REVIEW

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The Microbiome-Brain Axis in Burning Mouth Syndrome and Its Comorbidities: An Integrated Perspective

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ABSTRACT

Burning mouth syndrome (BMS) is a chronic nociplastic pain condition of unknown etiology, predominantly affecting women and highly comorbid with depression and anxiety. This narrative review proposes a comprehensive model integrating the significant role of the oral and intestinal microbiomes in BMS pathology. We explore how microbial dysbiosis compromises barrier functions, leading to systemic and neuroinflammation, and subsequently modulates key brain networks involved in pain processing and emotional regulation. Evidence suggests that dysbiosis within the oral microbiome (e.g., increased *Streptococcus, Rothia, Bergeyella, Granulicatella, Neisseria*) and/or the intestinal microbiome contributes to BMS pathology. This dysbiosis can compromise oral and intestinal barrier functions, leading to the systemic dissemination of bacterial components and inflammatory mediators. These factors induce neuroinflammation, which directly influences and dysregulates key brain networks such as the default mode network and salience network, crucial for pain processing and emotional regulation. The vagus nerve serves as a critical bidirectional communication pathway within this axis. Preliminary studies indicate potential therapeutic benefits of probiotics (e.g., *Lactobacillus reuteri* in BMS), but large-scale evidence is still emerging. The pathology of BMS, intertwined with depression and anxiety, can be significantly influenced by the oral and intestinal microbiomes. Dysbiosis contributes to chronic systemic and neuroinflammation, driving maladaptive changes in brain networks and neurotransmitter systems. While promising, the field is nascent, requiring further causal studies, detailed mechanistic insights, and robust clinical trials to establish the full therapeutic potential of microbiome-targeted interventions.

Key words: burning mouth syndrome – oral-gut-brain axis – neuroinflammation – nociplastic pain – brain networks – probiotics.

Abbreviations: BBB: blood-brain barrier; BMS: burning mouth syndrome; CEN: central executive network; DMN: default mode network; LPS: lipopolysaccharides; SCFA: short-chain fatty acid; SN: salience network; GABA: gamma-aminobutyric acid.

INTRODUCTION

Burning mouth syndrome is a persistent and often debilitating intraoral burning or dysesthetic sensation, occurring daily for at least two hours for more than three months, in the absence of any identifiable causative oral lesions or systemic disease [1]. Classified as a nociplastic pain condition, its etiology remains enigmatic, often involving a complex interplay of neuropathic, hormonal, and psychological factors [2]. A striking clinical feature of BMS is its high comorbidity with psychiatric symptoms, particularly depression and anxiety, a pattern also observed in other chronic nociplastic pain disorders like fibromyalgia [3]. Furthermore, BMS predominantly affects postmenopausal women, hinting at gender-specific vulnerabilities that likely involve hormonal influences [4].

Historically, the focus of BMS research has largely been on local oral factors or central nervous system changes [5]. However, emerging evidence on the intricate relationship between the human microbiome and systemic health necessitates a broader perspective [6]. This narrative review aims to synthesize current knowledge and propose a comprehensive model that integrates the role of oral and intestinal bacterial flora in the pathology of BMS and its comorbid mood disorders. It explores how microbial dysbiosis can contribute to chronic inflammation, impact crucial barrier functions, and ultimately modulate large-scale brain networks, thereby shaping the pain experience and emotional states in affected individuals.

REVIEW METHODS

This paper presents a narrative review, a synthesis of existing literature rather than a systematic meta-analysis. The information presented is derived from a comprehensive search of peer-reviewed scientific articles, reviews, and clinical trials indexed in databases such as PubMed, Scopus, and Web of Science. Search terms included, but were not limited to: “burning mouth syndrome”, “nociplastic pain”, “oral microbiome”, “gut microbiome”, “oral-gut-brain axis”, “central sensitization”, “neuroinflammation”, “depression”, “anxiety”, “brain networks”, “functional MRI”, “probiotics”.

The selection of articles prioritized those that addressed the shared biological pathways linking chronic pain (especially nociplastic pain and BMS), psychiatric comorbidities, and the microbiome. Emphasis was placed on studies elucidating mechanisms related to barrier function, inflammatory signaling, and brain network modulation. While specific bacterial species are discussed, the focus remains on their collective role within the broader microbial ecosystem and their functional implications for host physiology. This narrative approach allows for the integration of diverse findings into a coherent theoretical framework, highlighting both established knowledge and areas requiring further investigation. This study was approved for study registration by the Ethics Review Board of the Sunlight Brain Research Center on October 22, 2024, approval number: SBRC-508-3.

MICROBIOM-BRAIN AXIS

The Oral-Brain Axis: Local and Systemic Influences

Current scientific literature supports a strong conceptual link between microbial dysbiosis, systemic inflammation, and altered brain function, providing a compelling framework for understanding BMS and its comorbidities [7]. The oral cavity harbors a complex and dynamic oral microbiome. In BMS, studies have begun to identify specific alterations in this microbial community [8]. While a universal “BMS microbial signature” is still under development due to study heterogeneity, research consistently indicates decreased microbial diversity in the oral cavity of BMS patients [9]. Qualitative shifts in bacterial populations are also observed, with some studies reporting an increased relative abundance of genera such as *Streptococcus*, *Rothia*, *Bergeyella*, *Granulicatella*, and *Neisseria* in the saliva or tongue dorsum of individuals with BMS [8]. These shifts are often associated with pro-inflammatory states [10]. Conversely, a reduction in beneficial commensal species, though less specifically characterized for BMS, might also contribute to dysbiosis and a loss of protective functions [11].

These oral microbial changes can influence the central nervous system through two primary routes: direct neural modulation and hematogenous dissemination. Oral bacteria or the inflammatory mediators they produce can directly interact with peripheral nerve endings, most notably those of the trigeminal nerve [12]. Chronic, low-grade inflammation or the production of neurotoxic metabolites by dysbiotic oral flora could induce small fiber neuropathy or functional sensitization of trigeminal afferents, leading to the perception of aberrant burning pain signals even without overt tissue damage [13]. A critical mechanism involves compromised oral mucosal barrier function. Oral dysbiosis can lead to increased permeability of the oral mucosa, allowing bacterial components like lipopolysaccharides (LPS) from Gram-negative bacteria (e.g., *Porphyromonas gingivalis*) and inflammatory cytokines to escape the oral cavity and enter the systemic circulation [14]. These circulating microbial products and inflammatory mediators can then cross the blood-brain barrier (BBB), contributing to central neuroinflammation [15].

The Oral-Gut-Brain Axis: Systemic Amplification

The oral cavity is intimately connected to the gut via the oral-gut axis. Swallowing leads to the continuous transit of oral bacteria into the gastrointestinal tract. In a state of oral dysbiosis, opportunistic or pathogenic oral bacteria can translocate to and colonize the gut, disrupting the existing balance of the intestinal microbiome [16]. This can either initiate or exacerbate gut dysbiosis, which is typically characterized by reduced microbial diversity and an increased proportion of pro-inflammatory species.

Analogous to the oral mucosa, a dysbiotic gut often exhibits impaired intestinal barrier function, commonly termed “leaky gut”. This heightened intestinal permeability allows a greater influx of microbial components and pro-inflammatory mediators into the systemic circulation, significantly intensifying the body’s overall inflammatory burden [17]. This amplified systemic inflammation then profoundly influences the brain via the gut-brain axis, a well-established bidirectional communication pathway that involves the vagus nerve, immune pathways, and microbial metabolites.

Impact on Brain Networks and Neuroinflammation

The chronic inflammatory signals and altered metabolite profiles originating from oral and gut dysbiosis significantly disrupt the function and connectivity of large-scale brain networks, driving the shared characteristics of nociplastic pain, depression, and anxiety [18].

Systemic inflammation, triggered by microbial dysbiosis and compromised barriers, leads to the release of pro-inflammatory cytokines (e.g., TNF-alpha, IL-6). These cytokines can cross the BBB, activating resident immune cells in the brain (microglia and astrocytes). This neuroinflammation sensitizes central pain processing pathways, resulting in central sensitization, a hallmark of nociplastic pain like BMS [19]. This manifests as allodynia and hyperalgesia, amplifying pain perception [20]. Neuroinflammation also contributes to the “sickness behavior” often seen in depression, including fatigue, anhedonia, and cognitive dysfunction [21].

The microbiome profoundly influences brain networks through various mechanisms. Microbial metabolites, particularly short-chain fatty acids (SCFAs) like butyrate, acetate, and propionate (produced by beneficial gut bacteria), can cross the BBB and modulate neuronal activity, gene expression, and brain plasticity [22]. Conversely, dysbiosis can reduce beneficial SCFA production or increase potentially neurotoxic metabolites [7]. Microbial-derived neurotransmitters or their precursors [e.g., serotonin, gamma-aminobutyric acid (GABA)] can also directly impact neural signaling [23]. Immune activation by microbial components can alter BBB integrity and facilitate immune cell trafficking into the brain, affecting neuronal function and connectivity.

Chronic pain, especially nociplastic pain like BMS, often becomes deeply integrated into an individual's self-perception, leading to an overactive and internally focused default mode network (DMN) [24]. The salience network (SN), critical for detecting salient stimuli, becomes hyperactive [24]. Microbial-induced inflammation and altered neurotransmitter availability can heighten SN activity, leading to an exaggerated focus on oral sensations in BMS. Aberrant connectivity between the DMN, SN, and Central Executive Network (CEN) is observed in these conditions [26]. This disrupts cognitive control, impairing the ability to disengage from pain or negative thoughts, thereby compounding the suffering. Dysregulation in monoaminergic systems, notably dopamine, is crucial, linking the pain experienced in BMS to the anhedonia and reward pathway dysfunction seen in depression [27].

The observed female predominance in BMS and its comorbidities may be partly explained by the intricate interplay between sex hormones (particularly estrogen fluctuations), immune responses, and the microbiome [28]. Hormonal changes, especially during perimenopause and menopause, can influence oral and gut microbiome composition, barrier function, and neuroinflammatory susceptibility, thereby increasing vulnerability in women [29].

The proposed model offers a compelling, integrated framework for understanding the complex interplay between BMS, depression, and anxiety, positioning the bacterial flora as a central, albeit often overlooked, orchestrator. The consistent finding of dysbiosis in the oral and/or gut microbiomes of affected individuals points to a shared initiating or contributing factor that can trigger systemic and neuroinflammatory cascades.

Effects on Barrier Function

The identification of specific bacterial genera in BMS, such as increased *Streptococcus*, *Rothia*, *Bergeyella*, *Granulicatella*, and *Neisseria*, challenges the notion of BMS as purely idiopathic [30]. These shifts, even if subtle, suggest that the oral environment is not merely a localized site of discomfort but a dynamic ecosystem whose imbalances can have far-reaching systemic and neurological effects. This aligns with broader research indicating that specific microbial species can drive pro-inflammatory processes that impact neuronal function. For instance, species known for producing toxins (like certain Gram-negative bacteria) can exacerbate barrier permeability and trigger immune responses, creating a fertile ground for chronic inflammation [31]. The concept of the oral-gut-brain axis clearly illustrates how localized oral dysbiosis, via direct translocation to the gut or systemic inflammatory overflow, can contribute to a widespread inflammatory state that ultimately influences the central pain matrix [32].

The impact of this microbial-driven inflammation on specific brain networks provides a neurobiological basis for the observed high comorbidity. Neuroinflammation, characterized by activated glial cells and elevated pro-inflammatory cytokines, directly perturbs neuronal function and synaptic plasticity [33]. This can lead to the hyperexcitability of pain circuits (central sensitization) where even minimal trigeminal input from the oral cavity is amplified, creating the intense burning sensation of BMS. Concurrently, neuroinflammation influences the balance within the DMN and SN [34]. An overactive DMN, fueled by inflammatory signals, can entrench the chronic pain experience into the individual's self-narrative, fostering rumination and a preoccupation with their symptoms. This mirrors the self-focused negative thought patterns characteristic of depression. Simultaneously, an overzealous SN, reacting to chronic internal inflammatory or pain signals as "threat," can heighten attention to oral sensations and contribute to the anxious vigilance often seen in comorbid anxiety disorders [35]. The altered interplay between these networks and the CEN further impairs cognitive control, making it difficult for individuals to disengage from pain or negative thoughts, thereby compounding their suffering.

Effects on Neurotransmitters

Beyond inflammation, the microbiome's influence extends to neurotransmitter modulation. Gut microbiome is known to produce or influence the availability of precursors for key neurotransmitters like serotonin, dopamine, and GABA. Dysbiosis can disrupt these delicate balances. For instance, a reduction in the output of the basal ganglia dopamine system, specifically implicated in BMS pain, resonates with the anhedonia and motivational deficits seen in depression [24]. Similarly, altered availability of GABA, an inhibitory neurotransmitter, can contribute to increased neural excitability and anxiety. This direct neurochemical impact provides another layer of mechanistic explanation for the intertwined nature of BMS and mood disorders [36]. The vagus nerve emerges as a particularly critical nexus within this framework. As a major component of the parasympathetic nervous system, it provides a direct, bidirectional communication highway between the gut, brain, and immune system. Dysbiosis can impair vagal tone, shifting the autonomic nervous system towards sympathetic dominance, which perpetuates a state of chronic stress and low-grade inflammation. The vagus nerve's capacity to directly convey immune signals (via cytokine receptors) and microbial metabolites to the brainstem makes it a primary conduit through which peripheral microbial imbalances can centrally impact pain modulation, emotional regulation, and general well-being. This positions the vagus nerve as a prime target for potential therapeutic interventions aimed at restoring systemic balance.

Gender Differences

The notable female predominance observed in BMS, fibromyalgia, and comorbid depression/anxiety is a crucial aspect that the microbiome model can help elucidate. Sex hormones, particularly the decline in estrogen during perimenopause and menopause (a common onset period for BMS), are known to significantly influence both the composition and function of the oral and gut microbiomes [37]. Estrogen receptors are found throughout the gut, and hormonal fluctuations can alter gut permeability and immune responses, potentially creating a more permissive environment for dysbiosis and inflammation [38]. Furthermore, gender differences in immune responses, stress reactivity, and genetic predispositions may interact synergistically with microbiome alterations to increase vulnerability in women, highlighting the need for gender-sensitive research and treatment strategies.

Integrated Perspective

In essence, the microbial-driven inflammatory and metabolic signals create a “noise” within the central nervous system that sensitizes pain pathways, dysregulates emotional processing, and impairs cognitive control. This integrated perspective shifts the understanding of BMS from an isolated idiopathic condition to a systemic disorder deeply influenced by the intricate relationship between the host and its microbial inhabitants. This holistic view not only offers a more mechanistic explanation for the clinical presentation but also opens new avenues for innovative diagnostic and therapeutic approaches that extend beyond traditional symptomatic management [39]. The components of the oral-gut-brain axis in BMS and their functions are summarized in Table I. The effects of major microbial metabolites in BMS on the brain axis are summarized in Table II.

Limitations

While the microbiome perspective offers compelling insights, it is crucial to acknowledge the significant limitations and remaining unknowns that warrant further investigation:

Causality vs. Association

A primary limitation in microbiome research, including for BMS, is establishing clear causality. While associations between specific microbial profiles and BMS/comorbidities are observed, it remains often unclear whether microbial dysbiosis is a direct cause, a consequence of the underlying disease or associated factors, or a co-factor in a complex interplay. Rigorous longitudinal studies, prospective cohorts, and targeted interventional trials are needed to confirm causal links.

Heterogeneity of BMS

BMS itself is a heterogeneous condition, and different subtypes (e.g., primary vs. secondary, neuropathic vs. idiopathic) may have distinct underlying pathologies, potentially involving varying microbial contributions. Current research often aggregates BMS patients, which might obscure specific microbiome signatures related to different etiologies or response to treatment.

Unknown Molecular Mechanisms

While we propose general mechanisms (e.g., inflammation, metabolites), the precise molecular pathways by which specific bacterial species or their products interact with host cells, modulate neural circuits, or cross biological barriers are still largely unknown. Detailed metagenomic, metatranscriptomic, metabolomic, and proteomic studies are needed to identify the exact microbial effectors and their targets.

Individual Variability and Sample Size

The human microbiome is highly individual, influenced by genetics, long-term diet, lifestyle, geographical location, and medication use. This high variability makes it challenging to identify universal microbial biomarkers or therapeutic targets applicable to all patients. Sample sizes in current BMS microbiome studies are often small, limiting the generalizability of findings.

Table I. Components and proposed mechanisms of the oral-gut-brain axis in BMS

Component	Role in healthy state	Proposed dysregulation in BMS	Outcome in BMS pathology
Oral Microbiome	Maintained diversity; production of protective factors.	Decreased diversity; increased pro-inflammatory genera (e.g., *Streptococcus, Rothia*).	Localized inflammation; production of neurotoxic metabolites; impaired mucosal barrier.
Oral Mucosal Barrier	Restricts bacterial/toxin entry into systemic circulation.	Increased permeability (“leaky mucosa”) due to dysbiosis and inflammation.	Systemic dissemination of LPS and inflammatory cytokines.
Intestinal Microbiome	High diversity; SCFA production; maintains gut barrier integrity.	Gut dysbiosis (often initiated by translocating oral flora); reduced beneficial taxa (SCFA producers).	Reduced anti-inflammatory signals (SCFA); systemic inflammatory amplification.
Intestinal Barrier	Selective permeability; prevents passage of luminal contents.	Compromised integrity (“leaky gut”) due to gut dysbiosis and systemic stress.	Increased influx of LPS/ toxins, further driving systemic inflammation.
Blood-Brain Barrier (BBB)	Regulates exchange between blood and CNS; protects the brain.	Compromised integrity due to systemic inflammation (cytokines, LPS).	Increased entry of peripheral inflammatory signals; activation of microglia/astrocytes.
Vagus Nerve	Bidirectional communication; transmits gut signals; regulates inflammation (cholinergic anti-inflammatory pathway).	Impaired vagal tone; dysregulation of central pain/emotional circuits.	Facilitates transmission of inflammatory signals from periphery to CNS.
Brain Networks (DMN/SN)	Balanced processing of self-referential thought and salient stimuli.	DMN Hyperactivity (rumination, pain entrenchment); SN Hyperactivity (exaggerated pain/threat perception).	Central sensitization; chronic pain; anxiety/depression comorbidity.

BMS: burning mouth syndrome; SCFA: short chain fatty acid; CNS: central nervous system; LPS: lipopolysaccharide; DMN: default mode network; SN: salience network.

Table II. Key microbial metabolites and their effect on the brain axis in BMS

Metabolite Class	Example Compound	Microbial Source	Proposed Effect of Reduction in BMS	Proposed Effect in BMS
Short-Chain Fatty Acids (SCFAs)	Butyrate, Acetate	*Faecalibacterium, Roseburia*	Loss of BBB integrity; reduced anti-inflammatory signaling; decreased T-regulatory cells; impaired neurogenesis.	N/A(generally beneficial)
Neurotransmitter Precursors	Tryptophan	*Clostridium, Bacteroides*	Reduced availability of Serotonin (5-HT) for brain signaling; contributing to low mood/anhedonia.	N/A(generally beneficial)
Inhibitory Neurotransmitters	GABA	*Lactobacillus, Bifidobacterium*	Increased neuronal excitability; heightened pain/anxiety signaling.	N/A(generally beneficial)
Bacterial Toxins	Lipopolysaccharides (LPS)	Gram-negative bacteria (*P. gingivalis, Bacteroides* sp.)	N/A (generally detrimental)	Direct activation of systemic/ brain immune cells (Microglia/ Astrocytes); disruption of BBB integrity; promotion of neuroinflammation.
Secondary Bile Acids	Deoxycholic Acid (DCA)	*Clostridium* sp.	N/A	May have neurotoxic effects or alter gut motility/signaling, contributing to dysbiosis-related symptoms.

BBB: blood brain barrier; GABA: gamma-aminobutyric acid. For the rest of abbreviations see Table I.

Bidirectional Nature of the Oral-Gut-Brain Axis

The oral-gut-brain axis is inherently bidirectional. Psychological stress and central nervous system changes can directly influence microbiome composition and function. Disentangling the precise directions of influence is complex and often a reinforcing loop.

Nascent Evidence for Biotic Interventions

While promising, the evidence for specific biotic interventions in BMS is still nascent. More large-scale, well-controlled clinical trials with standardized biotic formulations, clear outcome measures, and long-term follow-up are required to establish their consistent efficacy and optimal dosing for BMS and its comorbidities.

Multifactorial Etiology

The microbiome is only one piece of a very complex puzzle. Hormonal influences (especially in women), genetic predispositions, immune system variations, and psychological factors all contribute significantly to the development and maintenance of BMS and its comorbidities.

CONCLUSIONS

The complex interplay between BMS, depression, and anxiety can be significantly illuminated by considering the pivotal role of oral and intestinal bacterial flora. Evidence suggests that dysbiosis within these microbial ecosystems contributes to compromised barrier functions, leading to systemic and neuroinflammation. This inflammation, in turn, acts as a crucial modulator of key brain networks, driving the chronic pain and emotional distress characteristic of BMS and its comorbidities. While specific bacterial genera are beginning to be identified, the precise mechanisms and causal links remain areas of active investigation.

The burgeoning field of probiotics offers a promising avenue for therapeutic intervention, with preliminary studies suggesting benefits for oral probiotics in BMS. However, the existing evidence is largely correlational, and the specific molecular mechanisms by which microbial shifts influence brain function are yet to be fully elucidated. Moving forward, rigorous, multi-omics research with larger cohorts and well-designed interventional trials are essential. Unraveling the full complexity of the oral-gut-brain axis in BMS will undoubtedly pave the way for novel, targeted, and truly holistic diagnostic and therapeutic strategies, offering hope for improved management of this perplexing condition and its debilitating emotional comorbidities. What new insights will future research reveal about the silent orchestrators within us?

Conflicts of interest: None to declare.

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