# Brain and Oral Microbiota

Subjects: Dentistry, Oral Surgery & Medicine
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There is an oral microbiota of the mouth, a microbiota of the skin that has many subcategories (e.g., the armpits, nose, feet), and gut microbiota, among many others. Disruptions to these different microbiomes are increasingly becoming associated with numerous inflammatory, immune, and nervous system-related diseases by a communication pathway called the microbiome–brain axis.

mental health | oral microbiota | oral microbiome | mental disorders

## 1. Introduction

While the microbiota defines the population of microbes in a specific ecosystem, the microbiome refers to microorganisms and their genes. These definitions are important because bacteria that live on different parts of the body (skin, gut, and oral cavity) prefer different nutrients and perform different functions. There is an oral microbiota of the mouth, a microbiota of the skin that has many subcategories (e.g., the armpits, nose, feet), and gut microbiota, among many others. The human microbiota is increasingly recognized as a superorganism that is believed to play a role in health and disease [1]. The number of microorganisms inhabiting the human body has been estimated at about $10^{14}$ prokaryotic organisms with an absolute number of species varying according to the microbiome's body location [2]. As a rough estimate, the 1000 bacterial species in the gut have 2000 genes per species, which yields 2,000,000 genes, 100 times the approximately 20,000 human genes [3]. This includes bacteria, fungi, viruses, protozoa, and archaea, whose diversity will vary from person to person depending on lifestyle and physiological differences [4]. Disruptions to these different microbiomes are increasingly becoming associated with numerous inflammatory, immune, and nervous system-related diseases by a communication pathway called the microbiome–brain axis [5][6][7][8][9][10].

Research supports microbe-brain interactions, most notably with anxiety and depressive-like behaviors, with accumulating evidence pointing to specific microbial genes that can regulate neurotransmitter activity [11]. The gut microbiome has been shown to play a major role in the development and function of the hypothalamic–pituitary–adrenal axis, [12] which mediates the stress response and is of interest in a range of psychiatric disorders, in particular depression and anxiety disorders. Our gut bacteria also heavily influence the immune system [13] and may represent the link to the immune dysfunction that is characteristic of mental illnesses such as depression and schizophrenia. In mice, *Clostridium* produces dopamine. This neurotransmitter enables communication within the nervous system and is a molecule that directly influences behavior [14]. A strong correlation was shown between functional disorders caused by dysbiosis and the subsequent presence of mood disorders [15]. The dysregulation of the gut–brain axis has emerged as a possible area of research to better understand the pathophysiology of mental disorders and has provided psychiatry with a new paradigm from which to approach mental illness [16][17][18][19].

In the same way, the human oral microbiota has become a new research focus area aimed at promoting the progress of disease diagnosis, complimenting disease treatment, and developing personalised medicines. Evidence suggests that disturbance to the oral microbiota ecological balance can cause a series of infectious oral diseases including dental caries and periodontal diseases. The oral microbiota is also associated with several systemic diseases, including but not limited to cardiovascular disease, pneumonia, rheumatoid arthritis, pancreatic cancer, colorectal cancer, oesophageal cancer, stroke, and adverse pregnancy outcomes. Accordingly, the oral microbiota is increasingly being recognized as a potential biomarker for human diseases [20][21][22][23]. The oral microbiota is composed of a large number of microorganisms housed in a complex environment, that encompasses distinct, small microbial habitats, such as teeth, buccal mucosa, soft and hard palate, and tongue, which form a species-rich heterogeneous ecological system [24]. About 50 to 100 billion bacteria have been identified in the oral cavity and 600 prevalent taxa at the species level, with distinct subsets predominating different habitats [25]. These species belong to 185 genera and 12 phyla, of which approximately 54% are officially named, 14% are unnamed (but cultivated) and 32% are known only as uncultivated phylotypes [26]. The 12 phyla are Firmicutes, Fusobacteria, Proteobacteria, Actinobacteria, Bacteroidetes, Chlamydiae, Chloroflexi, Spirochaetes, Synergistetes, Saccharibacteria and Gracilibacteria [27]. Oral-derived bacteria such as *Porphyromonas gingivalis* and *Actinobacillus actinomycetemcomitans* can colonize the intestines and persist there, leading to activation of the intestinal immune system and chronic inflammation [28].

Oral microbiota such as *Streptococcus mutans*, *Porphyromonas gingivalis*, and *Gemella haemolysans* may play a role in cardiovascular disease [29] and oral pathogens, especially *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* are associated with a high risk of pancreatic cancer [30]. In general, the oral microbiota has an impact on the health of the body by digesting food. Salivary DNA sequencing has shown that core species abundance ratios significantly correlate with diet. For example, the abundance of *Neisseria* and *Haemophilus* differs between the hunter–gatherers population living in the western part of the island of Luzon, in the east of this island and in the central part of the island of Palawan (Philippines) [31]. The oral microbiota can also produce metabolites in the mouth that can affect the development of a range of oral diseases. Microorganisms found on the surfaces of teeth tend to form multispecies biofilm communities that are often embedded in a matrix of extracellular polymeric substances (EPS). The production of EPS and acidic metabolites are closely related to the oral microbiota for dental caries [32]. In periodontal diseases, polymicrobial communities induce a dysregulated and destructive host response through a mechanism referred to as polymicrobial synergy and dysbiosis induced by a pathogenic triad of *Porphyromonas gingivalis*, *Tannerella forsythia* and *Treponema denticola* named the red complex [33]. The oral microbiota directly influences dental caries and periodontal diseases [34]. Specific genetic composition and structure of the microbial community can even be identified in the pathogenesis and evolution of periodontal disease. When the microbiota isolated from patients with periodontal disease were compared with health controls, the most striking difference was the relative proportions of the four most abundant phyla, Bacteroidetes, Actinobacteria, Proteobacteria, and Firmicutes [35][36]. Likewise, the researchers observed change in oral microbiota in systemic diseases like, for example, an elevation of proinflammatory cytokines in saliva patients suffer from oral squamous cell carcinoma [37]. A link between composition and diversity of the oral microbiota and type II diabetes is suspected [38]. There are indications that periodontitis precedes rheumatoid arthritis [39] and saliva would be able to provide informative clinical markers to obesity [40]. Oral bacteria could, therefore, be linked to or serve as biomarkers for certain systemic diseases. However, it remains to be established whether there is a causal relationship between the oral microbiome and these systemic disorders.

## 2. Brain and Oral Microbiota

While many studies highlight the link between the gut microbiota and mental disorders, studies on the impact of the oral microbiota and the pathophysiological mechanisms are little emphasized in their relationship with mental disorders. The studies carried out in this area mainly concern cognitive disorders associated with AD (13/22 identified studies). The public health problem linked to the growth of AD, dementia, and cognitive disorders in the general population due to its overall aging [41] is certainly a cause that might explain this preferential research orientation.

The identification of a specific microflora in patients with mental disorders suggests that these disorders could influence the oral microbiome. This hypothesis presumes that the CNS (Central nervous System) is capable of modifying the oral environment to favour the preferential selection of particular microbes, as is the case for the intestinal flora [42]. This hypothesis is tempered by the poor oral condition usually associated with patients with mental disorders. Among persons with severe mental illness, dental caries and periodontal measurement indexes often reach twice the level found in the general population [43][44]. Many combined factors contribute to the poor oral health of these individuals, including orals infectious diseases interacting with the metabolic disturbances induced by antipsychotic treatments (e.g., diabetes, obesity), and also poor diet and lifestyle choices (e.g., high sugar diet, use of psychoactive substances such as tobacco, and inadequate oral hygiene) [45][46].

Periodontal diseases and dental caries are the two main oral pathologies in humans [47]. The increase in oral bacteria load (*Porphyromonas gingivalis*, *Streptococcus mutans*, *Treponema denticola*, etc.), and the elevated concentrations of the inflammatory markers they induce (TNF α and cytokines), appear to be found in patients suffering from mental illness. Many psychiatric conditions including AD are associated with chronic low-grade inflammation and elevated level of pro-inflammatory cytokines [48]. Gut microbiota disturbances may represent a possible mechanism linking chronic stress, cytokine production and neuropsychiatric disorders such as depression [49]. Oral microbiome disturbances may represent another such link achieved through the translocation of microbes from the oral cavity into the bloodstream. The oral microbiome and the gastrointestinal microbiomes share many common microbes, another potential link through which the two sites both contribute to inflammatory diseases. Taken together, it is not surprising that oral and intestinal microbiota show concordant disease associations [50]. The oral dysbiosis and the inflammatory phenomena it induces could play a part in the development of mental illnesses, just like intestinal dysbiosis [51]. Since the oral cavity represents the main entry point to the intestinal tract, it can be assumed that the accumulated evidence regarding the link between the intestinal flora and mental disorder is in favour of future studies related to the oral microbiota [26].

Mental illnesses (e.g., schizophrenia, depressive syndromes) involve neurotransmitter dysfunction. Gut bacteria can directly produce neurotransmitters used in the human body including GABA, serotonin, noradrenaline, acetylcholine and dopamine [52]. However, the quantities produced by bacteria are relatively small and unlikely to influence human neurotransmission directly to any great extent. The oral microbiota can also produce metabolites. In 2019, Lin et al. explored the association between fluctuations within the oral microbiome and the brain functional network in smokers and suggested the biological pathways underlying for the microbiome–brain link, but were unable to assign causality among the features [53].

In the interdental biofilm of young and healthy periodontal subjects with no signs of periodontal disease, there are periodontopathogen bacteria such as *Porphyromonas gingivalis* [54] that also appear to be involved in the development of Alzheimer's disease. Thus, the setting up as the youngest age of individual oral prophylaxis directed towards the interdental spaces, with the use of interdental brushes, would help to combat dysbiosis of the oral microbiota and could potentially prevent the onset of diseases such as Alzheimer's disease [34][55].

Differences in the gut microbiome profiles of people with ASD have been reported like an increase in the abundance of *Clostridium* species [56] and high levels of *Sutterella* [57], although the results vary from study to study. In addition, the oral microbiome of children with ASD differs from that of neurotypical children in several taxa predominantly related to energy metabolism and lysine degradation pathways [58]. Although several studies to investigate the effects of various probiotics on ASD symptoms, they are greatly limited by small sample sizes and methodological challenges, and, as such, it is difficult to draw any concrete conclusions [59]. Concerning the oral microbiota in people with ASD, multiple studies have identified species specifically associated with this disorder [58][60][61].

In accordance with reports of higher level of certain bacterial species in the oral microbiota of patients with, DS, Biagi et al. [62] highlight that the general makeup of their microbiomes were similar to those of healthy individuals, though, some subpopulations of bacteria were more or less abundant in patients with DS. Individuals with DS have elevated levels of *Parasporobacterium* and *Sutterella* and reduced levels of *Veillonellaceae*. Specifically, in this study, *Sutterella* abundance positively correlated with the Aberrant Behaviour Checklist (ABC) scores individuals with DS. This positive correlation indicates that in the gut at least, this bacterium may contribute to the maladaptive behaviour in patients with various conditions.

Several studies examine the composition of the microbiome in patients with bipolar disorder [63] and report different levels of *Faecalibacterium*. In 2019, Coello et al. reported that *Flavonifractor*, a bacterial genus that can induce oxidative stress and inflammation, was associated with bipolar disorder and that probiotics from *Lactobacillus* and *Bifidobacterium* appear to have therapeutic potential [64]. Cunha et al. [65] who, to the best of the researchers' knowledge, are the only authors to have studied the oral microbiota composition in patients with bipolar disorder, found a higher frequency of all periodontopathogens in this populations.

Despite the mounting evidence in support of a link between the oral microbiome and mental health, it must be kept in mind that the relative abundance and diversity of bacteria vary considerably from one individual to another [66].

As a consequence, studies generally only focus on simple correlations between the abundance of particular taxa and the pathological conditions associated with the host. These association patterns do not allow a discrimination between effect and cause [67].

A consensus has yet to be reached on a precise definition for the characteristics of a bidirectional relationship between the oral microbiome and the brain as it can be advanced in the context of the gut–brain axis [68]. The identification of specific oral dysbiosis signatures associated with various mental disorders raises the question of whether the CNS modulate the oral microbiome. This would constitute the complementary element of a bidirectional relationship suggesting the existence of an oral cerebral axis equivalent to the gastrointestinal axis. However, if, within the framework of the intestinal–brain axis, various modulation mechanisms are well established (e.g., alteration of mucus and biofilm production, motility, permeability and immune function [68], no mechanism underlying the particular microbial signature in patients with mental disorders has been studied or even envisaged in the many studies included here.

## 3. Conclusions

The research argues for correlations between oral microbiota and AD, dementia or cognitive disorders, ASDs, DS, mental retardation, and bipolar disorders. This field remains little explored, and further studies are needed with a larger sample size involving different type of mental disease are required to clarify the biological link or interconnections between the oral microbiota and all mental health disorders and to develop consistent patterns to generate more concrete data.

The concept of the oral brain axis is an area with growing interest that is likely to facilitate the diagnosis of mental disorders by providing novel disease-specific biomarkers. Future research efforts should focus on developing new therapeutic approaches for better patient management, even though there is still a lot to learn about the oral microbiome, and its potential reaction to therapeutic manipulation. While the literature represents a basis for a reciprocal interaction between the oral microbiome and the brain in the context of mental disorders, the exploratory nature of the studies and their many limitations underline the importance of supporting research in this field.

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