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Systemic gastrointestinal pathogen-induced neuroinflammation as a potential common pathway for stress, sleep, and mood dysregulation

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The co-occurrence of gastrointestinal and affective symptoms along with loss of sleep, commonly referred to as insomnia, remains one of the most common yet conceptually fragmented clinical constellations in medicine. Historically, this triad has been repeatedly explained through a psychosomatic framework, in which stress is regarded as the main determinant, whereas the somatic components are viewed as downstream clinical manifestations. Nevertheless, emerging evidence suggests that chronic infections originating from epithelia may constitute an underreported biological substrate linking sleep disturbance, mood dysregulation, and stress vulnerability through systemic neuroinflammatory pathways.^[1] Rather than replacing psychosocial models, the present framework proposes that chronic mucosal infection may biologically amplify the physiological consequences of stress through persistent neuroimmune activation. Beyond symptom burden, emerging evidence suggests that insomnia and obstructive sleep apnea (OSA) are not solely epiphenomena of stress-related disorders, but

biologically active disorders associated with accelerated biological aging. Systemic inflammation, oxidative stress, mitochondrial dysfunction, and telomere attrition have been consistently implicated as shared mechanisms linking disturbed sleep with long-term cardiometabolic and neuropsychiatric vulnerability.^[2] Consequently, populations with sleep disturbances experience poorer cardio-cerebrovascular and psychological outcomes compared with those without sleep problems, and sleep disorders are increasingly recognized as significant contributors to cognitive decline and neurodegenerative vulnerability, underscoring that routine screening and targeted sleep management are essential to help slow disease progression and mitigate both cardio-cerebrovascular and mental health risks in affected populations.

In this respect, in a monocentric cross-sectional study of 969 participants, *Helicobacter pylori* infection (*Hp*-I) was independently associated with the co-occurrence of gastrointestinal symptoms, sleep disturbances, and affective disorders, with *Hp*-I severity correlating clearly with the probability of

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belonging to the so-called “positive triad” phenotype.^[3] Interestingly, this association remained statistically significant even after adjustment for age, sex, and body mass index, suggesting that microbial burden may contribute proportionally to systemic symptom burden. The relationship between stress and somatic gastrointestinal diagnoses further complicates the historical dichotomy. Of note, in a large-scale Danish prospective cohort study (n = 3 379), psychological stress significantly and independently elevated the incidence of peptic ulcer disease.^[4] Furthermore, *Hp*-I seropositivity, stress, socioeconomic status, and smoking emerged as independent predictors. Rather than representing competing explanations, these findings suggest possible synergistic or additive pathophysiological mechanisms, whereby chronic infection and stress converge upon shared inflammatory and behavioral pathways. Moreover, sleep disturbance should not be interpreted solely as a secondary or epiphenomenal manifestation. The frequent coexistence of insomnia and OSA, termed comorbid insomnia and sleep apnea (COMISA), has emerged as a distinct high-risk clinical phenotype. Large-scale cohort data demonstrate that individuals with COMISA display a markedly elevated risk of incident arterial hypertension and cardiovascular disease compared with those affected by either condition alone, supporting the hypothesis that sleep disruption is an active contributor to systemic cardiometabolic vulnerability.^[5]

Beyond *Hp*-I, increasing attention has turned to further pathogens, particularly *Porphyromonas gingivalis* (*Pg*), the main implicated oral pathogen in chronic periodontitis. Recent work of our research group has highlighted striking pathogenic commonalities between *Hp* and *Pg*, including immune evasion strategies, biofilm formation and persistence, systemic inflammation, and metabolic dysregulation.^[6] Additionally, gingipains, the virulence hallmark of *Pg*, are cysteine proteases and facilitate tissue invasion, complement degradation, cytokine cleavage, and immune deviation. *Hp* possess analogous cysteine proteolytic activity, reinforcing the aforementioned hypothesis of common pathophysiologic mechanisms.^[6]

The interplay between the two aforementioned microorganisms may not be exclusively theoretical. Co-incubation experiments have demonstrated enhanced *Pg* virulence and increased internalization into oral keratinocytes in the presence of *Hp*, proposing therefore a potential synergistic pathogenicity.^[7] Both microorganisms can coexist

within polymicrobial biofilms, especially within dental plaque, and periodontal pockets, where *Hp* may serve as a main extragastric reservoir.^[8] Such interactions may amplify chronic inflammatory signaling and complicate their eradication.

Beyond *Hp* and *Pg*, additional gastrointestinal, oral, and systemic pathogens may converge on the same neuroinflammatory pathway, underscoring that this framework need not be confined to a single organism. Unlike the largely indirect evidence available for several mucosal pathogens, *Chlamydia pneumoniae* has been experimentally demonstrated to infect circulating monocytes and promote their transmigration across endothelial barriers, supporting a “Trojan horse” mechanism of central nervous system invasion.^[9, 10] *Fusobacterium nucleatum*, an oral-gut translocating anaerobe increasingly implicated in dysbiosis-related pathology, has been shown to induce neurodegenerative changes and hippocampal amyloid-beta accumulation alongside altered gut microbiota composition in an Alzheimer’s disease rat model, paralleling mechanisms described for *Hp*.^[11] Viral triggers may act through convergent, if mechanistically distinct, routes: Epstein-Barr virus’ dUTPase induces neuroinflammatory mediators implicated in the fatigue, cognitive impairment, and mood disturbance characteristic of myalgic encephalomyelitis/chronic fatigue syndrome;^[12] cytomegalovirus seropositivity has been associated with microglial activation, neuroinflammatory markers, and mood disorders including suicide risk in postmortem brain tissue;^[13] and post-acute SARS-CoV-2 infection is increasingly acknowledged as an inducer of neuroimmune phenotype—marked by blood-brain barrier disruption (BBB), glial activation, and cytokine dysregulation—that manifests clinically as insomnia, fatigue, and mood dysregulation.^[14] Although mechanistically heterogeneous, these observations support the broader hypothesis that diverse mucosal and systemic pathogens may converge on a shared neuroinflammatory final common pathway, rather than implicating any single organism as uniquely causal.

Systemic dissemination of cytokines and other inflammatory mediators offers a biologically plausible explanation for neuropsychiatric outcomes. Both *Hp* and *Pg* activate NF- κ B-dependent pathways and upregulate circulating TNF- α and IL-6 levels, cytokines implicated in multiple processes, including insulin resistance, endothelial dysfunction, and BBB permeability.^[6]

Gingipain may additionally mediate the degradation of tight junction proteins and complement

components, processes that may further compromise BBB integrity. Likewise, *Hp*-derived lipopolysaccharide and VacA cytotoxin can activate immune cells and promote cytokine release.

The systemic inflammatory burden generated by these pathogens is further transmitted to the brain via direct neuronal routes. Beyond the humoral route implicating circulating mediators, the autonomic nervous system (ANS), particularly the vagus nerve, serves as a rapid and direct neuronal conduit linking mucosal inflammation with the brain.^[15] Dysregulation of the ANS has been widely implicated in stress-related symptoms, sleep disturbances, and mood disorders.^[16] Within this framework, the enteric nervous system (ENS), often referred to as the “second brain,” operates autonomously while remaining in continuous communication with the central nervous system through the gut-brain axis. This bidirectional network integrates vagal signaling, gut hormones, immune mediators, and microbial metabolites, thereby connecting gastrointestinal homeostasis with neurological function. Importantly, ENS dysfunction has been associated with altered neurotransmission, gut microbiota dysbiosis, and neuroinflammatory processes that may contribute to the development of neurological and psychiatric disorders,^[17] including stress-related signs, sleep and mood disorders.^[18] More specifically, pathogen-associated molecular patterns and local pro-inflammatory cytokines can stimulate afferent vagal terminals in the gastrointestinal tract, facilitating direct signaling to the nucleus tractus solitarius and subsequently to higher brain centers involved in affective and stress regulation, including the hypothalamus and amygdala.^[19]

Furthermore, the “cholinergic anti-inflammatory pathway,” mediated via efferent vagal fibers, normally suppresses systemic inflammation by inhibiting TNF- α release from macrophages.^[20] However, chronic infection-induced dysregulation or perpetual stress may impair this autonomic reflex, leading to a state of sympathovagal imbalance.^[21] This autonomic dysfunction may not only exacerbate neuroinflammation but also synergistically contribute to the clinical manifestations of the proposed triad, including fragmented sleep architecture, hypothalamic-pituitary-adrenal (HPA) axis hyperreactivity, and emotional instability.

Sleep disturbance is another crucial component of this interconnected network. Insomnia represents a relevant global burden; at least 40% of individuals with co-existing multiple sclerosis are affected, with insomnia associated with cognitive impairment,

fatigue, depression, as well as anxiety.^[22] Likewise, increased rates of insomnia and affective symptoms have been documented among healthcare students characterized by chronic stress ^[23, 24]. Although often explained purely within psychosocial models, persistent smoldering (low-grade) inflammation may partly explain such vulnerability in biologically susceptible individuals.

Neuroinflammation, on the other side, directly interfaces with stress physiology and sleep regulation. Proinflammatory cytokines including IL-1 β and TNF- α modulate sleep pattern; for instance, chronic elevation has been associated with fragmented and non-restorative sleep. Contrariwise, sleep deprivation may trigger systemic inflammation, creating a self-perpetuating cycle. Cytokine-induced activation of the HPA axis further amplifies cortisol dysregulation, affecting mood stability and stress responsivity. Chronic epithelial-associated infections may therefore serve as an inflammatory amplifier, lowering the threshold for stress-induced psychopathology.^[25]

Beyond mucosal and vagal mechanisms, infected or activated circulating monocytes may traverse a compromised BBB in a “Trojan horse”-like manner, carrying inflammatory signals into the brain parenchyma. In our previous systematic review of Alzheimer’s disease and gastrointestinal microbiota, we reported that most included studies demonstrated positive associations between cognitive deterioration and microbial dysbiosis, with *Hp* the most frequently reported pathogen, via chronic systemic inflammation and BBB disruption.^[26] Sleep disturbances per se have also been independently associated with unfavorable cognitive outcomes: large-scale meta-analyses indicate that both insomnia and OSA significantly elevate the risk of all-cause dementia, AD, and cognitive decline, positioning sleep disruption as a key player linking systemic inflammation with neurodegenerative vulnerability.^[27] In humans, successful *Hp* eradication has been associated with long-term cognitive benefits, including improved Mini-Mental State Examination scores among patients with AD, while preclinical models show that *Hp* filtrate can impair spatial learning and increase hippocampal amyloid-beta production. ^[28, 29] Genetic evidence supporting a potential causal relationship has also emerged: Mendelian randomization analyses indicate that the phylum Proteobacteria—which includes *Helicobacter*—may exert a causal influence on major depressive disorder risk ^[30], and a separate Mendelian randomization study has associated *Hp*-I with AD risk.^[31]

Preclinical data support microbiota modulation as a

promising future therapeutic avenue. In this respect, probiotic supplementation (*Lactobacillus rhamnosus*, *Lactobacillus plantarum*) reversed anxiety- and depression-like behaviors in *Hp*-infected rats by normalizing HPA axis activity and oxidative stress markers, anti-inflammatory cytokines, brain-derived neurotrophic factor levels, serotonergic signaling, and corticosterone concentrations [32]. Although translational extrapolation necessitates cautious interpretation, such findings lend support to the biological plausibility of infection-driven neurobehavioral modulation and further reinforce a bidirectional mechanistic framework within the gut-brain-sleep axis.

Apart from strategies that selectively target the causative pathogens themselves, recent evidence proposes that targeting sleep disturbance *per se* may yield favorable downstream clinical effects. CBT-I has been reported not only to improve insomnia severity, but also to meaningfully decrease OSA severity in patients with comorbid insomnia and sleep apnea, supporting the concept of sleep regulation as a modifiable therapeutic node within this integrated neuroimmune framework.[33]

On the other hand, establishing a definitive pathogenetic link along the gut-brain axis requires a careful weighing of both causal evidence and epidemiological inconsistencies. Currently, the observed associations between chronic mucosal pathogens and neuropsychiatric or cognitive outcomes do not fully meet Koch's postulates for direct, linear causality. In fact, several cohort studies and preclinical models have failed to demonstrate a significant relationship between *Hp*-I and either depression or all-cause dementia. As previously considered in our comprehensive review on the impact of *Hp* on AD, these conflicting findings are frequently attributed to clinical heterogeneity, variability in diagnostic criteria and methodologies, and the presence of systemic confounders across study populations.[26]

Taken all together, these studies provide encouraging evidence of a conceptual reframing: systemic pathogen-induced neuroinflammation may reflect a shared biological pathway linking gastrointestinal disorders, insomnia, stress vulnerability, and affective disorders (Fig. 1). Rather than viewing stress as solely a psychological trigger or

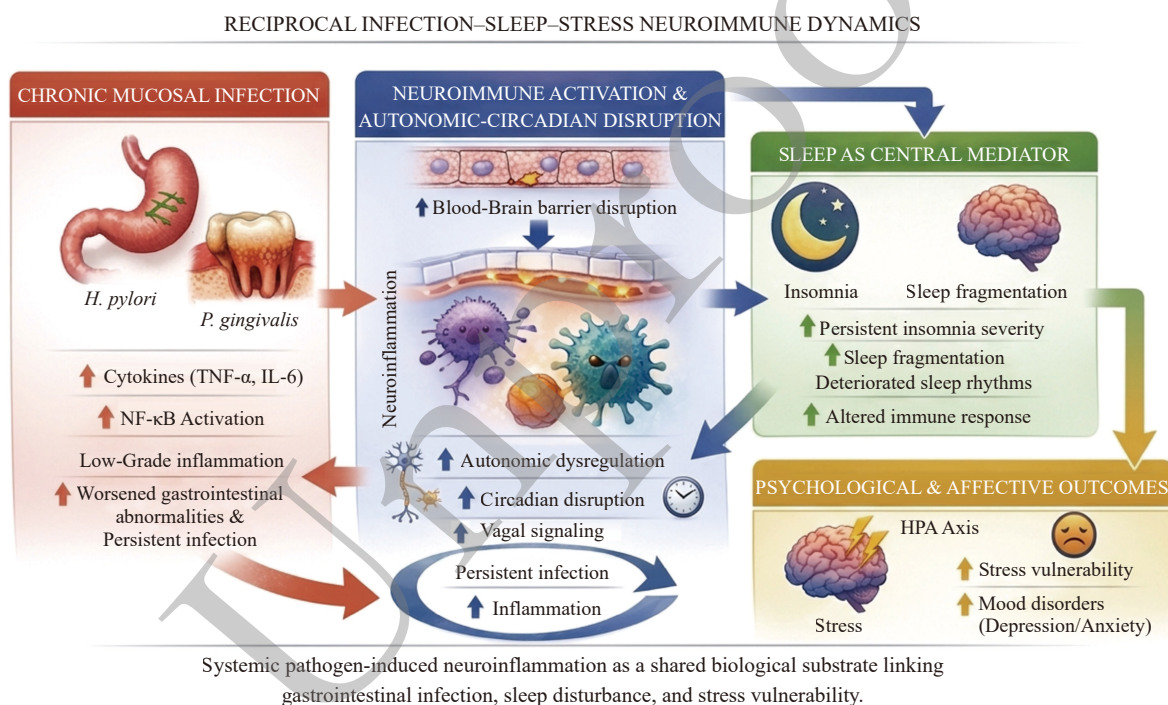


Fig. 1 Conceptual schematic of the proposed infection-sleep-stress neuroimmune pathway. Chronic mucosal infection with *Helicobacter pylori* and/or *Porphyromonas gingivalis* is hypothesized to drive low-grade systemic inflammation (elevated TNF- α and IL-6, NF- κ B activation) and gastrointestinal symptom persistence. This inflammatory state may contribute to blood-brain barrier disruption and neuroinflammation (glial activation), together with vagally-mediated autonomic dysregulation, HPA-axis activation, and circadian dysregulation, which in turn may manifest as insomnia and sleep fragmentation with associated alterations in immune function. Downstream, this cascade is proposed to interface with stress vulnerability and mood disorders (depression/anxiety). The lower feedback loop links persistent low-grade inflammation back to infection persistence, illustrating the proposed self-perpetuating cycle. This model is a conceptual synthesis of the evidence discussed in the text and does not imply established causality among the depicted components.

infection as a localized biological phenomenon, a bidirectional crosstalk of infection-stress feedback loop may exist. Chronic mucosal infection may promote smoldering systemic inflammation; inflammatory mediators may compromise sleep and HPA regulation; sleep fragmentation may further hamper immune competence; immune dysregulation may also contribute to microbial persistence.

This framework cannot prove or even insinuate deterministic causality nor does it negate psychosocial contributors. Socioeconomic stress, behavioral risk factors, genetic predisposition, and environmental exposures likely adjust susceptibility. However, acknowledgment of infection-driven inflammatory priming may refine in the future both diagnostic and therapeutic strategies. Screening for sleep and affective symptoms in patients with chronic *Hp*-I or periodontitis—and conversely considering mucosal infection in treatment-resistant insomnia or depression—may represent pragmatic clinical steps.

Future research should focus primarily on longitudinal study designs integrating microbiological assessment, biomarkers of inflammation, actigraphy-based sleep measures, HPA axis profiling, and high-resolution neuroimaging. Interventional trials evaluating whether *Hp* eradication, periodontal therapy, or microbiota-targeted strategies modify sleep and mood patterns would offer valuable mechanistic insight.

In conclusion, accumulating evidence suggests that chronic mucosal pathogens such as *Hp*, *Pg*, and other implicated organisms may extend their virulence beyond local sites, contributing to systemic neuroinflammatory cascades that interface with stress physiology and sleep regulation. Systemic pathogen-induced neuroinflammation represents a potential unifying framework bridging gastroenterology, periodontology, psychiatry, and sleep medicine. Reconsidering stress-related disorders within this integrated neuroimmune context may ultimately refine prevention strategies and broaden therapeutic horizons.

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