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Mental health and periodontal and peri-implant diseases

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1 | INTRODUCTION

Periodontal diseases are characterized by microbial challenge in a susceptible individual and can result in destruction to the supporting tissues of the tooth with the potential for eventual tooth loss.[1,2] Peri-implantitis appears to be a multifactorial disease that is characterized by inflammation in the peri-implant mucosa with progressive loss of supporting bone surrounding a dental implant.[2,3] Epidemiologic studies have shown that periodontal and peri-implant diseases do not affect all the population in the same way, with clear variation in phenotypic expression.[4–7] The presence of keystone pathogenic species with the potential to cause dysbiotic disease, coupled with variations in genes that encode the componentry of the host's immune system, sets the stage for individual differences in periodontitis risk.[8,9] Less is known about the heterogeneous infection that includes periodontopathic microorganisms[10] and an individual's genetic susceptibility[11,12] in relation to peri-implantitis risk. It is apparent that periodontal and peri-implant diseases have a complex pathogenesis and are multifactorial in etiology.[13] Epidemiologic and experimental evidence exists for the role of a number of risk factors in the initiation, progression, and severity of periodontal and peri-implant diseases. For periodontal disease, these risk factors include male gender, smoking, poorly controlled diabetes mellitus and possibly obesity, osteoporosis, and low dietary calcium and vitamin D.[14] For peri-implantitis, risk factors with strong evidence include a history of periodontitis, poor plaque control, and lack of regular maintenance.[15] In addition, implant failure may cluster in patients.[16] A substantial body of evidence indicates that psychosocial stress may play a role in periodontal diseases, with less evidence available to support the role of mental health disorders. Interestingly, there is increasing evidence to show that the gut microbiota has an important function in modulating brain functionality and, therefore, behavior. The connection has been termed the brain-gut axis and is a significant area of study to understand mental disorders, particularly depression.[17] Little research has evaluated the relationship between the oral microflora, their interactions with the brain, and mental health disorders. Increasingly, mental health disorders and some of their pharmacotherapies have been linked to higher rates of implant failure.[18–21] Possible mechanisms involve inconsistent compliance with dental visits, a lack of adherence to oral hygiene regimes, and use of antidepressants. Understanding the relationship between mental health disorders, periodontal diseases, and peri-implantitis may allow for improvements in the prevention and treatment of these diseases.

2 | WHAT ARE MENTAL HEALTH DISORDERS AND WHO GETS THEM?

Mental health disorders are a group of diseases that are often chronic in nature, presenting with high comorbidity rates and poor treatment outcomes.[22] High-prevalence mental health disorders include mood (affective) disorders. According to the International Classification of Diseases-10, mood disorders comprise a spectrum of diseases that reflect a change of affect and mood. One end of the spectrum represents a depressed state (eg, a depressive episode), whereas the other is an elated state (eg, a manic episode). Patients can experience both; for example, in bipolar disorder. Mood disorders tend to be recurrent and often are initiated by environmental stressors.[23] Disorders such as schizophrenia, Alzheimer disease, and substance use disorders remain in other arms of the International Classification of Diseases-10.

Depressive disorders are characterized by sadness, loss of interest and pleasure, feelings of guilt or low self-esteem, disturbed sleep or appetite, feelings of tiredness, and poor concentration. They can be persistent and recur, leading to problems functioning at work or

coping with daily life. Anxiety disorders are characterized by feelings of anxiety and fear. They can be broadly described as a group of disorders in which anxiety is induced in situations that may or may not be well defined. These situations often produce a feeling of strong avoidance, or they are endured with apprehension. Examples of physical symptoms include palpitations, shortness of breath, or feeling faint, and they are often accompanied with irrational thoughts, such as fears of dying, losing control, or going mad. Anxiety and depression are often coexistent conditions.[23]

Data from 2015 indicate the prevalence of depression to be 4.4%, and more prevalent in females. This is roughly 322 million people worldwide. Prevalence appears to peak around older adulthood, 55-74 years. Between 2005 and 2015 there was an 18.4% increase in the number of people living with depression. In the United States in 2009, US$22.8 billion were spent on the treatment of depression with the loss of productivity estimated at US$23 billion in 2011.[24] The prevalence of anxiety disorders is around 3.6% and again more common in females, equating to 264 million people worldwide. Interestingly, prevalence does not vary considerably between age groups. The largest single contributor to nonfatal health loss is depressive disorders.[25]

Mental health disorders have been associated with cardiovascular disease and diabetes mellitus. This may be through lifestyle factors, such as smoking, reduced activity, poor diet, obesity, hypertension, or a lack of adherence to health programs or advice commonly seen in patients with mental health disorders. Though biological effects may be due to alterations in neurotransmitter and hormone levels such as serotonin and cortisol, which influence the immune response, systemic inflammation may also play a role through bidirectional relationships.[26]

Risk factors for depression in adults include sex, age, race/ethnicity, education, marital status, geographic location, employment status, chronic illness, substance abuse, and family history of psychiatric illness.[24] Exposure to traumatic childhood events is now recognized as an antecedent to future major depressive disorder. The risk factors in older adults are slightly different and reflect a greater age. They include disability, complicated grief, chronic sleep disturbance, loneliness, and a history of depression. Different factors may influence the relapse and recurrence of depression than those that influenced the initial onset. Moreover, major depressive disorder is associated with poorer health and earlier death. This includes a higher prevalence of heart disease, diabetes, obesity, cognitive impairment, disability, and cancer. In addition, unhealthy lifestyles are common, with poorer self-care and adverse effects of medications.

2.1 | Biological mechanisms to explain mental health disorders

No established mechanism can explain all aspects of depression.[27] Major depressive disorder clusters within families, with a threefold risk for first-degree relatives and a suggested 35% heritability. However, it is highly polygenic and involves many genes with small effects. Single-nucleotide polymorphism analysis is inconclusive, and there has been limited success with genome-wide association analysis.[28] This may be due to the heterogeneity of the diseases, the need for large sample sizes, the influence of environment, or patient phenotypes, which is very similar to periodontitis. Gene expression studies have shown increases in tumor necrosis factor, interleukin-1β, cyclo-oxygenase, inducible nitric oxide synthase, and calcium signaling genes. However, it is thought that the environment and gene-environment interactions are likely to have large role in inflammation-related depression. In addition, the effects of some single-nucleotide polymorphisms may only become evident in the presence of life stressors. Stress-dependent epigenetic deoxyribonucleic acid methylation of glucocorticoid-response elements may lead to glucocorticoid receptor resistance. Immune genetic variants that increase risk of depression are likely to increase risk for obesity, diabetes, and cardiovascular disease and contribute to overlap between depression and other medical conditions.

There are several pathophysiological pathways that have been implicated in mental health disorders, including the hypothalamic-pituitary-adrenal axis, autonomic nervous system, and the immune system. Childhood exposure to risk factors for mental health disorders may persistently increase the activity of corticotropin-releasing hormone containing neural circuits leading to reduced glucocorticoid receptor function. Hypothalamic-pituitary-adrenal alterations correlate with impaired cognitive activity and increased cortisol levels are a risk factor for subsequent impairment.[29] Chronic low-grade inflammation triggers changes that contribute to mental ill health. Neuroinflammation is a term for the immune-related process that occurs within the brain and can result from peripheral infection. It is associated with sickness behaviors such as fatigue, anhedonia, and sleep disturbance.[30] Depression has been suggested to be a chronic overextended version of sickness behavior. Any acute infection can affect mood state by the production of proinflammatory cytokines that can play role in generation of psychological phenomena. However, chronic infection is detrimental due to the effects on brain homeostasis. Although the brain lacks the adaptive arm of the immune response, peripheral immune events will affect the brain, such as immune cells entering the central nervous system or cytokine activation of brain cells. Chronic stress can cause inflammasome complex expression in the microglia of the hippocampus and other mood-regulating areas, where prolonged activation of microglia is thought to be detrimental and may occur in depression.[31] The peripheral release of inflammatory cytokines can activate the hypothalamic-pituitary-adrenal axis. Nitrous oxide is an important gaseous neurotransmitter normally found at low concentrations in noninflammatory conditions, but it is increased due to induction of nitrous oxide synthase by inflammatory cytokines and can cause neuronal damage. The glucocorticoid inflammation hypothesis of depression (see later) describes how chronic stress affects glucocorticoid expression and sensitivity, which may result in less repair of damaged neural cells and an overall increase in inflammation. Reduced neuronal repair and decreased protein synthesis can contribute to changes in the brain that are seen in depression.

Recently, Miller and Raison[32] have argued for the pathogen host defense hypothesis of depression (Figure 1). They explain that an active immunity was required in early human evolution for survival, which resulted in the integration of immunological and behavioral responses to conserve energy for recovery. This immune response was "held in check" by the coevolved nonfatal immunoregulatory microflora present throughout the human body. In the clean, modern world relatively absent of the same exposure to the immunoregulatory flora, risk factors result in activation of the host defenses, leading to the release of proinflammatory cytokines and onset of sickness with depression-like behavior. They suggest women appear to be more sensitive to the effects of inflammation on behavior, which may account for the sex differences in disease prevalence. Analyses of blood in subjects with major depressive disorders show increased levels of proinflammatory cytokines and receptors, interleukin-6, interleukin-8, tumor necrosis factor alpha, and toll-like receptor 3 and 4, as well as acute-phase reactants.

Miller and Raison[32] suggest another pathway for how inflammation affects the brain (Figure 2). Inflammasomes are cytosolic protein complexes that form in myeloid cells in response to pathogens or nonpathogenic stressors, which lead to the production of cytokines such as interleukin-1β and interleukin-18. There is evidence to suggest that inflammasomes may be activated by endogenous damage-associated molecular patterns, including heat shock proteins, uric acid, and adenosine triphosphate, or microbial-associated molecular patterns leaked from the gut. The increased levels of inflammation access the brain through humoral and neural routes. Microglial cells are also activated to an M1 proinflammatory phenotype that attracts activated myeloid cells to the brain via the cellular route, where macrophages can perpetuate central inflammatory responses. Increased levels of interleukin-1β and tumor necrosis factor alpha can induce p38 mitogen-activated protein kinase, which increases the expression and function of reuptake pumps and leads to decreased availability of serotonin, dopamine, and noradrenaline. Changes in the availability of these signaling molecules have important effects in guiding motivated behavior.

3 | WHAT IS STRESS?

The term "stress" describes the effects of psychosocial and environmental factors on physical and/or mental well-being.[33] These psychosocial and environmental factors are known as stressors, and they challenge the organism's normal homeostatic mechanisms, thereby eliciting a set of physiological reactions.[34] In situations where stress is acute, the stress response initiates the host's immune system for subsequent challenge.[35] By contrast, chronic stress may result in long-term inflammatory processes that can contribute to disease either locally or systemically, such as diabetes mellitus,[36] cardiovascular disease,[37] and periodontitis.[38]

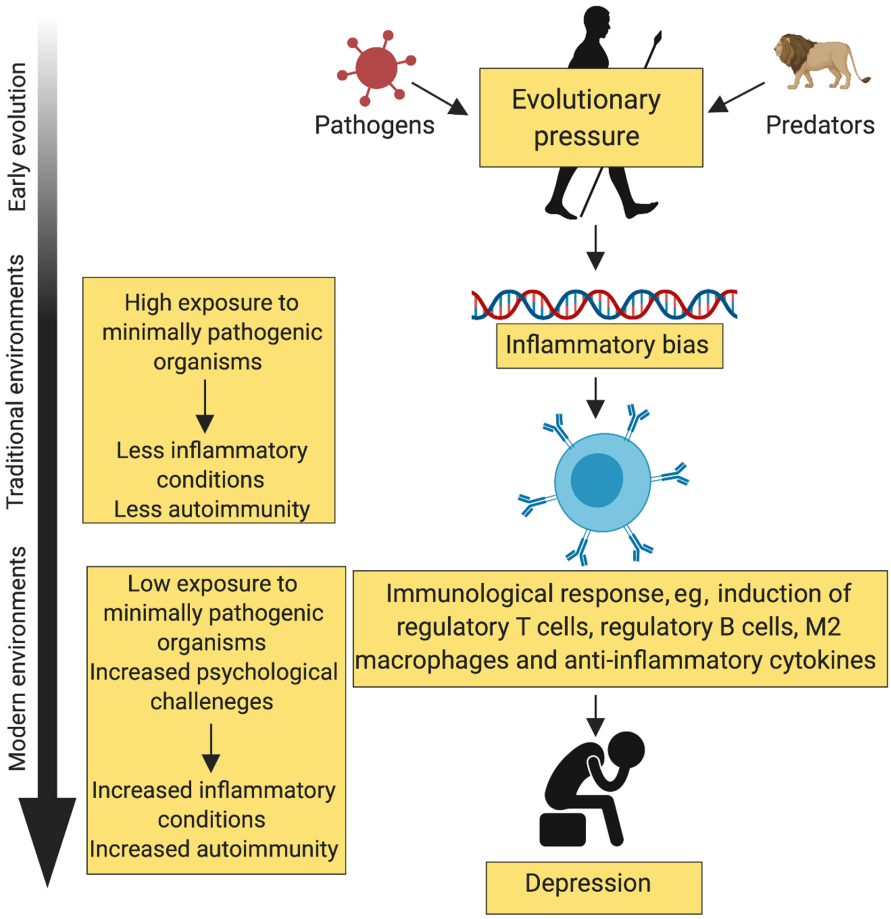

FIGURE 1 Pathogen host defense hypothesis (redrawn from Miller and Raison,[32]). Early human evolution required an active immunity for survival that was held in check by the immunomodulatory microbiome. Modern society lacks the same exposure to an immunomodulatory microbiome, resulting in the onset of a "sickness" with depression-like behavior

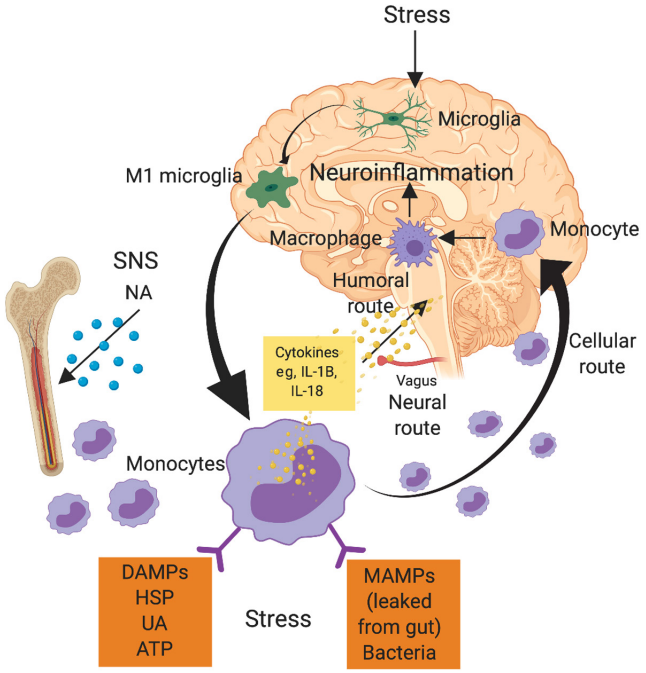

FIGURE 2 Inflammasome model of neuroinflammation (Miller and Raison[32]). Inflammasome formation in monocytes results in the production of proinflammatory cytokines, increasing the levels of neuroinflammation through humoral, neural, and cellular routes. ATP, adenosine triphosphate; DAMPs, damage-associated molecular patterns; HSP, heat shock protein; IL: interleukin; MAMPs, microbial-associated molecular patterns; NA, noradrenaline; SNS, sympathetic nervous system; UA, uric acid

3.1 | Stress pathways

The duration of stress, either acute or chronic, has a significant influence on both innate and cellular immune responses and has been the focus of significant research.[39] Acute stress appears to have fast-acting, short-term effects resulting in the upregulation of the innate immune response, including alterations to the quantity and composition of circulating leukocytes and increases in inflammatory cytokines.[39] By contrast, chronic stress seems to have long-term effects associated with dysregulation of innate and cellular immune responses, resulting in promoting of proinflammatory cytokine responses, decreased quantities of leukocytes, and increases quantities of regulatory/suppressor T cells.[40]

The mechanisms that influence these systemic immune alterations start in the hypothalamic-pituitary-adrenal axis (Figure 3). At the onset of stress, the hypothalamic-pituitary-adrenal axis is activated, and hypothalamic secretion of corticotropin-releasing hormone and arginine vasopressin occurs. Corticotropin-releasing hormone, synergistically with arginine vasopressin, stimulates the pituitary gland to release adrenocorticotropic hormone.[41] Circulating adrenocorticotropic hormonecauses target organs, the adrenal glands (specifically the adrenal cortex) to increase the production and release of the glucocorticoid hormone, cortisol. Glucocorticoids are the final effectors of the hypothalamic-pituitary-adrenal axis and take part in regulating homeostatic mechanisms and stress. The autonomic nervous system also modulates the hypothalamic-pituitary-adrenal axis in stress through the release of several substances

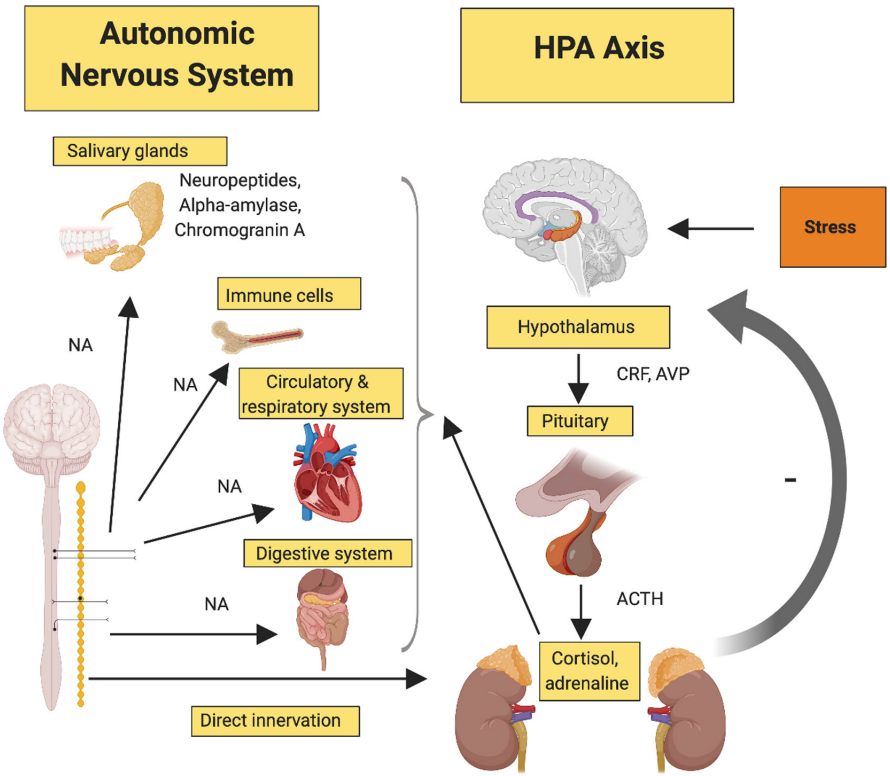

FIGURE 3 Effect of stress on the hypothalamic-pituitary-adrenal (HPA) axis. Activation of the hypothalamic-pituitary-adrenal stimulates the pituitary gland. Adrenocorticotropic hormone (ACTH) release results in increased cortisol from the adrenal glands, which then affects the autonomic nervous system. AVP, arginine vasopressin; CRF, corticotropin-releasing factor; NA, noradrenaline

including catecholamines (eg, adrenaline and noradrenaline).[42] In turn, this can stimulate the central nervous system and peripheral nerve fibers to release substances required to counteract the stressor; for example, neuropeptides (substance P), salivary alpha-amylase, and chromogranin A.[43]

3.2 | Stress and mental health

It has been suggested that psychosocial stress plays an important role in the onset, maintenance, and exacerbation of psychopathological disorders.[58] This can be illustrated by the effects of psychosocial stress on schizophrenia, where it further impairs cognitive functions but also can enhance positive or negative symptomatology, thereby increasing hallucinations or delirium and impairing social functioning to the point of complete withdrawal.[59,60] In subjects with dependency disorders, stress may induce maladaptive behaviors, such as alcohol consumption, tobacco smoking, drug use, and food cravings.[61] In some cases, stress can act as a direct etiological agent in disease. For example, posttraumatic stress disorder results from a well-defined relationship that exists between a stressful life event and the onset of a clinical syndrome. Moreover, a history of childhood physical or sexual abuse has been shown to increase the risk of developing posttraumatic stress disorder following the traumatic event.[62] Major depressive episodes have been correlated with severely stressful events (eg, loss of job or divorce/separation) prior to their onset.[63] It has been demonstrated that chronic stress can impair emotionally dependent learning tasks[64] and affects the flexibility of a person's behavior[65] and their decision-making process.[66] In addition, it may decrease social motivation and willingness for social interaction.[67] Several mental health disorders appear to be stress related resulting from a dysregulation of corticotropin-releasing hormone. These disorders include depression,[68] anxiety,[69] and schizophrenia,[70] all resulting in hyperactivity of the hypothalamic-pituitary-adrenal axis. As already described, the hypothalamic-pituitary-adrenal axis has numerous biological functions, one of them relating to the mobilization of the immune response, thereby regulating inflammatory processes. Corticotropin-releasing hormone dysregulation has been observed in autoimmune disorders/chronic inflammatory diseases, including rheumatoid arthritis and osteoarthritis.[71] Corticotropin-releasing hormone dysregulation provides a biological link between stress and mental health. Considering these immunomodulatory effects that occur, it is plausible that periodontitis may also be influenced by this stress-mental health relationship.

3.3 | Stress markers and receptors in the oral cavity

The periodontal tissues have glucocorticoid receptors sensitive to the release of glucocorticoids from the hypothalamic-pituitary-adrenal axis. Keratinocytes have been shown to be directly responsive to adrenocorticotropic hormone and capable of producing the glucocorticoid cortisol, which may result in local immunosuppressive and anti-inflammatory effects,[44] including inhibition of T lymphocyte cell formation[45] and suppression of macrophage[46] and natural killer cell function.[47] Blood, saliva, and gingival crevicular fluid have been used to assess the relationship between stress and periodontal diseases. Catecholamines are responsible for modulating several immune functions, including the production of proinflammatory cytokines (eg, interleukin-1 and tumor necrosis factor alpha)[48] and suppressing lymphocyte proliferation[49] and natural killer cell function.[50] Chromogranin A is an acidic phosphorylated secretory glycoprotein that is stored and released at the same time as catecholamines from the adrenal medulla. Chromogranin A is also stored and secreted from sympathetic nerve endings[51,52] and the ductal cells of the human submandibular gland.[53] Chromogranin A has been shown to give rise to several bioactive peptides, such as catestatin, which may contribute to inflammation.[54] Salivary alpha-amylase has been found to be a reliable marker reflecting sympathetic nervous system activity during stress.[55] It also displays antimicrobial activity.[56] In addition, neuropeptides such as substance P are important mediators of neurogenic inflammation, resulting in the initiation and maintenance of inflammation by stimulating proinflammatory cytokine production.[57]

3.4 | The role of stress in modulating the host response in periodontal diseases

A review by Monteiro da Silva et al[72] concluded that there is substantial evidence for the role of psychosocial stress as a predisposing factor in acute necrotizing ulcerative gingivitis; however, there was limited evidence for its role in periodontitis. Since this conclusion, a greater number of studies are strengthening evidence to support the notion that stress can modulate behaviors and immune system activity impacting periodontal diseases.

Correlational studies have shown positive relationships between psychosocial stress and poorer periodontal clinical parameters. Deinzer et al[73] conducted a prospective study, evaluating a cohort of medical students that had undergone a stressful period of academic examinations. Severe deterioration of gingival health was more frequently observed in stressed students when compared with their baseline levels. In addition, deterioration of gingival health was more frequently observed in stressed students than in their peer control group. A subsequent experimental study by Deinzer et al[74] evaluated medical students using a split-mouth study design where they induced experimental gingivitis in two quadrants while maintaining high levels of oral hygiene in the remaining two quadrants. They found that students sitting examinations had significantly higher levels of interleukin-1β in gingival crevicular fluid at both experimental gingivitis sites and sites of good oral hygiene. Interleukin-1β is a cytokine that has been thought to play a role in the destruction of periodontal tissue during periodontal disease.[75] The authors concluded that stress may affect the health of the periodontium by suppressing the immune system and that this

relationship may be more pronounced during periods of poor oral hygiene.

Proinflammatory cytokines and cortisol in serum, gingival crevicular fluid, and saliva have been investigated in relation to periodontal status. It has been shown that women on long-term sick leave due to stress experienced greater severity of periodontitis and have increased concentrations of interleukin-6 in gingival crevicular fluid compared with healthy controls.[76] Other studies have also observed increased quantities of proinflammatory cytokines, such as interleukin-1β, interleukin-6, and interleukin-8, in the gingival crevicular fluid of periodontally diseased subjects that correlate with psychosocial stress levels.[77] Elevated levels of serum and salivary cortisol have been associated with worse clinical periodontal parameters, including bleeding on probing, clinical attachment level, and probing pocket depth.[78,79] Salivary cortisol and chromogranin A levels in relation to periodontal disease were evaluated by Haririan et al,[43] revealing that a positive association exists between these stress markers and the extent of periodontitis. The impact of psychological stress on the release of these stress markers was not evaluated. A more recent study by Haririan et al[80] evaluated the impact of psychological stress on the release of stress markers in saliva and serum in relation to periodontal health and disease. They found that elevated levels of stress markers (neuropeptides; eg, substance P) occurred in the saliva of patients with aggressive periodontitis and chronic periodontitis regardless of psychological stress status. A positive association between psychological stress and stress markers cannot be entirely discounted due to a low response rate (66%) to the stress evaluation questionnaire in this study.[80] Further research to elicit the relationships between psychological stress status, stress markers, and periodontal diseases is required.

In addition to psychosocial stress, there appears to be an association between an individual's ability to cope with stress and levels of periodontitis. A cross-sectional, epidemiological study by Genco et al[81] showed a significant relationship between financial strain in relation to alveolar bone and clinical attachment loss, after adjusting for confounding factors such as age, gender, and tobacco smoking. Furthermore, individuals that had a problem-solving coping ability for managing stress in daily life showed better periodontal clinical parameters than those that were more emotional in their focus with less-adequate coping strategies for psychosocial strain. It was concluded that the effects of psychosocial stresses on periodontal disease can be modified by instituting adequate coping behaviors. A relationship between stress-coping patterns and periodontitis was also found in a case-control study by Wimmer et al,[82] where, after adjusting for smoking, age, and education, periodontitis patients with inadequate stress behavior–coping strategies were at a greater risk for severe periodontitis.

3.5 | Relationship between stress and periodontal microorganisms

In recent years, our understanding of periodontal microbiology has evolved to the polymicrobial synergy and dysbiosis model.[83] This model describes the role keystone pathogens have in modulating the host's response by impairing immune surveillance and causing a change from homeostasis to dysbiosis. Considering the interaction between pathogens and the host's immune system, it is plausible that stress caused by psychosocial factors may influence the periodontal biofilm. It has been reported that the growth of *Tannerella forsythia* and *Fusobacterium nucleatum* are increased in the presence of stress hormones catecholamine, dopamine, and cortisol.[84] Also, catecholamines appear to influence periodontal bacterial growth, depending on the bacterial species. Noradrenaline can reduce the growth of *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis*; however, it can also increase the growth of *Eikenella corrodens*, *Actinomyces naeslundii*, and *Campylobacter gracilis*.[85] Interestingly, noradrenaline has been shown to increase the expression of the gingipains, a virulence factor of *P. gingivalis*.[86] It can be deduced from these findings that stress-related hormones may modulate bacterial growth and virulence factors of selected species driving a shift to dysbiosis. Interestingly, it has been hypothesized that a dysbiotic flora at the start of the alimentary system may have effects further along.[87] However, further research is required to understand these relationships and mechanisms.

3.6 | Stress and periodontal and peri-implant wound healing

The influence of psychosocial stress on periodontal wound healing can be divided into health-impairing behaviors and pathophysiological effects.[88] Health-impairing behaviors tend to increase during periods of psychosocial stress and have been shown to include tobacco smoking,[89] poor oral hygiene practices,[90] and alcohol.[91] The pathophysiologic effects of psychosocial stress and wound healing are yet to be completely elucidated; however, associations between stress and poor periodontal treatment outcomes have been made. Axtelius et al[92] investigated whether a stress system disorder played a role in the pathogenesis of therapy-resistant periodontitis. It was observed that patients who did not respond to conventional periodontal therapy showed higher levels of psychosocial strain along with a higher prevalence of a passive-dependent personality compared with the treatment-responsive group. Although they are interesting observations, these findings were based on a small sample size and have not been reproduced in subsequent publications. Vettore et al[93] also evaluated the influence of psychosocial stress on the response to nonsurgical periodontal treatment in patients with chronic periodontitis. After adjusting for confounding variables, they found that 3 months following nonsurgical periodontal treatment, stressed subjects did not show a reduction in the frequency of periodontal probing depths greater than 6 mm, indicating a relationship between psychosocial stress and the response to nonsurgical periodontal therapy. The ability to cope with psychosocial stress has been shown to influence periodontal treatment outcomes. Individuals with passive coping strategies showed more advanced periodontal disease and tended to have a poor response to nonsurgical

periodontal treatment,[94] whereas individuals with active coping strategies had milder periodontal disease and a more favorable response to nonsurgical periodontal treatment.

4 | THE LINK BETWEEN MENTAL HEALTH AND PERIODONTAL DISEASES

The literature evaluating the relationship between anxiety and periodontal disease has shown conflicting results. Some studies have shown positive associations,[95–98] whereas others have not.[99–101] A recent case-control study by Levin et al[97] investigated whether dental anxiety differs between individuals with and without chronic periodontitis. They found that patients with chronic periodontitis showed a significantly higher percentage of high anxiety and phobia than subjects in the control group did. In addition, patients with chronic periodontitis were significantly more likely to consider themselves as suffering from dental anxiety. This study shows an association between chronic periodontitis and anxiety; however, biological mechanism and associations were not explored. Recently, a meta-analysis showed that periodontitis was positively correlated with anxiety, with the authors suggesting links to health risk behaviors and changes in the hypothalamic-pituitary-adrenal axis activity.[102]

4.1 | Depression and periodontitis

Evidence investigating the association between depression and periodontal diseases has received a significant amount of attention in the literature and is conflicting. A large number of studies have shown positive associations,[76,81,95,103–105] and others no association.[99,101] Araújo et al[106] conducted a systematic review that included 15 studies (one cohort study, six case-control, eight cross-sectional). A total of six studies reported a positive association between depression and periodontitis, whereas nine studies reported no association. A meta-analysis of seven cross-sectional studies found that there was no significant association between depression and periodontitis (odds ratio: 1.03, 95% confidence interval: 0.75-1.41). A more recent meta-analysis of 18 studies by Zheng et al[102] found that patients with periodontitis had higher depression-scale scores. The authors concluded from their analysis that more high-quality prospective studies are required to confirm the relationship as there is currently significant heterogeneity in the literature.

Limited studies have reported the influence of depression on periodontitis treatment outcomes.[107,108] Petit et al[108] found that patients with increased depression scores and poor coping strategies showed worsened nonsurgical periodontal therapy outcomes for the management of their advanced periodontitis. When antidepressant medications (such as selective serotonin reuptake inhibitors) have been evaluated it has been found they may have immunosuppressive effects by reducing levels of oxidative stress[109,110] on periodontal disease severity in animal models[111,112] and human studies.[113]

Depression and periodontitis appear to share common risk factors, including older age,[14,114] low education levels,[115,116] ethnicity[5,117] and low socioeconomic status.[118,119] Poor lifestyle choices, such as tobacco smoking and alcohol consumption, have also been shown to be shared risk factors for both periodontitis[14] and depression.[120] Moreover, both diseases potentially share contributory genetic factors. Depression studies have reported an association with genetic polymorphisms in genes coding for brain-derived neurotropic factor and serotonin (5-hydroxytryptamine-transporter-linked promoter region).[121] Dias Corrêa et al[122] found that brain-derived neurotropic factor genotype GG was associated with increased levels of brain-derived neurotropic factor and tumor necrosis factor alpha in chronic periodontitis patients. Moreover, a study by Costa et al[123] suggested that 5-hydroxytryptamine-transporter-linked promoter region polymorphism might be associated with aggressive periodontitis.

Proposed mechanisms by which depression contributes to periodontal disease include the dysregulation of the hypothalamic-pituitary-adrenal axis and changes in health behaviors. It is suggested that the dysregulation of the hypothalamic-pituitary-adrenal axis results in adrenal disturbances, immune system dysfunction, and excessive production of proinflammatory cytokines.[124,125] Now that depression is understood to be a neuroinflammatory disease it provides support for a bidirectional relationship with periodontitis. Animal studies have demonstrated that this dysregulation may influence the progression of periodontal infections.[126,127]

Evidence suggests that periodontitis may contribute to the onset of depression. Meta-analyses show that patients with depression are associated with chronic, low-grade inflammatory states reflected by higher serum levels of proinflammatory cytokines, including tumor necrosis factor alpha, interleukin-1, and interleukin-6,[128,129] along with increases in acute-phase proteins (ie, C-reactive protein)[130] and reactive oxygen species.[131] However, the source of this inflammation is not well understood.[132] Periodontitis has also been shown to have elevated serum levels of these systemic inflammatory mediators, particularly interleukin-6, tumor necrosis factor alpha, C-reactive protein, and reactive oxygen species,[133–135] that may potentiate or exacerbate a preexisting inflammatory state, increasing susceptibility to depression. More research is required to understand the potential biological links between these two disease entities. It should be mentioned that sequelae of periodontal diseases, such as halitosis, unsightly migration of teeth, and gingival recession, may have a psychosocial impact that could lead to a depressive state in a susceptible individual.[136] At first glance, it might seem that poor mental health is the driver in the relationship between oral and mental health; however, a large-scale ($n > 60\,000$), longitudinal (10-year follow-up) study detected that there was a higher incidence of subsequent development of depression in individuals with periodontitis compared with those without periodontitis.[137]

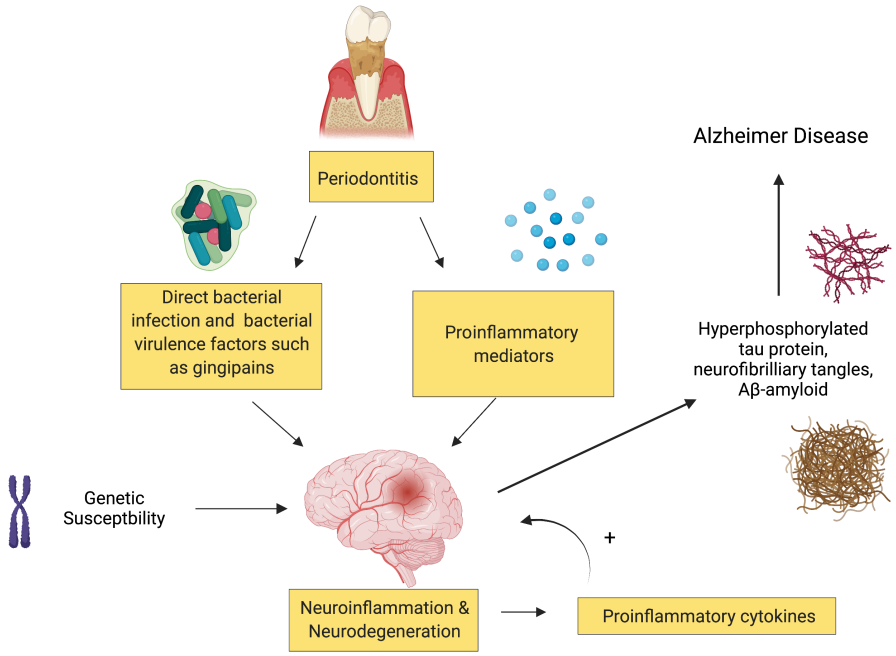

FIGURE 4 Possible mechanism how periodontal disease may affect Alzheimer disease through increased chronic inflammation and infection of the brain by oral bacteria

4.2 | Bipolar disorder

Bipolar disorder is characterized by a variation within an affected individual's mood, thought process, and their behavior that can vary between elation (mania) and depression. These cycles often can vary in their duration and are unpredictable in nature.[138] During depressive episodes, it is not uncommon for patients to show a significant decline in oral hygiene levels, often coupled with an increase in periodontal disease.[139–141] Conversely, during periods of mania, heavy use of toothbrushes and interdental cleaning aids may result in mucosal or gingival lacerations.[142] Evidence shows that a chronic, low-grade inflammation exists systemically during bipolar disorder. Proinflammatory cytokines, such as interleukin-1, interleukin-2, interleukin-4, interleukin-6, and tumor necrosis factor alpha, are elevated during periods of mania, whereas during depressive episodes only interleukin-6 levels increase.[143] It is plausible, therefore, that inflammation could be a common factor between bipolar disorder and other inflammatory-meditated systemic diseases, such as periodontal disease; however, more research is required.

4.3 | Schizophrenia

Schizophrenia is a disorder that is distinguished by characteristic distortions of thinking and perception, along with affects that are incongruent or blunted. Normally, the individual maintains their intellectual capacities. Specific positive features include auditory hallucinations, thought broadcasting, the insertion or withdrawal of thoughts, thought disorganization, and delusional states. Specific negative features include lack of motivation, poor self-care, and social withdrawal.[23]

It has been shown that, in general, individuals with schizophrenia irregularly attend the dentist, have poorer oral health, and a greater number of missing teeth compared with the general population.[144] Eltas et al[145] evaluated the association between periodontal health and schizophrenia. They found that there was a high risk of periodontal disease in patients with schizophrenia with high scores for plaque index, bleeding on probing, probing depths, clinical attachment loss, and missing teeth. It has been shown that individuals with schizophrenia undergoing a psychotic episode have increased serum concentrations of inflammatory cytokines, including interleukin-12, interferon-gamma, tumor necrosis factor alpha, and C-reactive protein.[146] Therefore, it is conceivable that the low-grade, chronic inflammatory state of schizophrenia may contribute to immune system abnormalities that predispose patients with schizophrenia to systemic diseases.[147]

4.4 | Alzheimer disease

Dementia is a syndrome due to disease of the brain that is progressive in nature and results in loss of higher cortical functions, such as memory, orientation, and cognition. It can be caused by diseases such as Alzheimer disease, dementia with Lewy bodies, and vascular dementia, among others.[23] There is limited epidemiologic data available on the prevalence of dementia in Australia; therefore, estimates are commonly used. In 2016, there was an estimated 400 833 Australians living with dementia, with higher prevalence in females and those over 65 years of age. The prevalence of dementia is projected to increase by 2.75-fold to 1 100 890 persons by 2056.[148,149]

Evidence is emerging to support a link between Alzheimer disease and periodontitis (Figure 4). A prominent hypothesis to describe the pathogenesis of Alzheimer disease is progressive inflammation

within the brain resulting in neurodegeneration.[150] It is suggested that this inflammation might be responsible for the pathologic features observed in the disease, including hyperphosphorylated tau protein, which forms neurofibrillary tangles, beta-amyloid 1-42 peptides found in senile plaques and components of degenerated neurons.[151] Several animal studies have supported the notion that these pathologic alterations induce glial cells to produce proinflammatory cytokines, such as tumor necrosis factor alpha, interleukin-1β, interleukin-6, and C-reactive protein.[152–154] Through a positive feedback mechanism, the elevated proinflammatory and C-reactive protein may stimulate glial cells further to produce additional hyperphosphorylated tau protein, beta-amyloid 1-42 peptide, and proinflammatory cytokines, thereby driving neurodegeneration.[155,156] Clinical studies supporting the link between inflammation and the pathogenesis of Alzheimer disease are limited. Holmer et al,[157] in a case-control study, reported a correlation between periodontitis, early cognitive impairment, and Alzheimer disease, highlighting the interactions between the disease entities are biologically plausible. Other studies have shown that elevated levels of C-reactive protein increase the likelihood of developing Alzheimer disease and cognitive decline in various populations.[158,159] Proinflammatory cytokines as predictors of Alzheimer disease have also been investigated, with increased levels of interleukin-6 and interleukin-1β suggesting an increased risk for disease.[160,161] Genetic evaluations indicate that the presence of interleukin-1α-899 and interleukin-1β+3953 polymorphisms have been shown to increase the risk of developing Alzheimer disease 11-fold.[162] Further support for the role of inflammation in Alzheimer disease stems from identified effects that nonsteroidal anti-inflammatory drugs have in delaying the onset of Alzheimer disease.[163,164] However, randomized control trials have not demonstrated this same positive effect.[165,166] It is speculated that the lack of effect in these studies could be related to the specific action of the nonsteroidal anti-inflammatory drugs used, low dosages, and high drop-out rates in these studies.

When evaluating the role of periodontitis in Alzheimer disease, it should be considered that periodontitis is a chronic inflammatory disease, which, over years, systemically exposes the host to proinflammatory cytokines and acute-phase proteins. Patients with moderate to severe periodontitis have been shown to have elevated systemic levels of C-reactive protein.[167,168] Studies evaluating the systemic inflammatory effects of periodontitis have shown elevated levels of prostaglandin-E2, interleukin-1β, interleukin-6, and tumor necrosis factor alpha.[169,170] It is plausible, therefore, that these periodontitis-produced inflammatory mediators could extend to the brain through systemic and neural pathways. The periodontal pocket provides a unique opportunity for extensive numbers of periodontal bacteria to gain access to the systemic circulation and neural tissue. This has been demonstrated in a study by Riviere et al,[171] where oral *Treponema* species (eg, *Treponema denticola*), were detected in pieces of brain frontal lobe in 14 out of 16 human autopsy specimens with Alzheimer disease but only detected in four out of 18 without. The suggested mechanism by which bacterial invasion of the brain may occur is via the trigeminal nerve, where *Treponema* species were detected from three Alzheimer and two control specimens in the trigeminal ganglion. A recent study offered evidence that *P. gingivalis* and gingipains may play an important role in the pathogenesis of Alzheimer disease. In a mouse model, they showed that *in vivo* oral administration of gingipain inhibitors blocks gingipain-induced neurodegeneration, reduces quantities of *P. gingivalis* in the brain, and decreases host beta-amyloid response to *P. gingivalis* infection within the brain. These results are suggestive that gingipain inhibitors may be useful in the treatment of neurodegeneration associated with Alzheimer disease.[172] A recent systematic review evaluating 23 studies found that infection with oral pathogens correlated with developing neuropathological degeneration seen in Alzheimer disease and the detection of bacteria in the brain. In addition, when a dysbiosis is associated with oral bacteria there is evidence of a microbiological susceptibility to developing Alzheimer disease.[173]

4.5 | Substance use disorders

Substance use disorders include a variety of disorders that differ in their severity and clinical manifestations, but are all attributable to the use of one or more psychoactive substances (eg, alcohol, nicotine, cannabis).[23] These psychoactive substances elicit pathological changes to the brain, causing the addict to be less responsive to interpersonal and social relationships. These changes also render the addict with the inability to regulate the drive to seek drug reward.[174] The biological basis of addiction is that the psychoactive substance will cause the release of dopamine into the nucleus accumbens, the reward center of the brain, thereby reinforcing behaviors to obtain more of the substance.[175] Physiologically, repeated exposure to the same stimulus results in the development of tolerance, where progressively less dopamine is released, eventually to the point of undetectable levels unless there is a change in stimulus.[176] By contrast, continued use of psychoactive substances pharmacologically stimulates the release of dopamine and, in general, does not diminish with ongoing exposure.[177] It is this process that drives continued neuroplastic change promoting drug-seeking behavior for biological rewards. Environmental stress has been shown to influence the development substance use disorders in susceptible individuals.[178] Studies indicate that the interactions between stress and dependency on psychoactive substances are modulated by drug- and stress-induced corticotropin-releasing factor release, responsible for the regulation of dopamine levels.[179] Furthermore, stress has the ability to enhance the addictive nature of psychoactive substances and contribute to relapse of substance dependency by increasing the strength at excitatory synapses on midbrain dopamine neurons.[180]

There is clear evidence to support tobacco smoking as a risk factor for periodontitis.[181] There are numerous mechanisms by which tobacco smoking has effects on the periodontium, including microbiological shifts to periodontopathic species,[182] reduced gingival blood flow,[183] impaired polymorphonuclear cell phagocytosis,[184] increased proinflammatory cytokine production,[185] and impaired periodontal wound healing.[186] The use of marijuana has also been linked to periodontitis.

Thomson et al[187] showed in a prospective cohort of young adults that, after controlling for confounding factors, regular cannabis smoking was strongly associated with periodontal disease, showing a dose-response effect. A significant number of studies have explored the influence of alcohol on periodontitis. However, fewer studies exist evaluating the relationship with alcoholism. Khocht et al[91] investigated the effects of alcoholism and cocaine abuse on the periodontium. The results showed that persistent alcohol abuse increased loss of clinical attachment through recession of gingival margins in alcohol-dependent subjects. No significant associations were seen between cocaine misuse and periodontal disease.[91] A systematic review including 11 cross-sectional and five longitudinal observational studies concluded there is sound evidence to suggest alcohol consumption is a risk indicator for periodontitis. However, the available evidence is too sparse to draw a link between alcohol dependence and periodontitis.[188]

5 | MENTAL HEALTH AND THE MICROBIOME

Currently, no one factor can be implicated in mental health disorders. Instead, it is thought to be an interaction of many factors, as mentioned earlier herein. Increasingly, research is evaluating the influence of the microbiome on mental and neurological health, with the majority of interest being on the gut microbiome.[189-192] It is hypothesized that the gut microbiome can communicate and influence the brain through the gut-brain axis. A logical extension of this is the oral cavity-brain axis, which has been explored recently, particularly in the last 5 years.

5.1 | The gut-brain axis

The gut-brain axis is the "complex bidirectional interactions and processes utilised by the gut microbiome and brain to communicate",[193] integrating gut function with the cognitive and emotional centers of the brain. Increased permeability of the intestine, otherwise known as a "leaky gut," is thought to occur through immune activation, entero-endocrine signaling, and enteric reflex, allowing microbial metabolites into the bloodstream.[193,194]

The gut microbiome is a mixture of bacteria, viruses, fungi, and bacteriophages,[195] comprised of over 1000 microbial species. The microflora in the gut and oral cavity have coevolved with their host, and it makes sense that there is communication between using existing cellular and molecular pathways.[196] A symbiotic relationship exists between gut microbiota and the host critical for essential physiological functions within the human body. The gut microbiota has an important role in the promotion of nutrient absorption, host immune system modulation, digestion, and epithelial barrier function.[197,198] The brain exerts its influence on intestinal microflora and physiology through the autonomic nervous system, the hypothalamic-pituitary-adrenal axis, and the release of signaling molecules such as cytokines.[199] It is this complex bidirectional communication pathway that is known as the gut-brain axis.

5.2 | The oral microbiome and mental health disorders

Direct causal mechanisms have been proposed to explain the connection between oral microbiota, the brain, and how this relationship may influence the development of mental health disorders. The four direct causal mechanisms proposed are microbial and metabolite escape, neuroinflammation, central nervous system signaling, and response to neurohormones.[200] A common theme of these mechanisms is inflammation through a host reaction. In addition, exposure to physical or psychosocial stressors at a young age or continually may result in systemic and neuro-inflammation.[201]

Microbial and metabolite escape

Microbial species are commensal and usually have a resident niche where they are not pathogenic. However, as Bowland and Weyrich[200] suggest, owing to dysfunction, if a microbial species is able to disseminate via a bacteremia, then it or its products have the potential to cause disease. One of the possible mechanisms whereby the microbiota could contribute to neuroinflammation is via circulating endotoxins—that is, lipopolysaccharides, which are part of the outer membrane of Gram-negative bacteria—or other microbe- or pathogen-associated molecular patterns. In the case of lipopolysaccharide, toxicity is associated with the lipid component and immunogenicity is associated with the polysaccharide components, eliciting a variety of inflammatory responses.[202] Endotoxins can enter the circulation more readily through compromised internal barriers, such as the oral and intestinal mucosa, thereby allowing toxins to spread systemically, resulting in an inflammatory cascade in the central nervous system.

Some of the gut microbiome may affect the production and levels of monoamine neurotransmitters, such as serotonin, dopamine, and gamma-aminobutyric acid. In some cases, bacterial strains may be able to produce these transmitters. Mazzoli et al[203] showed that *Lactobacillus* and *Bifidobacterium* secreted gamma-aminobutyric acid, and *Escherichia*, *Bacillus* and *Saccharomyces* produce norepinephrine. In that study, *Candida*, *Streptococcus*, *Escherichia*, and *Enterococcus* produced serotonin, *Bacillus* and *Serratia* could produce dopamine, and *Lactobacillus* secreted acetylcholine. The essential amino acid tryptophan is necessary for the synthesis of serotonin. Metabolism of tryptophan by certain gut bacteria reduces the amount available to the host.[204] Regulation of these neurotransmitters and their production by the gut microbiome has important implications in the development and management of mental health disorders.

Neuroinflammation

Through the bloodstream, bacteria and their products stimulate a mild, but chronic inflammation. This systemic inflammation may induce changes in neurovascular functions, increase blood-brain barrier permeability, reduce of nutrition, and increase neurotoxic

compounds.[205] Release of reactive nitrogen and oxygen species and proinflammatory cytokines interleukin-1β and interleukin-6 in the presence of inflammation activate microglia and astrocytes, contributing to neural toxicity and damaging the blood-brain barrier.[206] Additional neurotoxins may be released to the activation of the enzyme indoleamine-2,3-dioxygenase (which increases the metabolism of tryptophan).[207] Miller and Raison[32] also suggested that inhibition of the synthesis of the monoamine neurotransmitters serotonin, dopamine, and norepinephrine may negatively affect brain function.

Central nervous system signaling

Neurological processes may be negatively influenced by bacteria, and so affect behavior. The production of metabolites and other compounds from bacteria may have neuroactive and immunomodulatory actions.[208] These include short-chain fatty acids, bile acids, choline and phenolic metabolites, indole derivatives, vitamins, polyamines, and lipids.[209] Caspani et al[210] suggested three mechanisms of action: (a) direct stimulation of central nervous system receptors; (b) peripheral stimulation of neural, endocrine, and immune mediators; and (c) epigenetic regulation of histone acetylation and deoxyribonucleic acid methylation. Bowland and Weyrich,[200] in their review, presented another potential mechanism of afferent signaling via the vagus nerve, which relays signals from the gut to the central nervous system and may be able to sense gut microbial metabolites.

Response to neurohormones

Hormones have been suggested to be the primary method of the interaction.[202] Catecholamines may modulate gene expression in bacteria. This has reported by Mudd et al,[211] who showed the presence of fecal *Ruminococcus* was negatively associated with serum cortisol and a biomarker for neurological health, *N*-acetylaspartate.

Oral-brain axis

As already discussed, there is a link between periodontal disease and mental health disorders. The oral microbiome has been implicated in a number of systemic diseases, but recently linked to mental health disorders. As outlined earlier herein, the gut microbiota has a close interaction with the central nervous system mediated through bidirectional neural, immune, and neuroendocrine pathways.[212,213] However, there has been little research on investigating the relationship with the oral microflora and its effect on the central nervous system. Low-grade chronic inflammation is now recognized as an important risk factor for mental health disorders, and research has clearly shown that periodontitis and/or the bacteria involved stimulate such a response[214] (Figure 5). Though animal studies have not been a focus of this chapter, they have provided insight into the possible mechanisms between periodontitis and mental health disorders. Altogether, they show dysregulation of the hypothalamic-pituitary-adrenal axis with a hyperinflammatory response and behavioral changes. In addition, they may also provide evidence of direct microbial involvement. For example, Watanabe et al[215] reported that *Streptococcus mutans* positive for the collagen-binding adhesin gene Cnm, normally associated with dental caries, was able to disrupt the blood-brain barrier and induce cerebral hemorrhaging following bacteremia. Release of oral bacteria or their metabolites into the bloodstream stimulates the neuroinflammatory response with the expression of proinflammatory cytokines, resulting in a chronic inflammation.[216] This systemic inflammation may induce changes in neurovascular functions, increase blood-brain barrier permeability, reduce nutritional uptake, and increase neurotoxic compounds.[205]

It was originally thought that the blood-brain barrier was impermeable, but this has been shown to be incorrect. Lipopolysaccharide can adversely affect the blood-brain barrier and lead to increased permeability.[217] It is then feasible that periodontal bacteria in the bloodstream can penetrate the central nervous system. Increased levels of lipopolysaccharide expression of toll-like receptor 4 increases neuroinflammation further.[216] Interestingly, and similar to the vagus nerve in the gut, the facial and trigeminal nerves have been suggested as routes of egress.[218] Another form of communication is through brain-resident microglia via leptomeninges.[219] This occurs through the activation of endothelial cells that express tumor necrosis factor beta and interleukin-1 signal to perivascular macrophages adjacent to cerebral endothelial cells. There is then communication with microglia, microglial activation, and subsequent neuroinflammation.[220] Periodontal bacterial extracellular vesicles, such as exosomes, are potent stimulators of the immune system, increasing the inflammatory burden.[221]

In comparing oral microbial studies, it is also important to consider how the samples were collected. Many studies have used saliva, whereas, although periodontal pathogens are present in saliva, subgingival plaque is more appropriate. Dubar et al[222] sampled two sites above 5 mm probing depth and a healthy control in patients with periodontitis before and after treatment. They assessed salivary cortisol levels and self-reported stress and anxiety. Cortisol was correlated with probing depth, but not with stress or anxiety. *T. forsythia* was found in higher levels in the pockets of all highly stress subjects, whereas *A. actinomycetemcomitans* was only detected in nonanxious patients.[222] This is further supported by Simpson et al[223] in a study of adolescents with depression and anxiety symptoms, who found major depressive disorder and anxiety were associated with changes in the abundance of certain taxa, including Spirochaetaceae, *Actinomyces*, Firmicutes, *Treponema*, *Fusobacterium*, and *Leptotrichia* spp, suggesting that composition can also be associated with mental illness symptoms in this population.[223]

Similar to the gut-brain axis, the host is able to modulate the oral flora, as mentioned earlier. Chronic stress dampens the diurnal secretion of salivary glucocorticoid and catecholamine. Therefore, the abundance and/or function of oral microbes may be affected.

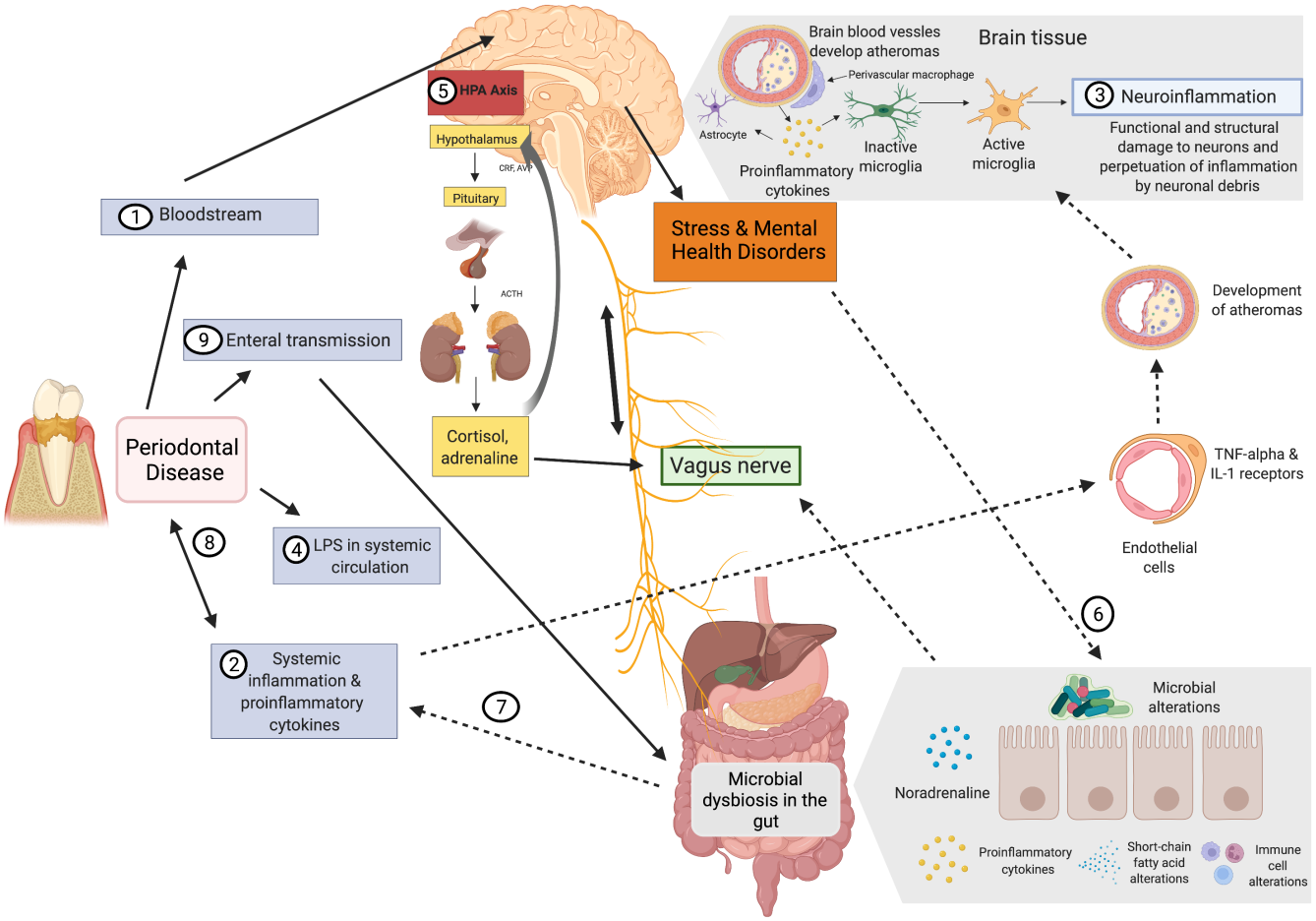

FIGURE 5 Oral-brain axis (redrawn from Martínez et al,[201]). (1) Bacteremia of the periodontal pathogens can reach the brain directly through the bloodstream and damaged blood-brain barrier. (2) Activation of endothelial cells by proinflammatory cytokines can indirectly affect the central nervous system. (3) Expression of tumor necrosis factor alpha (TNF-α) and interleukin-1 (IL-1) endothelial receptors activates microglia that results in inflammation. (4) Increased permeability of the periodontal vasculature results in "leaking" of lipopolysaccharide (LPS). (5) Lipopolysaccharide can activate the hypothalamic-pituitary-adrenal axis, thereby increasing stress hormones and/or neurotransmitters. (6) This then affects gut physiology, habitat, microbiome composition, and bacterial gene expression. (7) Changes in the gut microbiome can result in further systemic inflammation reinforcing the effect on the central nervous system. (8) Further, it may affect periodontal disease by increasing the inflammatory burden. (9) Transmission of the oral bacteria to the gut by saliva may also affect the gut microbiome composition and function. ACTH, adrenocorticotropic hormone; AVP, arginine vasopressin; CRF, corticotropin-releasing factor

Roberts et al[224] noted host modulation of oral bacterial gene expression through cortisol. The level of stress may also affect the variability and levels of the microbiome.[225]

The interrelationship between the gut and oral microbiome

Given the oral cavity is the start of the alimentary system, it is not unreasonable to consider the transmission of bacteria from the oral cavity to the intestine. About 1.5 L of saliva is swallowed every day.[226] However, the acidity of the stomach, barrier functions along the gastrointestinal tract, and the commensal gut microbiome prevent colonization.[227] Dysregulation or disruption of the normal gut physiology or flora may allow the oral bacteria to colonize. The subsequent disruption and/or dysbiosis of the gut flora could affect central nervous system functioning. In addition, a dysbiotic oral microflora increases overall inflammation, with a knock-on effect of altering the gut flora making the composition more proinflammatory.

With all research we need to recognize its limitations. Sampling the intestinal flora is complex, and stool samples are unlikely to be completely representative.[228] Confounding variables relating behaviors associated with mental health disorders may influence study outcomes, as may variations in diagnostic criteria for cases of periodontitis.

6 | MENTAL HEALTH, STRESS, AND IMPLANT OUTCOMES

There are limited studies examining mental health disorders and implant survival and success.[229] This may in part be because mental disorders are more common in low or middle socioeconomic groups who may not have access or the resources to afford an implant.[230]

Patients with severe mental health disorders are unlikely to attend for implant treatment.

It can be extrapolated that the relationship between mental health disorders, stress, and peri-implant disease are similar to what is reported with periodontitis. It seems likely that peri-implant disease and wound healing following implant placement may be influenced by the same dysregulation of the hypothalamic-pituitary-adrenal axis and adrenergic nerve signaling and health risk behaviors as seen in periodontitis. It has been suggested that all wound healing phases are influenced by stress, resulting in dysregulation to cytokine and immune function, cellular function, matrix metalloproteases, and increases in hypoxia.[231] Changes in inflammatory and glucocorticoid signaling as a result of stress affect functional brain circuits, including the affective-salience circuit, which is important in guiding motivated behavior.[32] As already discussed, health risk behaviors tend to increase with mental health disorders and stress[232]; in particular, lack of compliance with professional and home care and smoking appear to increase and are considered risk factors for peri-implant disease.[15]

Associations between antidepressant medications and implant failure have been found.[20] In particular, associations between selective serotonin reuptake inhibitors and implant failure have been shown in numerous studies.[21] A common side effect of antidepressants is xerostomia, where increased discomfort on brushing may result in increased plaque accumulation and the development of peri-implant mucositis. The role of serotonin in bone homeostasis provides the biologically plausible link between selective serotonin reuptake inhibitor use and implant failure. Serotonin receptors are found in nervous tissue, cells of the digestive tract, platelets, and bone cells (osteocytes, osteoclasts, and osteoblasts). When acting on bone cells, serotonin blocks serotonin transporters on bone cells, which decreases bone formation by increasing osteoclast formation and decreasing osteoblast formation,[233] resulting in decreased bone mineral density and bone mass.[234]

Wu et al[18] showed that treatment of depression with selective serotonin reuptake inhibitors was linked to an increased failure rate of osseointegrated implants compared with those not taking selective serotonin reuptake inhibitors after controlling for a number of factors. They suggested that the main reason for implant failure due to selective serotonin reuptake inhibitors was likely related to problems with the mechanical loading of the implants, since it has been shown *in vivo* that serotonin plays a critical role in the response of bone to mechanical loading.[235]

Recently, it has been reported that serotonin-norepinephrine reuptake inhibitors and tricyclic antidepressants pose the highest risk for failure when compared with non–antidepressant users.[20] In this study it was found that serotonin-norepinephrine reuptake inhibitors yielded a much higher risk of implant failure than selective serotonin reuptake inhibitor antidepressants did. Although the link between serotonin and bone metabolism appears clearer, it is not the same for norepinephrine. It has been demonstrated in mice that lack of norepinephrine reuptake can lead to reduced bone formation and increased bone resorption, leading to poor bone mass and suboptimal bone mechanical properties.[236] Similarly, it is suggested that tricyclic antidepressants exhibit their actions and increase the risk of implant failure through serotonin and norepinephrine pathways; however, there have been limited investigations.

Further well-designed prospective studies are required to understand the effects on dental implant biology.

7 | CONCLUSION

Current evidence suggests a positive relationship between stress, mental health disorders and periodontal disease. It appears that stress and mental health disorders, such as anxiety disorders, depression, bipolar, schizophrenia, Alzheimer disease, and substance use disorders, are associated with more severe periodontal disease and in some cases poorer healing outcomes to nonsurgical periodontal therapy. Evidence suggests that stress and mental health disorders can result in behavior modification, such as poor oral hygiene practices, tobacco smoking, and alcohol abuse, which are also risk factors for periodontal disease and which, therefore, may have a contributory effect. In addition, stress has immunomodulatory effects regulating immune cell numbers and function, as well as proinflammatory cytokine production. The biological pathways between psychosocial stress and systemic pathophysiology have received significant scientific attention; however, the roles of the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system are insufficiently understood. Psychosocial stress and a number of mental health disorders (ie, anxiety disorders, depression, bipolar, schizophrenia, and Alzheimer disease) appear to be accompanied by a low-grade chronic inflammation. Systemic effects of inflammation have been shown to have adverse systemic health effects, influencing diseases such as cardiovascular disease.[237] Therefore, it is plausible that the presence of low-grade chronic inflammation may be involved in a bidirectional relationship between stress, mental health disorders and periodontal and peri-implant disease. There is less evidence available evaluating the relationship between mental health, stress, and peri-implant disease. Associations have been made between antidepressant use and implant failure, which seem biologically plausible, particularly for selective serotonin reuptake inhibitor and serotonin-norepinephrine reuptake inhibitor medications. With increasing interest, over the last few years, it has become increasingly clear that there is a bidirectional relationship between the brain/central nervous system and the gut microbiome. There is evidence to suggest that alterations or dysbiosis of the gut flora and consequent inflammation or changes in hormone levels may promote the development of mental health disorders. There is less available evidence exploring the link between the oral microbiome, stress, and mental health disorders.

These findings suggest that stress management and adequate treatment of mental health disorders may be a valuable adjunct in the periodontal treatment of patients. It is pertinent to note that, on review of the literature, significant heterogeneity exists between studies in relation to study methodology and analysis of data (eg, adjusting for confounding variables), making it difficult to draw

definitive conclusions on such relationships. The heterogeneity of mental health disorders in relation to their etiology, psychopathology, symptomatology, and level of disability further complicates the task of analyzing potential links with periodontal and peri-implant diseases. To date, only associations have been made.

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