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LITERATURE REVIEW

The narrative review of recent studies in understanding the relationship between gut (microbiota)-brain axis, nutrition and cognitive function

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Abstract

The concept of the gut (microbiota)-brain axis, which influences the development and function of the gastrointestinal, immune, neuroendocrine, and metabolic systems, is gaining popularity. Recent animal studies have demonstrated that the gut (microbiota)-brain axis also plays a role in establishing cognitive function. It is known that a disruption in the environment's microbiota balance can increase disease susceptibility in children. Historically, it has been hypothesized that neurodevelopmental disorders are the results of a disruption in children's health. However, it is becoming clear that the gut microbiota and the central nervous system communicate in both directions, which could explain how microbiota affects cognitive function. Dietary factors also play important role in the central nervous system via the gut (microbiota)-brain axis, demonstrating the importance of nutrition in optimizing cognitive function. This narrative review of recently published studies and current knowledge aims to elucidate the relationship between the gut (microbiota)-brain axis and cognitive function, as well as the variables that may influence it.

Keywords: gut-brain-axis, gut microbiota, cognitive function, central nervous system, dietary factors, Nutrition.

Introduction

Over the past few years, a concept known as the gut (microbiota)-brain axis has garnered a significant amount of interest. It has been demonstrated that the quick and densely populated microbiota that contain complex forms are created after birth during the first years of a person's existence. It has been demonstrated the microbiota is involved in the developmental programming of epithelial barrier function, angiogenesis, gut homeostasis, and both innate and adaptive immunological function. Numerous studies have demonstrated that the relationship between intestinal microbiota, the gut, and the central nervous system (CNS) is essential in immunological and metabolic processes that influence human health and disease. This interaction is referred to as the gut-brain axis.[1–4] However, it has only been proven relatively

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recently that the gut-brain axis also plays an important role in the establishment and maintenance of cognitive function.[5–7]

The gut and the brain are able to communicate with one another through neuronal, endocrine, and immunological channels. Each of these pathways has its own level of complexity that is involved in homeostasis and normal physiology. Numerous studies that involved alterations in the composition of the microbiota, either as a result of bacterial infection, probiotic administration, or in germ-free mice, all demonstrate that modulating the microbiota can affect behavior and cognition. This effect was observed in studies conducted in humans and animals, including germ-free mice and germ-infected mice.[3,6–8] A recent study that was conducted with mice also suggested that changing or removing the gut microbiota has an influence on the response of the hypothalamic-pituitary-adrenal (HPA) axis to behaviors associated with stress and anxiety. These mice models with altered microbiota can be utilized to explore the influence of the change on behavior and cognitive function as a whole. [9,10] The findings of the first study to establish links between gut microbiota and cognition in human newborns are consistent with the findings of the study conducted on mice. This may be an essential first step for further research.[11]

Cognitive function and behaviour are inextricably linked to early-life brain development. In every area of the brain, development begins and accelerates during fetal life or shortly after birth; thus, maintaining developed brain areas is critical not only for promoting behavior but also for cognition. [12] While nutrients are necessary for brain growth and function, certain nutrients have significant impact in early development. Diet also plays a role in maintaining microbiota composition, which is critical for health and development. [13]

Microbial interventions through diet may be an effective strategy to address potential adverse health outcomes and cognitive deficits. Supplementation with prebiotic and/or probiotic bacteria has been extensively studied and has been shown to be beneficial in preventing altered microbiota environments (dysbiosis). When administered in sufficient quantities, probiotics and prebiotics has several beneficial physiological effects on the host's metabolism, immune system, and gastrointestinal function. [2,14] Several studies also demonstrate that probiotics, prebiotics, and the combination of a specific prebiotic and probiotic (referred to as symbiotic) all benefit cognitive function. [15–18]

The connection between the gut (microbiota) and the brain as it relates to cognitive function is one that piques the interest of researchers. The data supporting the concept has been thoroughly investigated, however the majority of the research has been conducted on animals. The objective of this review is to explain the function that the gut (microbiota)-brain axis plays in mediating changes in cognition in research including both humans and animals, as well as the factors that may influence it.

Methods

This article emphasize the connection between the gut (microbiota) and the brain and also its relation with cognitive function. This literature review was prepared by looking for relevant papers and articles published in many electronic databases such as Pubmed and Medline between 2017 and 2022. Variants of "microbiota" "cognitive function" "dysbiosis" "nutrition" "probiotics" "gut-brain-axis were included in the research terms. Further papers were found, either in English or Indonesian, through manual search from the manual references cited in the corresponding reviews.

Nutrients and Cognitive Function

Numerous aspects of the qualities of nutrients have been found to be associated with cognition, mental wellness, dysfunction, and disease. Nutrition has an effect on a number of components of brain function, including cell membranes, metabolites, enzymes, and neurotransmitters. Nutrients like fatty acids, which have receptors in the nucleus of the cell, can exert a direct influence on a wide variety of

Table 1 Nutrition and Cognitive Function [7,9,21–23]

Nutritional intervention	Impact
Polyunsaturated fatty acid (AA, DHA)	Increase brain development and function
High protein diets	Positive association with cognitive abilities
High fat diets	Increase risk of dysbiosis and impairs cognitive function such as memory and learning
Dietary factors	Influence to gut (microbiota) – brain axis

brain activities by controlling the transcription of a large number of genes that are involved in both the construction and function of the brain.[19] Intake of certain nutrients is ultimately responsible for determining the development and function of the brain. [20] It has been known for a long time that fatty acid consumption is essential for optimal development, particularly a major polyunsaturated fatty acid like DHA. Recent research conducted on piglets suggests that the amount of n-3 fatty acids consumed is not the only factor that determines optimal cognitive health; rather, it is also important to maintain a healthy balance between the amounts of n-6 and n-3 fatty acids consumed. It is possible that the Western diet, which is high in n-6 fatty acids but low in n-3 fatty acids, is a contributor to lower DHA accretion, suppression of secondary neurite formation, and impaired brain development and function.21 Several studies have demonstrated a positive association between high-protein diets and cognitive abilities in children, while high-fat diets, such as Western diets, have a negative association.[22,23]

The capacity of the majority of these dietary factors to influence behavioral processes like learning has been studied in relation to their ability to directly influence neural activity in the central nervous system (CNS) via the gut (microbiota) -brain axis. Learning is an example of a behavioral process that can be affected by these dietary factors. Recent studies have shown that one's food can have an effect on their cognitive abilities, with the gut microbiota playing an important role in the connection between the two. The results of a study on mice that lasted for three months demonstrate that a high-fat diet (50 percent lean ground beef) changes the variety of the microbiota in the gut, which in turn hinders learning and memory. [7,9] The importance of diets and nutrition for long-term cognitive function is summarized in **Table 1**.

The gut microbiota and cognitive function

It is estimated that there are between 1 x 1013 and 1 x 1014 bacteria living in the human gastrointestinal system, which is more than ten times the number of human cells found in our bodies. Our knowledge of the dynamic link that exists between the microbiota, the microbiome, and the host is quickly expanding, and this interaction is currently understood to be mutually beneficial.[3] It is now common knowledge that the microbiota in the gut play an important part in the formation and function of both innate and adaptive immune responses, as well as in the regulation of gut motility, intestinal barrier homeostasis, nutritional absorption, and fat distribution.[24] The number of species that are predicted to be present in the gut microbiota varies quite a bit; nevertheless, colonization does not take place prenatally; rather, it begins during birth when the newborn is exposed to a diverse microbiota during vaginal delivery. After the age of one year, the microbiota in the gut may have reached a stable structure that is characteristic of the microbiota in adulthood.[2,3.]

Gut (microbiota)-brain Axis. Increased susceptibility to disease can be attributed to a change in the delicate balance of the microbiota. Infection, sickness, and the use of antibiotics are all factors that have the potential to momentarily disrupt the equilibrium of the normal composition

of the gut microbiota, which in turn has a negative impact on the health of the host. Because gut bacteria have such a significant impact on overall health, it should come as no surprise that a growing body of research is focusing on the effect of enteric microbiota on the brain and behavior. This has led to the development of the idea of a connection between the gut (microbiota) and the brain, which is known as the gut–brain axis. [4] It is a well-established fact that the microbiota in the gut and the central nervous system (CNS) interact with one another. The enteric nervous system, the neuroendocrine system, the neuroimmune system, the sympathetic and parasympathetic arms of the autonomic nervous system, and the gastrointestinal tract all serve as major communication pathways between these two systems, and the gastrointestinal tract acts as a scaffold for these pathways. These components come together to produce a sophisticated reflex network, with afferents projecting to integrative cortical CNS regions and efferents innervating the smooth muscle of the intestine. Notably, there is a growing realization that this communication is bidirectional, meaning that bacteria influence CNS function, and the CNS influences microbiota composition via the effects it has on the gastrointestinal tract. It is not understood what mechanism is responsible for this communication taking place.

Microbiotas exert their impact over the gut-brain axis in a number of different ways, both directly and indirectly. In this discussion, we will cover the endocrine (cortisol), immunological (cytokines), and neurological pathways (vagus and enteric nervous system). The hypothalamus-pituitary-adrenal (HPA) axis is responsible for the regulation of cortisol secretion. This axis can have an effect on immune cells both locally and systemically (including cytokine secretion). The permeability and function of the barrier that lines the gut, as well as the make-up of the microbiota that lives there, can both be altered by cortisol's presence. However, the microbiota in the stomach and the probiotics that are taken can change the circulating cytokines, which can have a significant impact on how well the brain works. In order for the influence of the gut microbiota to be transmitted to the brain, the vagus nerve and systemic tryptophan levels are both necessary components.[3,9]

a. Endocrine Pathway

Stress and its associated HPA axis activity can influence the composition of the microbiota. Maternal separation is one type of early life stress that has been shown to increase long-term HPA axis activity.[4,25] In monkeys (6-9 months of age), maternal separation resulted in a significant decrease in Lactobacillus bacteria three days after separation, which returned to baseline by day seventh.[26] Additionally, another study demonstrates that mice that were separated from their mothers for 3 hours per day on post-natal days 2-12 have a different microbiota composition than non-separated control animals.[27] Adult mice exposed to chronic stress also exhibit altered microbiota composition. Stress also affects the levels of interleukin and chemokine in the blood, which activate the immune system. Proinflammatory cytokine changes are associated with changes in the composition of several gut microbiota.[28] Several research involving humans have shown that stress-related psychiatric diseases, such as depression, are linked to an increase in the movement of germs throughout the body. This translocation can be avoided with the use of the potential probiotic lactobacillus farciminis. This probiotic has the ability to also alleviate the psychological strain that is brought on by the HPA axis.[12] This work contributes to the expanding body of information that demonstrates the crucial function that the gut (microbiota) -brain axis plays in both the stress response and behavior.

Recent research has shown that dysbiosis, the stress response, and its link with HPA-axis activation can have an effect on behavior and cause changes such as anxiety, depression, and cognitive impairments. These findings are supported by the observation that germ-free mice (GF) have a higher baseline activation of the HPA axis in comparison to controls that have a normal microbiota composition and aren't exposed to any

particular pathogens (referred to as specific-pathogen-free mice).[10] Colonization with the feces of control animals reversed the stress response in a partial manner, whereas Bifidobacterium infantis reversed it completely.[18,27] This discovery lends credence to the idea that bacteria can play a role in the maturation of mice' cerebral stress responses.

In terms of cognitive function, A recent mouse study demonstrated that germ-free (GF) mice have a deficit in non-spatial memory and impaired working memory at baseline when compared to specific pathogen-free (SPF) controls. Acute psychological stress, which activates the HPA-axis, had no additional effect on GF mice's learning and memory. This finding suggests that in GF conditions, the HPA-axis cannot be triggered by stress, which results in an exposed neuroendocrine system. GF situations include: This impaired cognition in GF mice is related with decreased levels of two proteins that are crucial for the regulation of hippocampal-dependent memory. These proteins are brain derived neurotropic factor (BDNF) and c-FOS. Both of these factors are associated with decreased levels. In particular, BDNF is a powerful regulator of synaptic plasticity when it is present in the hippocampus during the process of neurogenesis. In contrast, c-FOS is an immediate early gene that must be present in the hippocampus in order for long-term memories to be formed.[6] When compared to SPF controls, GF mice had lower levels of BDNF messenger ribonucleic acid (mRNA) in the hippocampus than SPF mice did. This finding was consistent with what was seen in the protein investigations. When considered as a whole, these data point to the existence of a potential connection between the microbiota and the levels of BDNF or c-FOS in the process of regulating brain physiology and memory.[9] Despite the results of these research, it is currently uncertain if cognitive impairments can be normalized through the early or mature colonization of GF mice. In contrast to their SPF counterparts, GF mice have been shown in a number of subsequent studies to exhibit behavior that is analogous to that of an anxiolytic drug. The results of these studies showed that conventionalizing mice could normalize their behavior, but only in the younger stages of their lives.[8,10]

b. Immune Pathways

A recent study found that animals that were not exposed to any germs had significantly higher hippocampal concentrations of the neurotransmitter 5-hydroxytryptophan (5-HT), as well as its primary metabolite, 5-hydroxyindoleacetic acid, and the neurotransmitter dopamine. Control animals that had been exposed to germs served as a comparison.[29] It has been shown that serotonin plays an important part in cognition, and that manipulation of the serotonergic system can result in changes in cognitive function that are independent of changes in mood.[30] Plasma tryptophan concentrations, which are a precursor to serotonin, increased in germ-free mice, which suggests that microbiota can alter serotonergic transmission in the central nervous system via a humoral mechanism. It is interesting to note that the colonization of germ-free animals after weaning returned peripheral tryptophan levels to control levels; however, it did not reverse the changes in serotonin levels in the CNS during adulthood that were caused by an absence of microbiota during childhood.[29] In addition, a study conducted on humans demonstrated that treating terminal lung cancer patients with heat to kill Mycobacterium vaccae improved both their emotional health and their cognitive function. This led researchers to hypothesize that the immune response to the bacteria involved neurotransmitters such as 5-HT, which resulted in an improvement in mood.[31] The administration of *Mycobacterium vaccae* resulted in a decrease in the amount of time it took mice to complete a Hebbs-Williams-style complex maze comprised of a close-field test apparatus used to study intelligence. This indicated an improvement in the animals' ability to learn and remember new information.[32] According to the findings of these investigations, the immune system, in part by way of the serotonergic system, plays a role in moderating the influence that commensal

Table 2 Gut (microbiota) -Brain Axis and Dysbiosis Direct/Indirect Mechanism Affecting Brain & Behavior [8,10,29,31–33]

Pathway	Involved system	Evidence	Impact
Endocrine	via HPA axis activity	Dysbiosis - Long term HPA Axis Activity	Psychiatric disorder, Anxiety and Cognitive defects
Immune	via Serotonergic system	Dysbiosis - Serotonergic transmission of plasma tryptophan transmission	Impair Learning, mood changes and Memory
Neural	via Vagus Nerve	Dysbiosis - Neuronal Activation & FOS expressing cells	Anxiety

microorganisms have on the brain and cognition. When taken as a whole, these data imply that illness and stress can interact with one another and produce a synergistic effect that can change the function and behavior of the central nervous system, most notably cognitive function.

c. Neural Pathways

The vagus nerve is one route that could theoretically explain the gut (microbiota)-brain axis mechanism. Following infection, some bacteria utilize this route for gut-to-brain signaling inducing an anxiety like behavior.[33] In one study, immunocytochemistry was used to map the temporal pattern of neural activation in mice that had been infected with the food-borne pathogen Campylobacter jejuni. *Campylobacter jejuni* is known to cause illness in humans. Visceral sensory nuclei of the brainstem, such as the nucleus tractus solitarius of the vagus nerve, had elevated levels of fructooligosaccharides (FOS), but areas involved in the stress response, such as the hypothalamic paraventricular nucleus, did not. This occurred one to two days after inoculation (2 days after inoculation). In addition, the animals showed signs of increased anxiety-like behavior when they were subjected to the hole board test. The level of anxiety was found to be correlated with neuronal activation, which was measured by the number of FOS-expressing cells in the bed nucleus of the stria terminalis. This region is an essential part of the extended amygdala fear system.[34] Although such studies with pathogens do not directly address the microbiota's ability to communicate with the brain, they provide critical insights into the mechanisms by which microorganisms communicate with the brain and affect behavior. The pathways how microbiota can affect brain and behavior are summarized in **Table 2**.

Evidence on the role of Gut microbiota in Cognitive function. According to research conducted on mice, microbiotas appear to have a part to play in the appropriate regulation of behavior and brain chemistry linked with mood, anxiety, and cognition. In addition to this, it is suggested that the make-up of an individual's microbiota may have an effect on their behavior as well as their cognitive performance. The human race has only a rudimentary understanding of the connection that exists between the microbiota and the maturation of the brain in the first few years of life. In a research of toddlers, different gut microbiota compositions were found to be connected with temperament. This association was determined by the phylogenetic diversity of the microbiota as well as the abundance of certain bacterial species.[35] Other studies found that newborns whose gut microbiota included an abundance of *Bacteroides* had improved cognitive performance, particularly on visual reception and language measures. This study also found that the diversity of the microbiome at 1 year of age can predict cognitive ability at 2 years of age, with a greater diversity likely being deleterious to neurodevelopment.[5]

Additionally, corroboration links dysbiosis to autism and other neurodevelopmental disorders. Comparative analysis of the diversity and composition of the gut microbiota of children with and without neurodevelopmental disorders. According to a study, neurodevelopmental disorders and autism spectrum disorders are associated with reduced microbial diversity in children. In patients with neurodevelopmental disorders and autism spectrum disorders, it is hypothesized that the early microbiome may influence GI disturbances and accompanying cognitive and behavioral issues.[36,37]

According to one study conducted in India, GI disturbances such as diarrhea may increase the risks of adverse neurodevelopment. This study shows that increase in days of diarrhea is associated with increased risk of lower skills in fine motor and problem-solving (cognitive function). The limitation of this study is they did not differentiate diarrhea etiology is it whether due to dysbiosis or not.[38] Albeit literature shows that children with gut dysbiosis have increased risk of GI problems.[39] Additional studies in humans are needed to significantly advance our understanding of the role of microbiota in cognitive and neurodevelopment processes.

Probiotics, Prebiotics and Synbiotics Role in Preserving Cognitive Function

In clinical practice, altered microbiota environments (dysbiosis) are frequently treated with dietary interventions (nutritional supplements or special diets). The maintenance of cognitive processes is another purpose served by this dietary intervention. It is possible that the capacity of nutrition to influence behavior and learning is not entirely attributable to an effect on neuronal cells in the central nervous system, but rather may be associated with the degree to which the microbiota of the gastrointestinal tract is altered (CNS).[7] Numerous studies have attempted to establish a connection between the diversity of gut microbes and diets. These studies demonstrated that probiotic, prebiotic, and/or symbiotic supplementation is a promising strategy for reversing gut dysbiosis and preserving cognitive function.[16]

Probiotics are live bacteria that, when taken in adequate doses, can bestow a variety of health benefits on the hosts to which they are provided. In various animal models with metabolic syndrome, probiotics were able to change the composition of the gut microbiota as well as the metabolism of that microbiota, which led to an improvement in the metabolic function of those models.[17] Consumption of probiotics is also advantageous for the brain via the gut (microbiota)-brain axis in order to restore cognitive function by activating microglia.[15,16,40] The mechanism of these probiotics' beneficial effects remains unknown.

Hanstock et al [41]. examined the impact of bacterial fermentation on colonic behavior. Rats fed a high-fermentable-carbohydrate diet display enhanced hindgut fermentation, resulting in an accumulation of fermentative end products such as lactic acid and volatile fatty acid. The cumulative effect of these fermented products is an increase in anxious and aggressive behavior.[41] On the other hand, one study found that mice fed a western diet high in fat and refined sugar while receiving Lactobacillus containing probiotics exhibited increased anxiety and decreased memory.[42] Studies have shown that the probiotic agent Bacillus infantis had antidepressant-like effects and normalized peripheral pro-inflammatory cytokine and tryptophan concentrations, both of which have been linked to depression and a maternal separation model of depression. This provides additional evidence for the beneficial effects that probiotics have on behavior. [43] Recent research has demonstrated that giving mice the *Bifidobacterium* breve strain NCIMB 702258 results in greater levels of fatty acids in the brain of the mice (including arachidonic acid and docosahexaenoic acid). It is interesting to note that this effect was reliant on the strain, as it was not caused by the B. breve strain DPC 6330.44 It is well recognized that arachidonic and docosahexaenoic acids play important roles in the processes of neurodevelopment, such as neurogenesis. The concentrations of these two acids in the brain may

Table. 3 Microbiota and Cognitive Function: Effect of Dysbiosis and The Use of Supplementation [15,16,36,38,44,46]

Intervention/Condition	Effect
Increased diversity of microbiota	Predictive of better cognitive function
Gut dysbiosis in children	Increased risk of neurodevelopment disorder and autism spectrum
Use of probiotics (*Bifidobacterium breve*)	Affect Gut (microbiota)-Brain-Axis and Neurodevelopment process
Supplementation of FOS, GOS	Improve attention, executive function, and memory
Administration of clinically proven synbiotic	Improved brain function, microglia activation and restore cognitive function

influence emotions such as anxiety and sadness, as well as learning and memory.[18,44,45] This demonstrates the nuanced relationship between probiotics, diet, and their effect on microbiota, cognitive function, and behavior. Prebiotics are an indigestible kind of dietary fiber that has been shown to have a favorable effect on the host's physiology. This effect is achieved by the prebiotic's ability to stimulate the growth or activity of a select group of native bacteria. Prebiotics are fibers that, when fermented by the microbiota of the intestinal tract, encourage the growth of bacteria such as *Lactobacillus* and *Bifidobacteria* that are good to human health.[14] According to a study on the cognitive benefits of prebiotic administration, supplementation with galactooligosacharides (GOS) and fructooligosacharides (FOS) may increase cognitive function in broad domains conceptualizing attention, executive processes, or memory.46 Probiotics, namely *Lactobacillus spp* and *Bifidobacterium Breve*, exerted multiple beneficial effects on various cognitive functions, including memory, verbal learning, attention, and a variety of cognitive tests, outperforming prebiotic supplementation, possibly due to their brief administration.[16]

Prebiotic and probiotic (Synbiotics) therapy has been shown to decrease pro-inflammatory cytokines via the apoptotic pathway. Proinflammatory cytokines released by activated microglia and microglia themselves have been shown to inhibit long-term potentiation of brain synapses, resulting in cognitive decline. A recent study showed that restoring cognitive function in rats that had been fed a high-fat diet could be accomplished with the help of prebiotic xylooligosacharide (XOS), probiotic Lactobacillus paracasei HII01, or both of these together as *synbiotics*. Consuming the prebiotic XOS, the probiotic L. paracasei HII01, or the synbiotics on a daily basis for a period of 12 weeks improved brain function in obese rats. This was accomplished by lowering gut and systemic inflammation, lowering brain and hippocampal oxidative stress, increasing dendritic spine density, attenuating microglial activation, and improving hippocampal dysplasticity and brain mitochondrial dysfunction, which resulted in restored cognitive function. In addition, the researchers found that obese rats given a diet had a reduction in microglial activation and a restoration of cognitive function when they were given either prebiotic XOS, probiotic L. *paracasei* I01, or synbiotics over an extended period of time.[15] The processes that underlie the role that microglia play in cognition as well as the signaling pathways that underlie neuroglia communication particularly in humans need to be elucidated through the conduct of additional study. The influence of dysbiosis on cognitive performance, as well as the potential benefits of taking pre-probiotic supplements, are summed up in **Table 3.**

Conclusions

Given the increasing acknowledgment of the importance of the gut microbiota in complex disorders such as anxiety and cognition, it is increasingly evident that clinical translation of animal research is necessary. Clearly, modulating gut microbiota can influence behaviour,

neurophysiology, and neurochemistry. The findings of this study may pave the way for future research into the relationships between microbiota and human cognitive function. Nutritional effects and how diets improve cognitive function in humans via neurogenesis and the gut (microbiota) -brain axis are critical areas for future research. Unravelling these relationships may eventually lead to new treatment techniques for addressing established risk factors of dysbiosis, such as the promising use of prebiotics, probiotics, and synbiotics to combat cognitive deficiency.

Author contribution: All authors have read and agreed to the published version of the manuscript.

Conflict of Interest

R.W.B., E.W., and T.S. are employees of Danone SN Indonesia. All other authors have no conflict of interest

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