The impact of the oral microbiome on our mental health and decision making

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Abstract

Worldwide, cases of mental illnesses have been on the rise largely due to the COVID-19 pandemic. While multiple factors such as the environment, genetics, and childhood experiences are known to impact mental illness in humans, a large growing body of literature has recently focused on the microbes that inhabit our bodies. This article focuses on how the oral microbiome develops, how bacteria communicate with our environment and brains, and how these interactions impact our mental health and decision-making processes.

Introduction

Worldwide, cases of mental illnesses have been on the rise; in the United States alone, approximately 52.9 million adults were known to live with mental illness in 2020.[1] This public health crisis has been recently magnified, largely due to the COVID-19 pandemic. While multiple factors such as the environment, genetics, and childhood experiences are known to impact mental illness in humans, a large growing body of literature has recently focused on the microbes that inhabit our bodies.[2,3]

The human body is colonized by a diverse set of microorganisms -- bacteria, fungi, parasites, and viruses -- that play critical roles in our health.[4] While there is still much to understand about microbial functions and roles in our body, researchers have established a correlation between the human microbiome and several known diseases in recent years. The human oral cavity, for example, is colonized by a diverse species of microbes that are known to aid and affect multiple functions including nutritional intake and maintenance of health through a state of equilibrium in the oral ecosystem.[5] Due to its critical role in human health, the oral microbiome has been the target of recent studies in their attempt to better decipher human diseases and conditions, including its influence on the brain and mental health.[3] In light of such speculation, this paper analyzes existing research on specific subsets of the oral microbiome and how they are thought to communicate with the brain and impact mental health diseases.

The development of the oral microbiome

While we have limited knowledge as to how oral microbiome communities reach their complexity, the oral cavity of a developing fetus is considered to be a sterile environment.[6] It is during (or immediately after) delivery in which babies acquire various microbes from its surroundings. What microbes a baby receives, however, largely depends on how a baby is delivered. Exposure to the maternal vaginal microbes, for example, plays a significant role in the composition of a child's microbiome since taxonomic differences between vaginally and Cesarian-born infants can be observed.[6]

Following birth, the oral microbiome goes through dramatic changes. While the microbiome community is relatively homogenous throughout the body after birth, within a few weeks, microbial compositions rapidly diverge into environment-specific communities that are distinct from one another. These communities arise based on factors such as competition between different species, what nutrients are present in the environment, and what order species colonize the mouth. For example, the first microbial oral colonizers are species such as *Streptococcus mitis, Streptococcus sanguinis*, and *Streptococcus gordonii*. They are able to

bind to tongue and cheek surfaces even before the emergence of the teeth — a characteristic that allows them to outcompete other bacterial species once teeth start coming in.[7] Over time, the community is thought to mature and stabilize. By 6 months the oral microbiota in the infants starts to exhibit similarities with that of their parents, and, although still in dispute, around the age of 2, the community is thought to be set and stable.[8]

Besides the delivery method, there are multiple factors that impact the composition of the human oral microbiota. While biological sex and weight status are the most significant elements determining the microbiome composition of youth, as one ages, researchers have identified the environment, oral habits, and genetics as factors contributing to a personalized microbiome.[7,9] Environmental factors such as place of living, use of medicines or antibiotics, and diet affect the composition of one's oral microbiota – it is said that major dietary shifts throughout human history are often accompanied by significant changes in the oral microbiome.[10] Similarly, oral habits such as smoking or toothbrushing are critical in determining oral health. Tooth brushing and flossing, in particular, can disrupt plaque known to cause tooth demineralization.[7]

The microbiomes in adults are largely categorized into two main types: 1) the core microbiome – the types of microbial taxa common to all people, and 2) the variable microbiomes – uniquely distributed among individuals based on their lifestyle.[11] In maintaining one's oral health, research suggests it is crucial to sustaining core microbial communities, such as *Streptococcus*, *Veillonella*, *Neisseria*, and *Actinomyces*, found in most individuals with good health conditions.[10,12]

Bacterial communication with the environment and our brains

While the causes of neuropsychiatric disorders (NPDs) are yet to be fully understood, recent research has largely focused on genetic, environmental, and physiological factors as playing a significant role in our mental health. In terms of environmental factors, recent studies have suggested that the human microbiome has an important link to neurological health.[13]

How do bacteria communicate with the environment?

Eukaryotes and prokaryotes have coexisted for millions of years, either in detrimental or beneficial ways.[14] While observing how the bacteria communicate with one another (through a process known as quorum signaling), scientists have recently discovered that bacteria are able to likewise communicate with their hosts through the production of hormone-like molecules.[15] This inter-kingdom signaling mechanism is now thought to play a fundamental role in multicellular eukaryotic physiology.[14]

On its own, the human body can only digest a limited number of polysaccharides in our diet. As a result, most dietary fiber ingested is largely broken down by specialized enzymes encoded by the bacterial communities within our body. This process has led to a symbiotic relationship between both bacteria and our cells — while our bodies provide bacteria a steady supply of food and a home to live in, the bacteria in turn break the food into forms that can be metabolized by human cells. In such a metabolic process of converting nutrients into absorbable, secondary molecules, bacteria produce many byproducts, such as short-chain fatty acids and gasses. These byproducts can be readily absorbed, metabolized, and/or used as signaling molecules by our cells.[16]

Host-bacterial interactions can play a significant role in host metabolism, immunity, and even behavior.[17,18] For instance, gut bacteria utilize tryptophan (Trp) as a source of nitrogen. In doing so, Trp is metabolized into a number of byproducts that are absorbed by the intestines,

many of which are identified to be Aryl-hydrocarbon Receptor (AhR) ligands (similar to the neurohormone serotonin). As such, Trp precursors and metabolites can bind to AhR-receptors found on various cells, which, when activated, are known to have multiple effects on the immune system.[19] They can also go into our circulation to act on our central nervous system (CNS), which can then lead to various responses, such as modulation of the host homeostasis.[19, 17]

How do bacteria communicate with our brains?: The Oral-Brain Axis

In the past, the study on the microbiome-brain interaction was mainly focused on the microbiome found in the gut. However, the communication between the host and human microbiome is not a unique characteristic to those inhabiting the gut; more recently, researchers have identified that the microbiome in the mouth may also have established pathways to engage with the brain, an anatomical communication collectively termed the "oral-brain axis". [20]

The mouth marks the beginning of the human digestive system, making it the primary entry way to the internal body.[21] As such, the importance of oral microbiome goes beyond simply oral hygiene — the disruption of the oral microbiome, in its composition or otherwise, may contribute to a variety of chronic diseases such as endocarditis, osteoporosis, or rheumatoid arthritis.[7,20] In particular, current literature has indicated that oral microbiomes are directly related to the development of NPDs or other neuropsychiatric and cognitive influences. While the direct mechanism by which the oral microbial communities interact with the host CNS (and thus the brain) is yet to be completely understood, previous research has proposed the connection between specific oral species and neuronal responses.[20] An interesting example of microbial influences on decision-making involves certain bacteria such as *Clostridia* and *Prevotella* species, which are linked with taste detection thresholds. Researchers have posited that the oral microbiota, in this way, may influence the dietary preferences of the host to sustain itself in the host's oral cavity.[7]

There are a few possible pathways by which the oral microbiome can influence and thus contribute to NPD outcomes. Some examples include bacterial-induced neuroinflammation and how bacteria are sometimes capable of responding to neurohormones themselves. Neuroinflammation is a condition in which microbes trigger an excessive proinflammatory immune response in the central nervous system. In some cases, inflammation can cause alterations in neurovascular functions, which results in an increase in blood-brain barrier permeability and/or the buildup of toxins in the brain. Certain oral microbes, such as the ones associated with dysbiosis, are known to play an essential role in the production of proinflammatory cytokines that lead to this condition.[20]

Further, microbes are able to respond to neurohormones themselves. For instance, through quorum sensing, some oral microbes may react to catecholamine hormones that bind and transport irons, which then can cause the bacteria to change the outer surface proteins. In some other cases, bacteria can respond to cortisol and change their gene expression pathways which can worsen some diseases.[22, 23] Some bacteria have been found to grow better or worse in the presence of stress hormones, which may result in an increased negative impact on periodontal diseases.[24]

Potential links between the Oral Microbiome and Emotional Responses

Mental disorders – most of the time associated with distress and/or damage to critical areas of the brain – are often characterized by a significant alteration in one's cognitive, behavioral, and emotional response. According to the World Health Organization, 1 out of 8

people around the world is known to be struggling with certain mental health conditions.[25] While there are various ways that mental disorders can arise, conditions such as anxiety, depression, and bipolar disorder are thought to be some of the most common manifestations.

Due to their interaction with the gut/oral-brain axis, microbial communities are now thought to have a consequential influence on the regulation of neural activity.[20] For instance, studies have shown that the gut microbiome has a major role in the development of the hypothalamic-pituitary-adrenal axis – a neuroendocrine system that mediates reactions to stress and emotions.[26] A study showed that women with higher *Prevotella* abundances had greater emotional responses when viewing negative images.[27] A correlation between the gut microbiota and neuroendocrine system is similarly suggested by certain disorders that are associated with a disturbance of both systems, such as depression and Irritable Bowel Syndrome (IBS).[27]

Recently, more research led to evidence to support that the oral microbiome, too, has an impact on the host's mental conditions such as anxiety.[20] For instance, Zhang et al. tried to analyze how the presence of certain microbes that cause gingivitis affected *in vivo* behavior.[13, 28] When C57BL/6 mice were treated with *P. gingivalis*, a species of bacteria inhabiting the oral cavity thought to be related to neuroinflammation, the researchers found that the treated-mice exhibited diminished spatial learning and memory loss during the Morris Water Maze test in comparison to the control. Interestingly, however, when the same test group was submitted to an open-field test, no significant differences were observed between the control and the experimental group. Such results suggested that the rodents injected with *P. gingivalis* were much more likely to have higher anxiety and difficulty in coping with stress, and thus could not leave the water maze, unlike the control group. The study further reasoned that the bacteria triggered a greater stress response in the animal's immune system, suggesting that the presence of certain bacteria may impact an animal's ability to handle stress and anxiety.

In total, these studies support the notion that there might be a link between the oral microbiome and neuropsychiatric health. Nonetheless, as the composition of one's oral microbial communities vary significantly between individuals, most current research has generally focused on correlations between particular taxa and the conditions associated with that type of bacteria. Such studies, unfortunately, do not discriminate between cause and effect, and further research is still necessary.

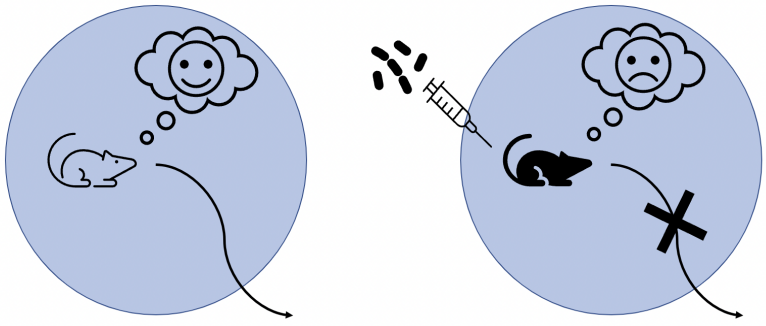

Figure legend: This figure represents the Zhang et al. study in which the rodents were injected with *P. gingivalis* to see how they would perform in the Morris Water Maze test. While the control group mice (shown on the left) were easily able to find their way out of the maze, the treated mice (shown on the right) showed symptoms of anxiety & high levels of stress and were unable to leave the maze.

Conclusion

As a whole, our body contains densely populated communities of microbes that dramatically impact our everyday health. Here, we've highlighted how our oral microbiome affects our mental health. Thought to form shortly after birth, the oral microbiota consists of a diverse community, consisting of core and variable species that vary depending on our diet, immune system, and overall environment. While the gut microbiome has already been shown to play a critical role in the development of neuropsychiatric diseases, new research has suggested that the oral microbiome also has a significant impact on the brain. These studies have only scratched the surface, however, as most of the existing works focus on the correlations between certain species of the oral microbiota and the development of NPD diseases, and not directly on the mechanism of such relationships. Since correlation does not necessitate cause-and-effect, there is more to be researched on this subject matter and thus further study is necessary to have any definitive claim.

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