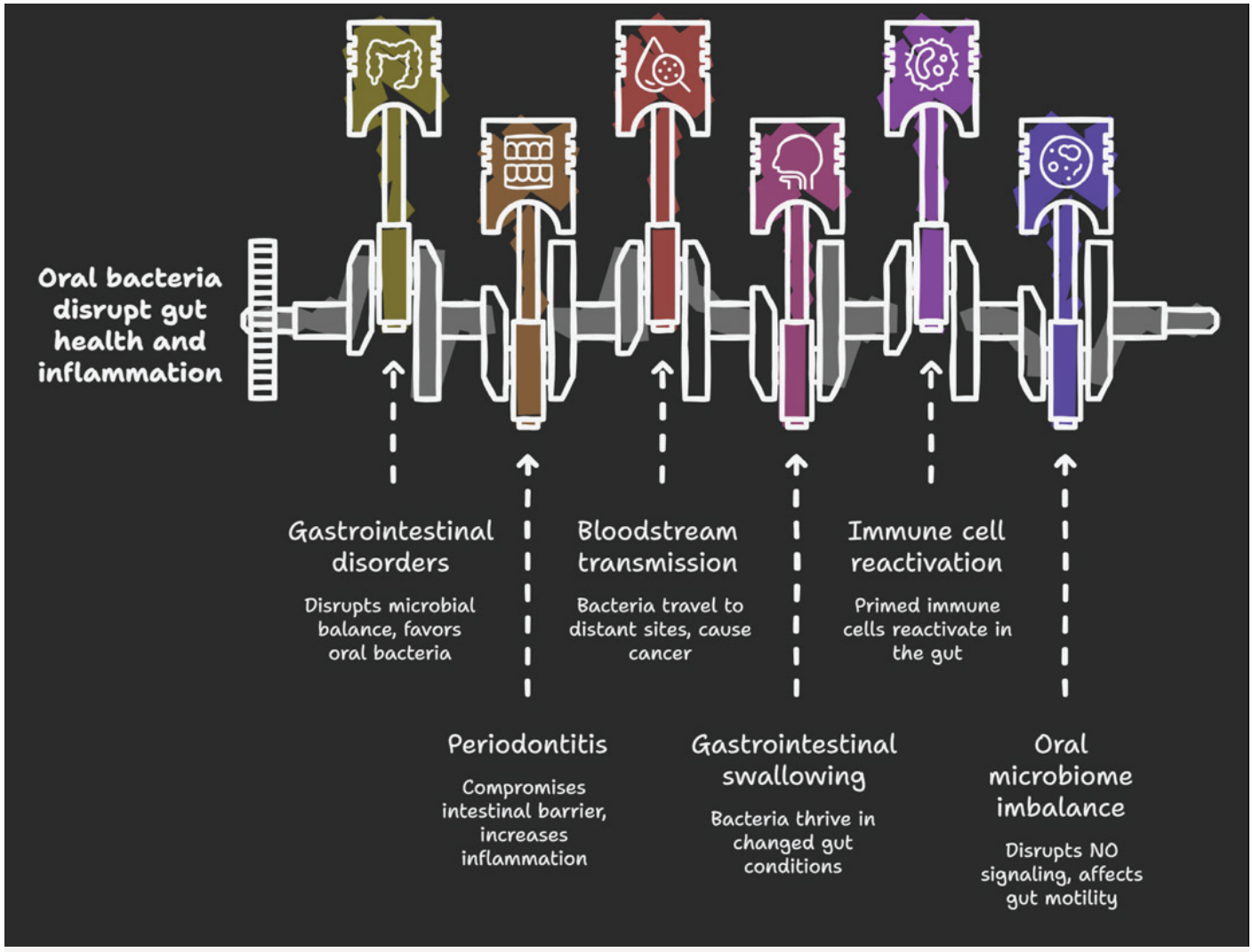

Figure 1. Interactions between the oral microbiome and the gut.

alerts perivascular macrophages, initiates a neuroinflammatory cascade, and activates the hypothalamic-pituitary-adrenal axis, which is closely associated with mood and cognition.

Inflammatory signaling also degrades the blood-brain barrier (BBB), a critical defense against harmful substances, and BBB breakdown has been linked to cognitive disorders and neurodegeneration. *P. gingivalis* exemplifies this threat (Fig. 2). It can breach the BBB, reach brain tissue, and release gingipains, enzymes that activate microglial cells and accelerate dopaminergic neuronal degeneration.[14]

Microbial and Metabolic Pathways

Beyond direct neural invasion, oral microbes influence brain health through the oral-gut-brain axis. Continuously swallowed saliva carries oral bacteria into the gastrointestinal tract, where, particularly after antibiotic use or in immunocompromised individuals, they may alter the composition of the gut microbiota, activate immune responses, and promote chronic low-grade inflammation. This weakens the gut lining, increases intestinal permeability, often referred to as "leaky gut," allows toxins and pro-inflammatory molecules to enter the bloodstream, further disrupts the BBB, impairs nutrient delivery, and ultimately compromises cognition.[3]

Studies have detected elevated levels of oral-origin bacteria in fecal samples, which may be explained by two hypotheses. The "expansion hypothesis" proposes active colonization and multiplication of oral microbes within the gut, whereas the "marker hypothesis" suggests that these microbes merely pass through, with their elevated presence reflecting a reduction in native gut bacteria rather than true colonization. In studies

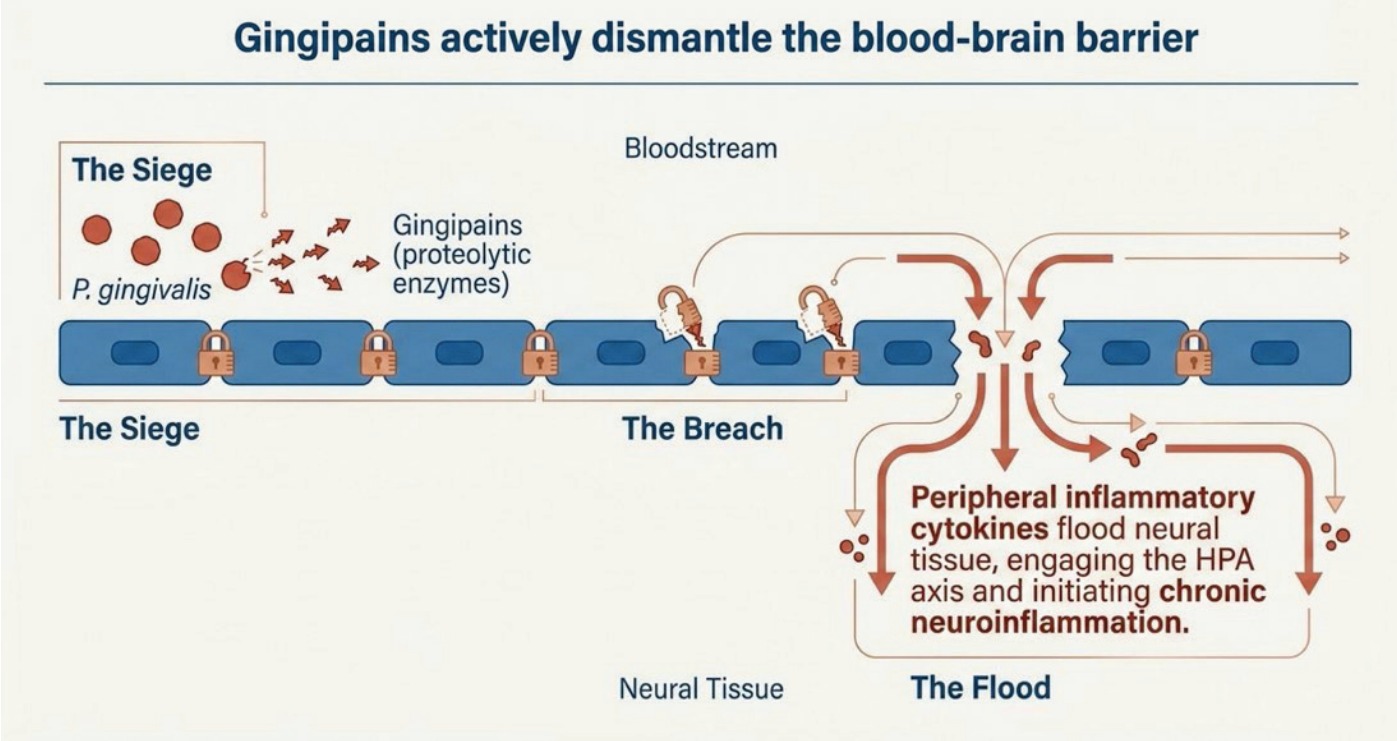

Figure 2. Mechanisms by which gingipains disrupt the blood-brain barrier.

of the oral-gut-brain axis in neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease, animal studies are currently predominant in establishing mechanisms and causality, whereas human studies are predominant in providing observational, epidemiological, and postmortem evidence of disease associations.

Oral-Gut Microbiota and Cognitive Impairment and Decline

Neural Pathways

Neurological disorders affect an estimated 15% of the global population, a figure projected to increase because of aging and growing environmental stressors.[15,16] Among these, neuropsychiatric conditions such as depression, schizophrenia, and autism spectrum disorder are particularly challenging because they are chronic, highly comorbid, and often resistant to conventional treatments.[1] Depression and anxiety alone affect approximately 15–20% of the population.[7]

Emerging research implicates the oral microbiome in cognitive function and mental health. Although individuals share a "core" oral microbiome, genetic, environmental, and lifestyle factors drive substantial interindividual variability.[17] One study by Adnan et al.[18] found that reduced cognitive function correlated with a higher prevalence of pro-inflammatory oral bacteria, including *Treponema*, *Parvimonas*, and *Filifactor*.[19] Whether these microbial shifts can serve as reliable biomarkers for cognitive decline remains unclear; however, the findings suggest that maintaining oral health or modulating the oral microbiome may help prevent or mitigate age-related cognitive deterioration, including Alzheimer's disease.[15,16]

Immune Pathways

Alzheimer's disease (AD), characterized by progressive cognitive decline, has been increasingly linked to chronic periodontitis. Research suggests that oral bacteria and their metabolic byproducts may reach the central nervous system (CNS) through either the bloodstream or peripheral nerves, where they may contribute to the development of neurodegenerative changes.[18] Key pathogens implicated in this process include *P. gingivalis*, *T. denticola*, *F. nucleatum*, *P. intermedia*, *A. actinomycetemcomitans*, and *Streptococcus species*. These microorganisms can produce virulence factors, such as lipopolysaccharides, gingipains, and peptidoglycans, which may cross the blood-brain barrier and provoke chronic neuroinflammation, one of the central mechanisms in AD pathology (Fig. 3).[11,17] Notably, postmortem studies have shown elevated levels of gingipains, produced by *P. gingivalis*, in the brains of individuals with AD compared with healthy controls.[16,20] The most abundant studies are postmortem studies, which show an association between certain microbes

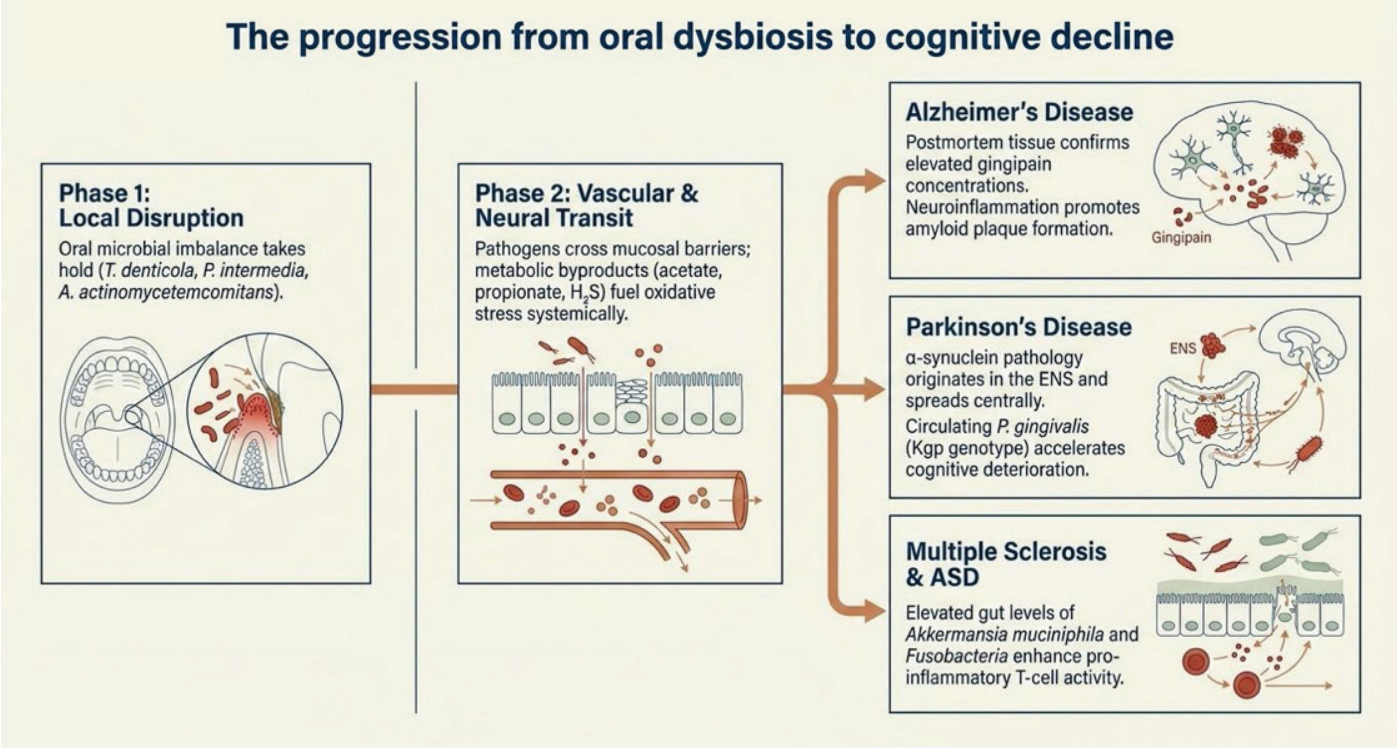

Figure 3. Progression from oral dysbiosis to cognitive decline.

and AD. Beyond direct microbial invasion, metabolites such as short-chain fatty acids, including acetate and propionate, and gases such as hydrogen sulfide (H_2S), produced during oral dysbiosis, may exacerbate neurodegeneration by promoting oxidative stress and inflammatory cascades.[14] Supporting this, experiments in mice in which saliva from patients with periodontitis was introduced into the gut led to intestinal inflammation and microbiota imbalances, suggesting a systemic effect of oral microbial imbalance.[17] To bridge this evidence gap, *P. gingivalis* and its toxins are currently being targeted in ongoing clinical trials, such as one evaluating a lysine-gingipain inhibitor, aiming to reduce its impact in patients with AD.

Microbial and Metabolic Pathways

Parkinson's disease (PD) also shows intriguing microbial associations, with α-synuclein pathology potentially originating in the enteric nervous system. Notably, up to 80% of patients with PD report constipation years before diagnosis. Circulating *P. gingivalis* has been detected in these individuals, with a specific Kgp genotype correlated with worsening cognitive symptoms.[6,21]

Multiple sclerosis (MS) and autism spectrum disorder (ASD) are similarly being linked to microbial imbalances. In MS, elevated levels of *Akkermansia muciniphila* and *Acinetobacter calcoaceticus* may enhance pro-inflammatory T-cell activity while reducing regulatory T-cell function. In addition, elevated gut *Fusobacteria* levels have been associated with future MS relapses.[22] Much of the current understanding of proposed causal relationships and mechanistic pathways is derived from animal studies, which limits direct extrapolation to humans. In contrast, human evidence is largely observational and demonstrates associations between oral pathologies and cognitive decline, along with altered microbial profiles in mild cognitive impairment and AD, although causal inference remains limited because of study design and potential confounding.

Oral Microbiota and Orofacial Pain

Neural Pathways

Orofacial pain, typically experienced in the face, jaw, or oral tissues, has traditionally been attributed to dental problems, muscular dysfunction, or nerve disorders. However, growing research indicates that the oral microbiome may play a more direct role in pain modulation by influencing both local and systemic inflammatory responses and nerve signaling.[23] Periodontitis serves as a prime example of how oral pathogens may contribute to pain. Bacteria such as *P.*

gingivalis, *T. denticola*, and *Tannerella forsythia* release harmful substances, including lipopolysaccharides, gingipains, and outer membrane vesicles. These components can disrupt immune balance and stimulate the release of inflammatory molecules, such as TNF-α, IL-1β, and prostaglandins, all of which increase sensitivity in local nerve endings and amplify pain perception. Specifically, *P. gingivalis* lipopolysaccharide can activate receptors such as TLR4 and TRPA1, which are found on sensory neurons of the trigeminal nerve, the main pain pathway for the orofacial region. Activation of these receptors has been associated with a cascade of inflammatory signals that heighten nerve activity and sensitivity.

Immune Pathways

The trigeminal nerve is not only critical for transmitting nociceptive signals but may also be susceptible to modulation by microbial products. Experimental studies, largely derived from *in vitro* and animal models, suggest that bacterial toxins and inflammatory mediators can stimulate neurons within the trigeminal ganglion, potentially inducing the release of neuropeptides such as substance P and calcitonin gene-related peptide.[10] These mediators are known to play a role in neurogenic inflammation and may contribute to pain persistence; however, direct causal evidence in humans remains limited. In chronic conditions such as burning mouth syndrome and idiopathic facial pain, alterations in the oral microbiome have been reported, but these findings are primarily associative. Consequently, although microbial dysbiosis may be implicated in the pathophysiology of these neuropathic pain conditions, the current evidence does not establish a definitive causal relationship, and further well-designed clinical studies are required. Another limitation is that studies use varied sampling and sequencing techniques, making it difficult to compare results across studies with small sample sizes.

Microbial and Metabolic Pathways

In addition, new evidence points to an important interaction between the oral and gut microbiomes. Certain oral bacteria, such as *F. nucleatum* and *P. gingivalis*, may migrate to the gut, where they disrupt the normal microbial environment, weaken the intestinal barrier, and provoke systemic inflammation. These inflammatory processes may extend to the nervous system through immune and hormonal pathways, potentially influencing brain function and increasing vulnerability to chronic pain and mood disorders. Although such mechanisms provide a plausible link between microbial imbalance and conditions such as temporomandibular disorders, which frequently coexist with anxiety and depression, current evidence is largely correlational and insufficient to establish a direct causal relationship.[23] In addition, long-term prospective studies tracking shifts in microbiome composition alongside the progression of orofacial pain are lacking.

Oral Health for a Healthy Oral-Gut-Brain Axis: Interventions

Diet

Diet has a substantial influence on oral microbial composition and its downstream effects on orofacial and systemic health. Diets high in refined carbohydrates and added sugars selectively favor acid-producing species, including *Actinomyces* spp. and *Streptococcus* mitis, which accelerate the development of dental caries and increase both local and systemic inflammatory burden, further worsening periodontal status. In contrast, dietary patterns characterized by high fiber content, whole grains, polyunsaturated fatty acids, and antioxidant-rich plant foods, as exemplified by the Dietary Approaches to Stop Hypertension (DASH) and Mediterranean dietary models, are associated with a substantially reduced risk of periodontal disease. An analysis of data from more than 6,200 adults found that close adherence to these dietary patterns was correlated with lower odds of periodontitis, whereas low intake of whole grains and dietary fiber was associated with a 32% and 27% higher likelihood of severe periodontitis, respectively.

Plant-based dietary patterns, including vegetarian and vegan diets, appear to confer periodontal benefits, likely because of their anti-inflammatory composition. However, potential reductions in calcium and vitamin B12 intake, as well as lower salivary pH, may increase susceptibility to enamel erosion and dental caries and should be considered in clinical counseling.[6,7]

Functional foods have attracted growing interest as adjuncts in periodontal management. These include mangosteen, a source of xanthone compounds, green tea, curcumin, and fermented lingonberry juice (FLJ). In a 1-year controlled human study, participants who rinsed daily with 10 mL of FLJ mouthwash for 30 seconds experienced significant improvements in salivary pH, buffering capacity, and flow rate, as well as improvements in clinical indicators, including bleeding on probing, plaque accumulation indexes, and microbiome composition.[24]

Probiotics and Prebiotics: Dosage and Regimen

Probiotics, defined by the World Health Organization as living microorganisms that, when administered in sufficient quantities, confer health benefits on the host, have demonstrated the capacity to modulate oral biofilm architecture, immune tone, and inflammatory activity. Clinical trial data indicate that lozenges containing *Lactobacillus reuteri* at a dose of 4×10^8 CFU per day, administered as one lozenge twice daily, over periods of

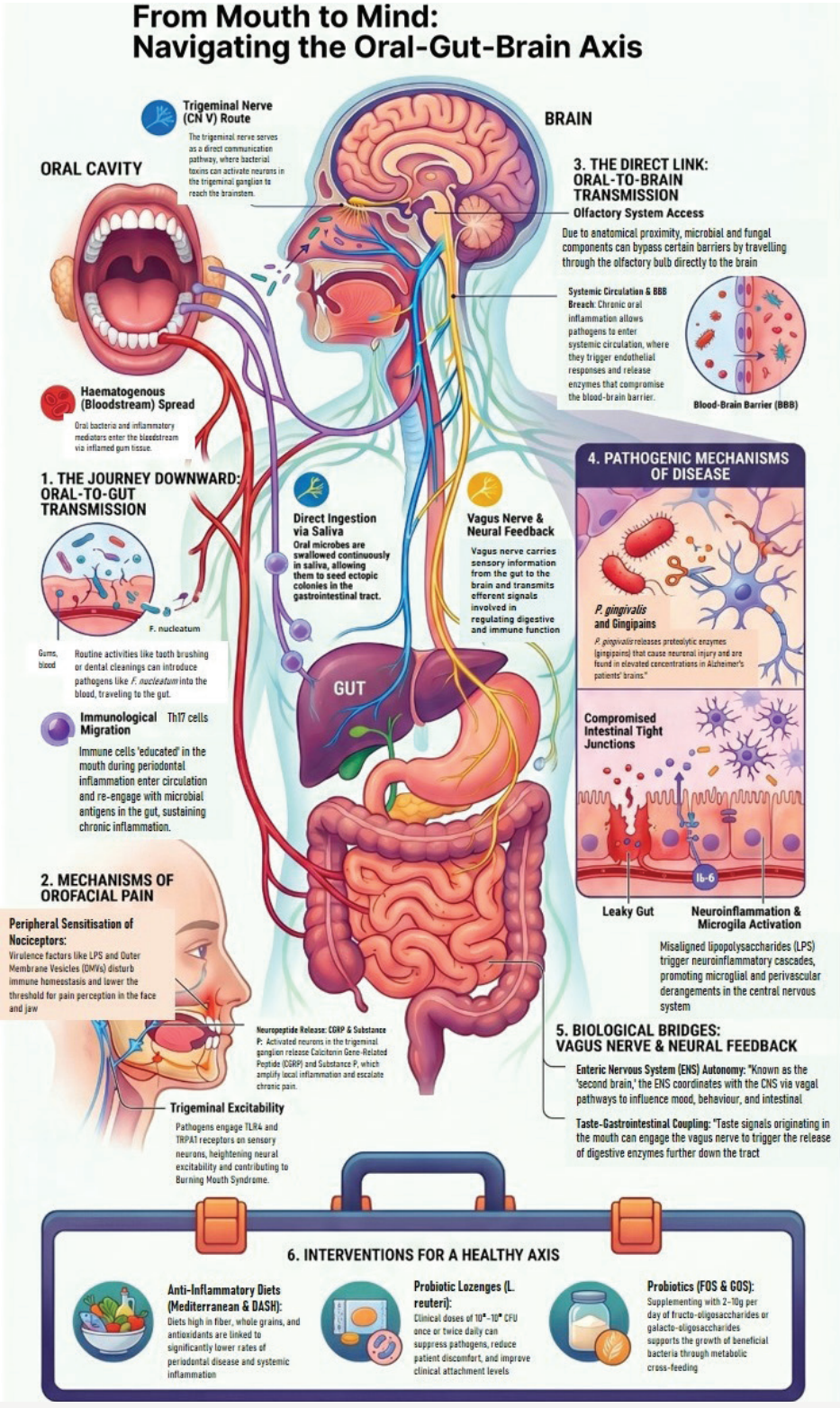

Figure 4. Summary of the article, illustrating how microbes travel from the oral cavity to the gut, how they interact with the gut, their role in neurodegenerative disorders, the possible mechanisms involved, and the interactions between the microbiome and the blood-brain barrier that contribute to the development of neurodegenerative disorders and orofacial pain.

Table 1. Key oral microorganisms, mechanisms, and clinical relevance in the oral-gut-brain axis

Key organism	Mechanism of action	Clinical relevance
Porphyromonas gingivalis	Produces gingipains and lipopolysaccharide; activates TLR4/TRPA1 on trigeminal neurons; disrupts the complement system; outer membrane vesicles transport virulence factors systemically; promotes blood-brain barrier disruption and neuroinflammation	Chronic periodontitis; implicated in Alzheimer's disease and Parkinson's disease
Treponema denticola	Sensitizes the trigeminal ganglion through inflammatory mediators; shows synergistic virulence with *P. gingivalis*	Periodontitis and orofacial pain; co-detected with *P. gingivalis* in postmortem brain tissue from patients with Alzheimer's disease; contributes to systemic inflammatory burden
Prevotella intermedia	Causes hemolysin-mediated cytotoxicity; collagenase degrades connective tissue; exhibits hormone-responsive growth related to estrogen and progesterone	Identified alongside *P. gingivalis* in postmortem studies of Alzheimer's disease; associated with adverse cerebrovascular outcomes
Fusobacterium nucleatum	FadA adhesin activates β-catenin/Wnt signaling; Fap2 suppresses natural killer/T-cell antitumor activity; disrupts enteric glial cells and gut barrier integrity	Colorectal cancer, with enrichment in tumor tissue and links to chemotherapy resistance; inflammatory bowel disease; neuroinflammation in preclinical models; elevated gut levels may predict multiple sclerosis relapses
Streptococcus mutans	Glucosyltransferases form the biofilm matrix; acid production demineralizes enamel; cnm-positive strains bind collagen and cross the blood-brain barrier	Dental caries; infective endocarditis; hemorrhagic stroke and cerebral microbleeds associated with cnm-positive strains

The associations listed do not imply causation. Much of the mechanistic evidence is derived from in vitro and animal studies; therefore, caution is warranted when extrapolating these findings to human clinical populations. TLR: Toll-like receptor; LPS: lipopolysaccharide; BBB: blood-brain barrier; OMV: outer membrane vesicle; AD: Alzheimer's disease; NK: natural killer cell; MS: multiple sclerosis.

3–12 weeks after scaling and root planing significantly reduce pocket depth, improve clinical attachment levels, lower plaque and bleeding indices, suppress key pathogens, including *P. gingivalis* and *A. actinomycetemcomitans*, and delay pathogen recolonization, with benefits maintained at 1-year follow-up. Comparable clinical improvements were achieved with *L. brevis* CD2 lozenges dosed at 1×10^8 CFU per day, with efficacy observed in both smoking and nonsmoking populations.

A recent randomized controlled trial used chewable tablets combining *L. salivarius*, *L. paracasei*, and *L. acidophilus* at 5×10^9 CFU per tablet taken once daily over 3 months, resulting in reductions in pocket depth and bleeding on probing, increased salivary IgA levels, and decreased *Fusobacterium* and *Porphyromonas* concentrations.[9]

Based on the available evidence, a recommended probiotic protocol would involve lozenge, tablet, or chewing gum delivery at a dosage of 10^8–10^9 CFU once or twice daily for 4–12 weeks, ideally administered alongside scaling and root planing, with continued maintenance use to prolong clinical benefit.

Prebiotics are defined, in line with the framework proposed by the International Scientific Association for Probiotics and Prebiotics in 2016, as substrates selectively metabolized by host microorganisms in ways that confer a health benefit.[6] Compounds in this category include inulin, fructooligosaccharides, galactooligosaccharides, resistant starches, and dietary polyphenols, each serving as a fermentable substrate that supports probiotic colonization and facilitates cross-feeding interactions among beneficial bacteria. Standard dosing ranges from 3–10 g per day for a minimum of 4–8 weeks. Synbiotic formulations combining probiotics and prebiotics in a single regimen may yield superior outcomes; however, clinicians should be aware that high prebiotic intake requires rigorous oral hygiene to reduce associated cariogenic risks.

In clinical applications aimed at improving health, prebiotics are most effectively used as adjuncts to probiotics within synbiotic regimens. Because certain prebiotic substrates are selectively fermented by particular bacterial taxa, this strategy can be used to deliberately support the establishment of targeted beneficial species. The metabolic byproducts of one

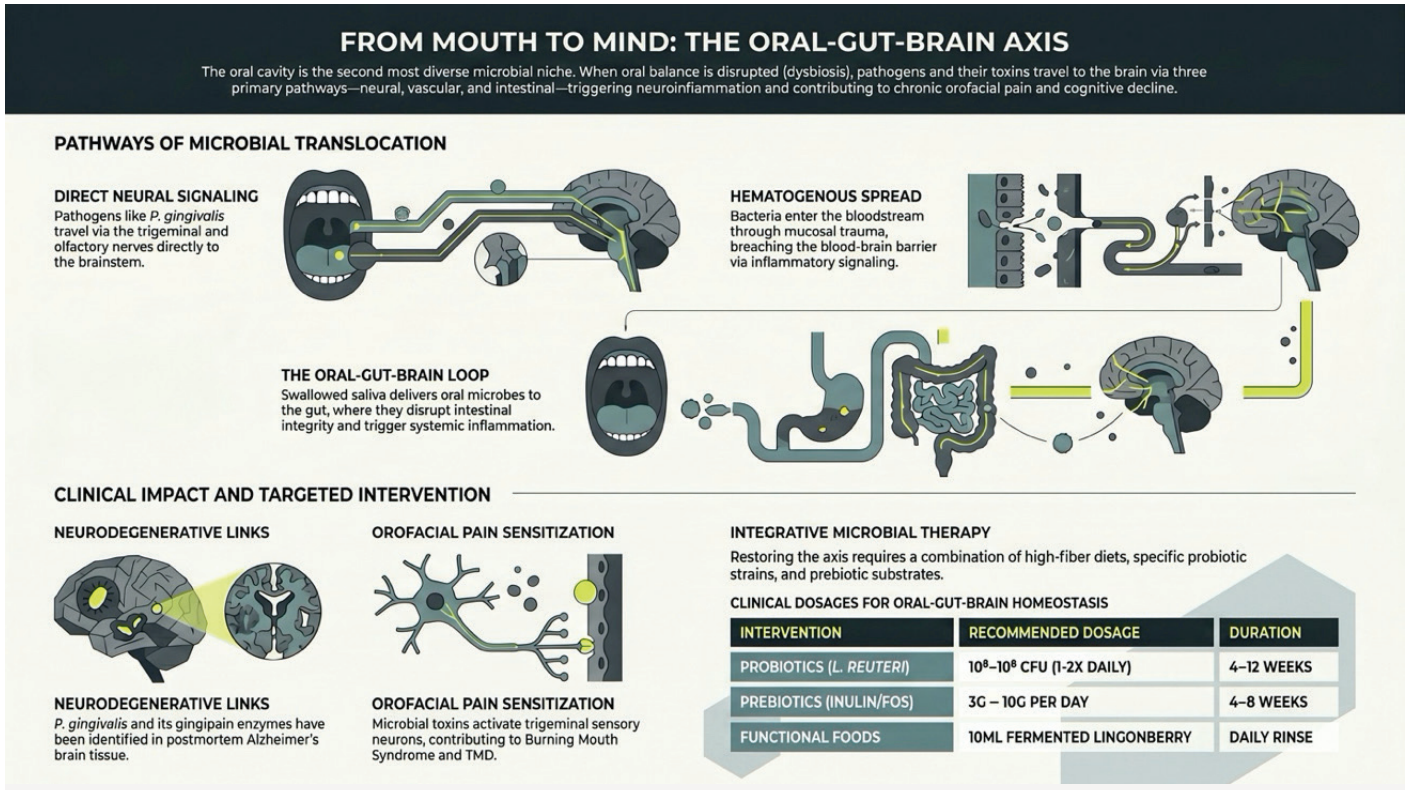

Figure 5. The three proposed pathways by which oral microbial dysbiosis may influence neurological and systemic health: **(a)** direct neural signaling, **(b)** hematogenous spread, and **(c)** the oral-gut-brain loop. The lower panel depicts the clinical associations and therapeutic implications of these pathways and integrative microbial therapy.

organism's fermentation activity may further serve as growth substrates for others, a cooperative metabolic process known as cross-feeding.[6]

Integrative Oral Care Approach

A comprehensive approach to oral health integrates dietary modification, evidence-based probiotic and prebiotic protocols, and consistent oral hygiene practices. Daily prebiotic supplementation in the range of 3–10 g, combined with probiotic lozenges dosed at 10^8–10^9 CFU and administered over a 4–12-week period, can meaningfully support oral microbial balance. Functional foods, including mangosteen and fermented lingonberry juice, provide complementary antioxidant and antimicrobial activity. These microbial interventions should be paired with standard hygiene practices, including twice-daily brushing, interdental cleaning, sugar-free gum use, and judicious mouthwash application. Broad-spectrum antimicrobial agents, such as chlorhexidine and triclosan, are clinically useful but may deplete beneficial microorganisms when used excessively; therefore, their use should be balanced with microbe-supportive strategies.

CONCLUSION

The intricate relationship among oral microbial communities, orofacial pain, and neurodegenerative disease is a rapidly advancing area of scientific inquiry with meaningful clinical implications. A growing body of evidence supports the view that oral dysbiosis is not merely a localized pathological process but a condition capable of contributing to systemic and neurological dysfunction through inflammatory, immunological, and neuroendocrine mechanisms. Figure 4 provides an illustrated and comprehensive overview of the various mechanisms and possible associations between the oral microbiome, neurodegenerative disorders, and orofacial pain. Pathogens such as *P. gingivalis* and *T. denticola* are implicated not only in periodontal disease but also in neuroinflammatory responses, blood-brain barrier compromise, and progressive cognitive decline. The trigeminal nerve, altered salivary microbial profiles, and the overarching oral-gut-brain axis together underscore the extensive systemic reach of oral microbial communities in shaping central pain processing and neurological outcomes. However, many of the mechanistic links identified thus far remain incompletely defined, and causal directionality has yet to be definitively established (Table 1).

There is an urgent need for rigorously designed longitudinal and interventional studies to clarify the specific pathways by which the oral microbiome contributes to orofacial and neurodegenerative pathology. Figure 5 provides an overview of interventions that could contribute to preventing the possible precipitation of the aforementioned diseases. Future research should prioritize the identification of microbial biomarkers capable of supporting early disease detection, the development of microbiome-targeted therapies, and the design of individualized oral care strategies with broader neurological benefits. As medicine moves toward a more integrated understanding of human biology, the oral microbiome may prove to be both a valuable diagnostic indicator and a modifiable therapeutic target in the prevention and management of chronic pain and neurocognitive disorders. Although animal models help clarify mechanisms, human studies are crucial to validate whether findings such as *P. gingivalis* invasion of the human brain represent clinically relevant processes rather than laboratory effects. The field is moving from proving association in humans to establishing causation in animal models and developing interventions.

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