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Does Alzheimer's disease begin in your gut? A review of the gut-brain axis effect on cognitive impairment and the potential for therapeutic targeted interventions.

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Purpose Statement:

Extensive studies on the gut-brain axis have established a bidirectional communication between the intestinal bacteria and the brain, leading to various physiological effects, including cardiovascular, immunologic, endocrinologic, and neurologic outcomes.[1] The focus of this review is to explore the connection between dysbiosis of gut microbiota and cognitive impairment. Additionally, this literature review aims to analyze the factors contributing to disturbances in the gut-brain axis and the potential for therapeutic interventions that can mitigate the progression of neurodegenerative disease.

Abstract:

Objective:

To summarize current data regarding the bidirectional communication of the gut microbiota and the brain, specifically in relation to cognitive improvement, microbiota diversity, and dietary interventions. Additionally, the mechanisms underlying these relationships will be explored.

Evidence Acquisition:

Using the key terms “gut-brain axis" and "Alzheimer’s disease” PubMed and Web of Science were searched for papers published between 2014 and 2023. This yielded 297 results, of which 23 were relevant to this topic. Articles that failed to address cognitive impairment or only studied animal subjects were excluded. After scanning each paper, nine review articles and 14 new studies were selected for this literature review.

Evidence Synthesis:

Numerous studies have demonstrated the remarkable communication between the microbiota residing in the intestinal tract and central nervous system function. The metabolites of gut microbiota transmit signals via the vagus nerve to both the brain and spinal cord, and feedback signals are sent back after higher processing occurs.[2] This bidirectional connection has been shown to influence the functionality and stability of both systems. Dysregulation in the gut microbiome can result in the transmission of inflammatory signals along the pathway, which can increase the permeability of the blood-brain barrier, promote neuroinflammation and ultimately lead to cognitive impairment.[3]

Conclusions

The current literature strongly supports the relationship between the gut-brain axis and cognitive impairment. The microbiome in the intestinal tract plays a critical role in maintaining neurochemical balance through the gut-brain axis, and alterations in the gut microbiome can lead to inflammation in the intestinal epithelium.[4] This inflammation allows toxic bacterial metabolites such as lipopolysaccharides and short-chain fatty acids to travel out of the gut, compromising blood-brain barrier integrity.[3] This process promotes neuroinflammation and neuronal injury and ultimately leads to the neuronal death involved in Alzheimer's disease.[5] Additionally, the vagus nerve plays a crucial role in facilitating communication between the lumen of the intestinal tract and the brain through afferent fibers.[6]

Several studies have shown that probiotic supplementation can effectively decrease proinflammatory bacteria in the body.[3] This has potential to improve cognition and decrease the severity of preclinical stages of dementia, ultimately reducing the risk of developing late-stage Alzheimer's disease.[7] Therefore, targeting the gut microbiota through therapeutic interventions may provide promising prevention and treatment modalities for those with cognitive impairment.

Introduction:

The human gastrointestinal tract is home to over a thousand different species of bacteria, collectively known as the gut microbiome.[1] The metabolites produced by these bacteria have the ability to influence cellular level activity and overall host health.[1] The vagus nerve and enteric nervous system are crucial in the interdependent relationship between the central nervous system and peripheral tissues.[4] Metabolites of gut bacteria send afferent signals to the brain via the vagus nerve, which in turn send efferent signals that influence the gut microbiota and human physiology.[4] Consequently, changes in the gut microbiota can alter the equilibrium of the human brain and body.

Alzheimer's disease is the most common form of dementia, characterized by abnormal amyloid-beta plaques and neurofibrillary tangles.[8] In 2010, 33 million people worldwide had dementia, a number projected to double every 20 years, reaching 66 million by 2030 and 115 million in 2050.[1] With increasing life expectancy, the incidence of Alzheimer's disease is expected to grow, putting a burden on loved ones and society.

While advancing age is the most potent precursor of Alzheimer's disease, research shows that dysbiosis of the bacteria inhabiting the digestive tract can also contribute to cognitive impairment.[9] Disturbances in the gut microbiome compromise the integrity of intestinal tight junctions, allowing toxic metabolites to enter the bloodstream and threaten the blood-brain barrier via vagal nerve transmission, leading to neuronal changes in the brain.[10] This phenomenon has been historically referred to as 'leaky gut,' leading to 'leaky brain' as the ability of the microbiome to communicate with the brain affects cognition.[4] As a result, disruption of the symbiotic environment limits optimal cognitive function.

For these reasons, this review aims to identify the current understanding of the relationship between the gut-brain axis and Alzheimer's disease, including the known and postulated mechanisms underlying their influence on each other. This paper will analyze both the homeostatic environment and the variations of bacteria in the gastrointestinal tract with a particular focus on how changes in the gut microbiome reach the brain as well as the crucial role of the vagus nerve in the bidirectional communication. Furthermore, the impact of bacterial metabolites on the stability of the blood-brain barrier and their association with pathologic characteristics of Alzheimer's disease will be discussed.

Additionally, this review will address potential therapeutic interventions targeting the gut-brain axis, such as dietary interventions and probiotic supplementation. Finally, the clinical implications of this review and future directions for research in this field will be included.

Evidence Acquisition:

Utilizing PubMed, an initial search of "microbiota gut-brain axis" was conducted. This returned 4,028 articles published between 2013 and 2023. Next, using the advanced search feature "gut-brain axis" and "Alzheimer's disease" were input, which narrowed the search to 490 articles. Further specification with publish dates in the past 5-7 years and filters of 'meta-analysis' and 'systemic review' offered 295 results. After reviewing all publications titles and abstracts, nine review articles were accepted for this paper.

Next, a search on Web of Science for "microbiota gut-brain axis" with a filter applied for "clinical trial" was applied which displayed 83 results published between 2013 and 2023. After vetting each study, those that failed to address cognitive impairment or studies only done on animal models were excluded, reducing the results and 14 new studies were selected for this paper. In all, a total of 23 papers were accepted for the purpose of this literature review.

Additionally, a PICO search using the keywords "cognitive impairment," "gut dysbiosis," "probiotic supplementation," and "memory improvement" yielded 1 result, likely due to the specificity of the search. Mesh terms including "cognitive impairment," "gut dysbiosis," and "probiotic" were input to gain insight to similar searches throughout the above process.

Evidence Synthesis:

Gut-brain axis:

The gut-brain axis has been the focus of recent research, which has shed light on the impact of dysbiosis within the microbiome of the gastrointestinal tract. Recent studies have shown that there is a complex and surprising relationship between the gut microbiome and the brain, known as the gut-brain axis.[8] Disruption of the gut microbiome can lead to proinflammatory metabolic products, which contribute to the development of various diseases.[3] For example, studies by Borsom et al.[2] and Xu et al.[1] identify a link between changes in gut microbiota composition and conditions such as obesity, hypertension, depression, and Alzheimer's disease. Similarly, Liang et al.[9] also found that microbial alterations were positively associated with cognitive impairment (odds ratio [OR]=1.94 and 95% CI [1.23-3.06]), demonstrating significance between increased bacterial diversity and suboptimal brain function. It is the community of microbes inhabiting the gut that impacts brain function and behavior via the gut-brain axis.

While the bacterial density, diversity, and species differ among individual persons, the gastrointestinal tract remains the largest reservoir of microbes in all humans.[8] Research conducted by Xu et al.[1] and Jiang et al.[8] concludes that the most dominant bacterial genera occupying the gut, in descending order of prevalence, include *Bacteroidetes, Firmicutes, Proteobacteria, Verrucomicrobiota, Fusobacteria, Cyanobacteria, Actinobacteria, Spirochetes,* etc. Liang et al.[9] found an abundance of *Bacteroidetes* associated with higher cognitive performance (β=0.14, 95% CI [0.00-0.27]), using the mini-mental status exam (MMSE), a neuropsychological test used to test for cognitive impairment. In contrast, patients with Alzheimer's disease were found to have a higher abundance of the *Firmicutes* and *Bacteroidetes*

genera and less abundant *Bifidobacterium* genera, demonstrating the potentially proinflammatory properties of the former.[11] The symbiotic environment of gut microbiota plays a vital role in host health by acting as a barrier for pathogenic bacteria trying to invade and colonize the gastrointestinal tract.[5]

Studies have shown evidence of reciprocal effects between the brain and digestive tract, specifically in the context of irritable bowel disease. Zhang et al.[12] discovered a significant correlation between irritable bowel disease and depression in patients, as evidenced by an odds ratio [OR] of 9.43, (CI [6.43-13.81]; $P < 0.001$), even after adjusting for confounding factors such as age, sex, income level, and residence urbanization level, thereby demonstrating statistical significance. However, it's important to note that while the study controlled for socioeconomic aspects, potential confounders such as environmental and lifestyle factors were not considered. In addition, the use of medications and severity of the participants' irritable bowel disease and depression were not assessed, limiting the result accuracy. Meng et al.[11] agree that patients with irritable bowel disease have a 22% higher risk of neurodegeneration than non-irritable bowel disease individuals (HR 1.22, CI [1.09 to 1.35]), likely due to the infiltration of toxic microbial molecules into the central nervous system. Identifying and understanding the effects of gut dysbiosis and neurocognitive decline could present the potential for reducing the burden of disease in the future.

Microbial infection

Microbial infection is a crucial area of interest in the context of the gut-brain axis. The human body is nearly sterile at birth, and environmental factors such as diet, infection, stress, and exposure to microorganisms can influence the development of gut bacteria throughout life.[1] Research has shown that exposure to pathogenic microorganisms can affect the onset of

dementia.[1] For example, bacterial amyloids secreted by various species such as *Escherichia, Pseudomonas, Streptococcus, Staphylococcus,* and *Salmonella* have the ability to cross the blood-brain barrier, potentially contributing to the pathogenesis of Alzheimer's disease.[10]

Kesika et al.[5] revealed that pathogenic bacteria such as *Escherichia coli, Salmonella, and Shigella* produce endotoxins that disrupt the intestinal epithelial cells' integrity by cleaving cell adhesion and impairing tight junctions. Similarly, Wastyk et al.[13] found that the presence of *Escherichia coli* infections was linked to an elevated cytokine response accompanied by chronic systemic inflammation (false discovery rate [FDR] ≤ 0.05; q-value ≤ 0.1). However, the exclusive use of healthy individuals limits the credibility of these results. Elkjaer et al.[14] discovered evidence of *Escherichia coli* DNA in the brains of Alzheimer's patients, which provides further support for this association. Another study found that *Escherichia* metabolites can act as circulating endotoxins, adversely affecting cognitive function and concentration ($p<.01$).[3] In a longitudinal cohort study, Mayneris-Perxachs et al.[15] found that the presence of *Blastocystis* increased the growth of *Escherichia coli* and inhibited the growth of beneficial bacteria, *Bifidobacterium longum* and *Lactobacillus* ($p<0.005$). Eligible subjects underwent cognitive testing, notably Phenomic Verbal Fluency, to measure language capacity and processing speed involving higher brain function.[15] The researchers found that all fecal samples containing traces of *Blastocystis* were negatively associated with cognitive tests for executive function and positively associated with altered gut bacterial composition ($r=-0.38$, $p=0.085$).[15] The presence of *Blastocystis* was also negatively associated with the abundance of beneficial bacteria, *Bifidobacterium* and *Lactobacillus* species, in both the discovery and validation cohorts ($p< 0.001$).[15] These findings demonstrate how microbial infections can compromise host defense

and contribute to the proinflammatory changes involved in the pathogenesis of cognitive decline, particularly in Alzheimer's disease.

Infectious microorganisms that breach the blood-brain barrier can trigger inflammation, neuronal death, and ultimately may contribute to the development of Alzheimer's disease.[4] One study used immunohistochemical analysis to isolate *Chlamydia pneumonia* proximal to amyloid plaques and neurofibrillary tangles in Alzheimer's patient's brains.[8] The study did not provide conclusive evidence of *C. pneumonia* infection in neurons, only in astrocytes and microglial cells.[8] Megur et al.[3] confirmed a significant association ($p<0.05$) between *Chlamydia pneumoniae* infected cells near neurofibrillary tangles and senile plaques in Alzheimer's patients.

Another study reported a positive correlation between Helicobacter pylori (H. pylori) infection and lower scores on the MMSE among Alzheimer's patients (OR=0.83, CI=[0.72-0.97], p=0.017).[8] However, the study had several limitations, including a small sample size, the absence of control patients, and the diagnosis of H. pylori infection solely through serum antibodies, which differs from the gold standard of gastric tests such as histology and cultures.[8] Conversely, a cross-sectional study found eradicating H. pylori infection in Alzheimer's cases was associated with significantly lower mortality risk (hazard ratio 95% CI [0.014-0.725]; p=0.008), and potentially confounding factors, such as baseline MMSE scores and age were taken into account, enhancing the validity of the findings.[8]

Furthermore, the presence of herpes simplex virus (HSV) 1 DNA was found in 90% of amyloid plaques of Alzheimer's patients, along with increased abnormal Tau protein, suggesting an association between HSV infection and hyperphosphorylation promotion in the brain.[1] Exposure to microbial infections changes the microbiome and significantly alters brain physiology and cognitive function.[1]

The 'wanderer'

The enteric nervous system is the largest component of the autonomic nervous system, consisting of more than 100 trillion interconnected neurons that function to communicate throughout the alimentary tract and spinal cord.[2] Communication within the enteric nervous system is facilitated by the vagus nerve, which directly links the central and enteric nervous systems.[2] The autonomic, sympathetic, and parasympathetic nervous systems send signals via the vagus nerve between the intestinal lumen and the central nervous system.[6] Carlman et al. conducted a randomized control trial to explore the connection between cognitive performance and the autonomic nervous system.[16] The study, despite its small sample size of 22 healthy participants, provoked vagal activity and sympathetic response subsequent to stressful circumstances with a significant p-value of 0.21.[16] This suggests that changes in gut microbiota could lead to changes in brain function and thus influence host behavior.[16] However, the small sample size and the use of linear model for ANOVA analysis may limit the generalizability of the findings.

The vagus nerve serves as a mediator for communication along the gut-brain axis, offering a target for potential treatment regimens. Empirical evidence has demonstrated the efficacy of surgical vagotomy as a treatment for refractory peptic ulcer disease, indicating the importance of the vagus nerve in gastrointestinal function.[4] Additionally, research indicated that the presence of *Lactobacillus johnsonii* in a healthy gut microbiome could enhance the activity of the vagus nerve within the gastrointestinal tract.[3] A cohort study involving patients with Alzheimer's disease who underwent vagal stimulation reported either the elimination of cognitive deficits or an improvement in cognitive decline ($p=0.040$).[4] The results from Clancy et al.[17] found that vagus nerve stimulation provoked a parasympathetic response ($p=0.026$) and

significantly decreased the frequency of sympathetic nerve activity (p=0.001). The study had a limited sample size (n=12), but the results align with other cohort studies demonstrating the bidirectional communication of brain and gut function via the vagus nerve. This reciprocal link enables signaling between metabolites produced by gut microbes and neurotransmitters released in the brain, as supported by previous research.[10]

Leaky gut

A leaky gut is characterized by an increased permeability of the gastrointestinal lining and may also play a significant role in the progression of neuroinflammation and neurodegenerative disease.[1] The dysregulation of the gut microbiome alters the intestinal epitheliums' integrity, leading to increased permeability and transportation of inappropriate bacteria.[1] This triggers enteroendocrine reactions of inflammatory cellular release, promoting dysfunction along the gut-brain axis.[4] This proinflammatory effect contributes to the progression of neuroinflammation and, ultimately, neurodegenerative disease.[18] Studies have shown accelerated inflammatory response in the blood and cerebrospinal fluid of Alzheimer's patients compared to healthy control subjects (rho=0.60, p<0.001), implying the role of inflammation in the pathogenesis of Alzheimer's disease.[3] However, varying sample collection and analysis protocols among laboratories can limit direct result comparisons.

The blood-brain barrier protects against the entry of pathogens into the central nervous system, and in a homeostatic environment, the amyloid precursor protein in the blood is cleared and excreted.[5] However, magnetic resonance imaging of Alzheimer's and elderly brains show blood-brain barrier disruption.[5] Patients with mild cognitive impairment and early onset Alzheimer's underwent contrast material-enhanced magnetic resonance imaging, and a positive association was identified between blood-brain barrier leakage and cognitive decline (p=<0.05).[2]

Thus, a decline in the integrity of the gastrointestinal barrier can trigger proinflammatory signals that disrupt the blood-brain barrier.[3] Additionally, a study using linkage disequilibrium score regression analysis (LDSC) found a significant negative correlation ($p=9.00x10^{-25}$) between gastrointestinal disorders and cognitive traits observed in Alzheimer's disease.[19] To account for potential limitations in capturing local genetic effects, the study conducted genetic correlation analyses alongside the LDSC method to identify specific genetic regions associated with cognitive traits and gastrointestinal disorders.[19] The gut microbiome plays a crucial role in maintaining the blood-brain barrier, and alteration in its composition can promote decreased brain function.[3]

Lipopolysaccharides

Many researchers have studied the major component of gram-negative cell walls, lipopolysaccharides.[1] These endotoxins comprise 50-70% of normal gut microbiota and are secured by tight junctions when the microbiota is in equilibrium.[1] However, changes in the composition of the gut microbiome can lead to the release of lipopolysaccharides into the bloodstream and subsequently into the brain, causing significant inflammatory reactions.[3] Research by Hu et al.[1] showed that plasma levels of lipopolysaccharides were three times higher in patients with Alzheimer's disease compared to healthy individuals ($p<0.005$). Additionally, RNA sequencing in Alzheimer's patients revealed the overlap of lipopolysaccharides with beta-amyloid deposits in the brain.[14] Similar findings by other researchers have shown that bacterial lipopolysaccharides in the brains of Alzheimer's patients are associated with cognitive impairment and neuroinflammation.[10] Alterations in the composition of the gut microbiome trigger the secretion of lipopolysaccharides and amyloid during a state of increased gastrointestinal tract and blood-brain barrier permeability, likely contributing to the pathogenesis of Alzheimer's disease.[5]

Clinical studies of cognitive impairment

The gut-brain axis has been extensively studied in the current literature, providing data on bacteria dysgenesis and cognitive impairment.[10] The bidirectional communication between the gut microbiota and the central nervous system directly affects peripheral intestinal function and the brain's emotion and cognition centers.[13] Studies have consistently found reduced gut microbiota diversity in neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, and multiple sclerosis.[14]

Advancing Age

Studies show the tremendous effects of advanced age as the predominant risk factor for neurodegenerative disease.[8] The gut microbiota undergoes physiological changes with age, and the incidence of neurodegenerative disease increases simultaneously.[20] Jiang et al. reported that gut microbiota composition in elderly patients shows a decline in beneficial bacteria such as *Bacteroidetes, Lactobacillus, and Bifidobacterium*.[8] Also, the blood-brain barrier is compromised with age, reducing the ability to eliminate amyloid plaques or toxic metabolites, leading to their accumulation and contributing to the pathogenesis of Alzheimer's disease.[8] Consequently, the age-related effects on the gut microbiome could serve as an alternative explanation for the increased incidence of neurogenerative diseases, such as Alzheimer's, in elderly individuals.[3]

Multiple studies have proposed how alterations in gut bacteria could lead to neurodegenerative disease. For example, Kesika[5] and Meng et al.[11] observed a reduction in gut microbial diversity and increased proinflammatory bacteria in Alzheimer's patients compared to healthy individuals. In particular, Meng et al.[11] discovered increased levels of *Firmicutes* and *Bacteroidetes* phyla and lower levels of *Bifidobacterium* and *Lactobacillus* in patients with

Alzheimer's disease, indicating that these changes could contribute to the pathogenesis of the disease.[11] The researchers hypothesized that the bacteria in question might produce endotoxins that damage intestinal epithelial cells and disrupt tight junctions, leading to increased intestinal permeability.[11] It should be noted that the study population was predominately Caucasian (>90%), with a majority of female participants (p=0.0785), and consisted of individuals with mild dementia.[11] Due to the resulting gut barrier dysfunction, microbiota dysbiosis is likely a significant contributor to neuroinflammation.[8]

According to Kesika et al.[5], patients with cognitive impairment tend to have higher levels of proinflammatory bacteria strains and lower levels of anti-inflammatory bacteria, including *Bacillus fragilis.* This finding is supported by Jiang et al.[8] and Megur et al.,[3] who also found a link between *Bacteroides fragilis* in the gut and neuroinflammation in Alzheimer's patients. However, Megur et al.[3] discovered that *Bacteroides fragilis* actually protects against demyelinating central nervous system disease in Alzheimer's patients, based on a small study of patients with spinal cord injuries. Nonetheless, the exotoxins produced from *Bacteroides fragilis* disrupt the epithelial cell integrity, damaging the tight junction and increasing intestinal permeability.[5]

Research indicates that changes in gut microbiota composition can affect brain function.[6] For instance, recent studies suggest that the development of neurodegeneration in Alzheimer's disease may start in the gut and then spread to the brain, although this evidence is preliminary.[3] A cohort study of Parkinson's disease patients by Cersosimo et al.[6] found that all participants experienced at least one gastrointestinal symptom (p=0.001). Although the study's small sample size (n=129) limit its conclusions, it highlights the significance of pathophysiological mechanisms in neurodegenerative disease.[21]

Dementia studies

Alzheimer's disease is an irreversible neurodegenerative disease of the central nervous system. The pathology is characterized by beta-amyloid plaques and neurofibrillary tangles.[2] According to the cascade hypothesis, amyloid-beta plaque deposition is the main contributor to hyperphosphorylation of tau protein buildup and the formation of neurofibrillary tangles, resulting in loss of neuronal cell function.[2] However, recent studies suggest that amyloid-beta plaque and tau deposition occurs between 10 and 20 years before the onset of dementia symptoms.[2] The cognitive dysfunction is likely due to amyloid-beta plaques located outside the neuron and neurofibrillary tangles within the neuron, which cause neuroinflammation, neuronal injury, and eventually neuronal death.[1] This descent presents primarily as declining memory loss, confusion, aggression, and paranoia in patients who have Alzheimer's disease.[2]

While research has linked the idea of leaky gut and proinflammatory signals to neurodegeneration, adding to disease progression, this may not be the primary pathway of the development of Alzheimer's.[2] Kesika et al.[5] found evidence to suggest that bacterial amyloid in the gut may contribute to the misfolding and buildup of senile plaques, similar to amyloid-beta peptide. However, further research is needed to establish a causal relationship between dysbiosis in the gut microbiome and cognitive deficit.[5] Nonetheless, ongoing research in this area is active and may provide a further understanding of the complex mechanisms involved in Alzheimer's disease.

Interventions

The imbalance of gut microbiota caused by infectious pathogens may lead to Alzheimer's disease, whereas a healthy gut microbiota could potentially reduce the risk.[13] The gut microbiota

has been found to be intricately linked to cognitive impairment and age-related memory loss, highlighting its potential as a therapeutic target for preventing dementia.

Dietary

Emerging evidence suggests a correlation between diet, gut microbiota, and age-related cognitive disorders.[22] High cholesterol intake has been found to have a negative effect on changes in memory score ($p=0.005$), while fat-soluble vitamin consumption has a significant positive association ($p=0.006$).[23] Moreover, Xu et al.[1] contributed that dietary intake of vitamins C and E, which contain antioxidant nutrients, could decrease the risk of Alzheimer's disease. Studies have also indicated that coffee, a rich source of antioxidant polyphenols, can decrease oxidative stress-related brain disease, lowering the pathologic process of neurodegeneration, such as Alzheimer's disease.[1] Gubert et al.[5] found that polyphenols can effectively mediate neuroprotection by reducing beta-amyloid oligomerization, the brain damage involved in Alzheimer's disease. A cohort study examined bacterial diversity and dietary habits in patients with a clinical diagnosis of mild cognitive impairment.[22] They found that diet contributes significantly to gut microbiota composition, thereby impacting host health and brain function.[22] Based on these findings, dietary intervention should be considered in preventing and treating neurodegenerative disease.

A cohort study demonstrated increased microbiota diversity and decreased proinflammatory markers by observing diets containing fermented foods (e.g., kombucha, yogurt, and kimchi).[11] In addition, fermented foods' impact on gut microbiota was emphasized in a randomized prospective study by Wastyk et al.[13] Using an inflammation panel linking cytokine levels to proinflammatory processes, 19 of 93 circulating inflammatory mediators were decreased after fermented food intervention.[13] Conversely, reduced bacterial diversity is

associated with impaired fine motor skills, cognitive decline, and memory loss.[2] Studies by Xu et al.[1] are consistent with previous cohorts, demonstrating that a healthy diet that includes fermented foods, fat-soluble vitamins, and a low-calorie intake is crucial for maintaining a healthy gut microbiome and delaying brain aging.

Probiotic supplementation

Manipulating gut microbiota through the use of probiotic bacteria has shown promise in improving cognition and stress response in preclinical and clinical settings.[16] Given that patients with Alzheimer's disease exhibit reduced levels of *Lactobacillus* and *Bifidobacterium*, it is suggested that probiotics containing these genera should be widely accepted. These bacteria are naturally found in yogurt, kefir, and fermented foods and are also available in supplement form.[8] Jiang et al.[8] found a positive impact on cognitive function in Alzheimer's patients after a 12-week randomized, double-blind, controlled clinical trial of probiotics containing strains of both *Lactobacillus* and *Bifidobacterium*. Similarly, Kim et al.[7] investigated the effects of 12-week probiotic supplementation containing *Bifidobacterium* species taken twice daily on cognition and mood in adults over 65. The gut microbiota was analyzed using rRNA sequencing, and the cognitive status was assessed via activities of daily living, instrumental activities of daily living, and the MMSE.[7] They found that probiotics improved mental flexibility and stress scores compared to the placebo group ($p<0.05$).[7] Interestingly, after the probiotic intervention, the amounts of *Eubacterium, Allisonella,* and *Prevotellacea,* gut bacteria associated with inflammation, significantly decreased ($p<.05$).[7] This is suggestive that probiotics containing *Lactobacillus and Bifidobacterium* could promote an abundance of beneficial bacteria and decrease those that are harmful.[7]

Probiotic strains, including *Lactobacillus plantarum* and *Bifidobacterium*, have also been found to improve intestinal barrier function and promote protein expression in maintaining epithelial tight junctions.[5] Kesika et al.[5] found that supplementation of probiotic milk containing strains of *Lactobacillus, Bifidobacterium bifidum*, and *I. fementum* improved MMSE scores and decreased inflammatory processes in Alzheimer's patients. Meng et al.[11] tested this hypothesis through a 12-week probiotic supplementation containing several genera, primarily *Lactobacillus and Bifidobacterium*, and varying colony-forming units or amounts of active microorganisms. While some randomized controlled trials found no significant improvement of neurocognitive function on MMSE scores with probiotic supplementation (mean difference 0.92, 95% CI [-0.05 to 1.89], p=0.0635),[11] others revealed significant effects for certain patient populations. For instance, Meng et al. reported that patients over 70 exhibited statistically significant improvements in MMSE scores when taking probiotics with higher colony-forming unit doses >1010 ($p < 0.001$).[11] Furthermore, a study by Kim et al.[7] investigated the probiotic OLL2712, containing *Lactiplantibacilis plantarum*, in patients with mild cognitive impairment.[23] They found a significant improvement in memory score (p=0.044) after 12 weeks of probiotic intervention in elderly patients with early memory decline.[23]

Overall, probiotics that increase the abundance of anti-inflammatory bacteria can potentially enhance cognitive function.[16] A balanced diet that includes fermented foods, vitamins A, D, E, and K, and probiotic supplements containing *Lactobacillus* and *Bifidobacterium* is essential for maintaining gut microbiome homeostasis and overall host health.

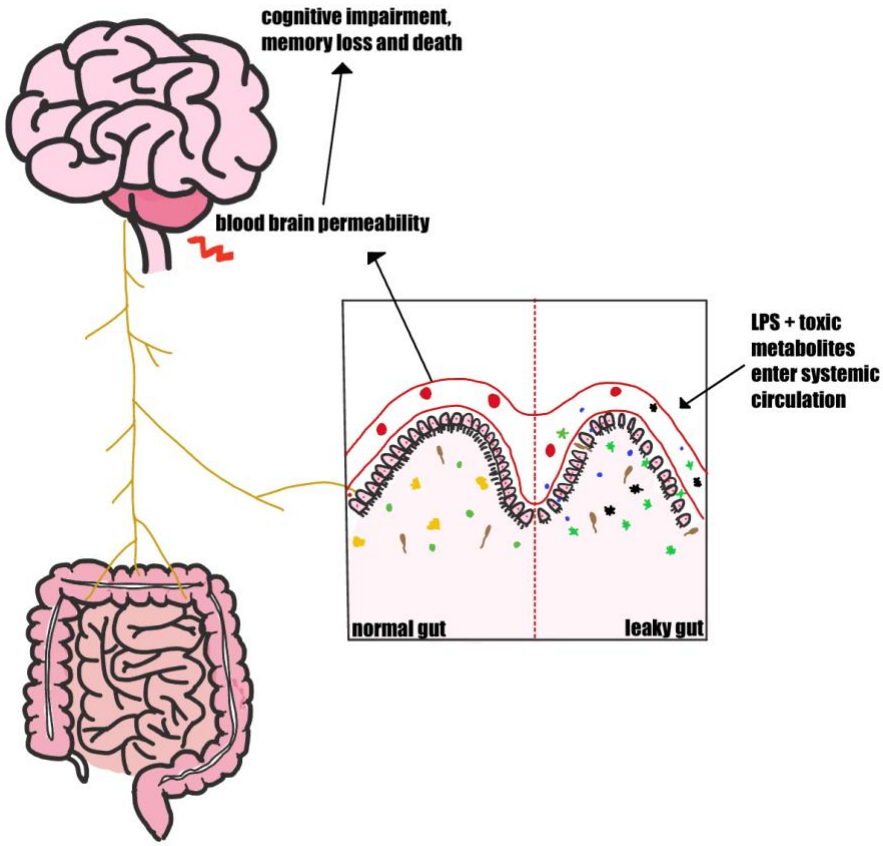

Figure 1: The role of gut microbiota on brain function.

Figure 2: Summary of probiotic clinical studies.

Author	Year	Study Design	Probiotic	Participants	Duration of Tx (weeks)	Primary Outcomes	Comments
Jiang et al.	2020	Randomized, double-blind, controlled clinical trial	*Lactobacillus, Bifidobacterium*	Alzheimer's patients	12	-probiotic group had significant improvement in MMSE score ($p<0.001$) compared to placebo -positive affects cognitive function and metabolic status	-Small sample size (n=60)

						-serum changes in high-sensitivity C-reactive protein (P <0.001) and serum triglycerides (P<0.003)	
Kim et al.	2020	Randomized, double-blind, placebo-controlled multicenter trial	*Bifidobacterium*	Healthy adults >65	12	-probiotics improved mental flexibility and stress scores compared to the placebo group (p<0.05) -amounts of *Eubacterium, Allisonella, and Prevotellacea*, gut bacteria associated with inflammation, significantly decreased (p<0.05)	-Small sample size (n=63)
Kesika et al.	2021	Randomized controlled trial	*Lactobacillus, Bifidobacterium bifidum, I. fementum*	Elderly patients >65 with mild cognitive impairment	12	-improved MMSE scores and decreased inflammatory processes (p<0.05)	- More randomized controlled trials with larger sample sizes are needed
Meng et al.	2019	Randomized controlled trial	*Lactobacillus, Bifidobacterium*	Elderly patients >65 with Alzheimer's disease	12	-some randomized controlled trials found no significant improvement of neurocognitive function on MMSE scores with probiotic supplementation (mean difference 0.92, 95% CI [-0.05 to 1.89], p=0.0635) -patients over 70 had statistically significant improvements in MMSE scores when taking probiotics with higher colony-forming unit doses >1010 (p <0.001)	- Risk of bias in selection of results - Utilized various colony forming units. ethnicities, and severity of cognitive impairment

Kim et al.	2020	Randomized, placebo-controlled trial	*Lactiplantibacillis plantarum*	Elderly patients >65 with mild cognitive impairment	12	-Significant improvement in memory score (p=0.044)	-Small sample size (n=78) -Compared with healthy elderly volunteers in the same community which limits generalizability

Conclusion

After conducting a comprehensive analysis of the available literature, it is evident that a significant association exists between the microbiota of the gastrointestinal tract and cognitive impairment. Numerous studies demonstrate that alterations in the homeostasis of gut bacteria correlate to cognitive impairment. This bidirectional communication likely occurs through the enteric nervous system and the vagus nerve. Dietary and other interventions that positively impact intestinal microbiota and that limits CNS insults can be a possible way to reduce the occurrence of cognitive decline.

In clinical settings, the focus should be on the link between psychiatric illness and gastrointestinal disease. However, there are limitations in current studies and while there may be an association between gut microbiota and cognitive impairment or neuroinflammation, further research is needed to establish a causal relationship. New interventions are required to develop preventative and therapeutic options for age-related cognitive decline in the broader population.

The mechanism and dose of administering probiotics for memory loss treatment is still not entirely clear from clinical trials. Further research with larger and more diverse sample sizes is necessary to validate the use of vagal nerve stimulation in reducing memory impairment and cognitive decline in Alzheimer's patients. In addition, a better understanding of gut microbial alterations across the lifespan can help enhance the management of Alzheimer's disease.

Based on the available literature, it is recommended that healthcare providers promote a balanced diet that includes fermented foods, vitamins, and probiotics containing *Lactobacillus* and *Bifidobacterium.* The close relationship between gut health and brain function is crucial to advancing population health.

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