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REVIEW ARTICLE

The Effect of Gut Dysbiosis on Memory Formation in Children: A Literature Review

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ABSTRACT: The gut-brain axis refers to the bidirectional communication system between the central nervous system and the enteric nervous system, linking the brain's emotional and cognitive regions with gastrointestinal functions, such as digestion and immune responses. The gut microbiome plays a crucial role in this interaction, influencing various aspects of health. However, factors like poor dietary habits and medications that alter the microbiome can disrupt this delicate balance, leading to gut dysbiosis. This imbalance is associated with numerous diseases and infections. Recent studies have suggested that the gut microbiome may also play a role in influencing brain function and behavior. This paper seeks to explore the impact of gut dysbiosis on memory formation in children. Are the effects of gut dysbiosis on memory formation consistent across different demographic groups? Additionally, is there empirical evidence to support the idea that therapeutic interventions could mitigate the impact of gut dysbiosis on memory formation in children? By conducting this literature review, we aim to provide a thorough understanding of the current state of research on the effect of gut dysbiosis on memory formation in children, highlighting its significance and identifying pathways for future investigation.

KEYWORDS: Biomedical and Health Sciences, Nutrition and Natural Products, Gut-brain Axis, Gut Microbiota, Gut Dysbiosis, Memory Formation, Children.

Introduction

The nervous system is crucial in governing, coordinating, and facilitating communication throughout the body. Comprised of the brain, spinal cord, and an intricate web of nerves, it divides into two main parts: the central nervous system (CNS), grouping the brain, cerebellum, brainstem, and spinal cord; and the peripheral nervous system (PNS), whose nerves extend from the CNS.

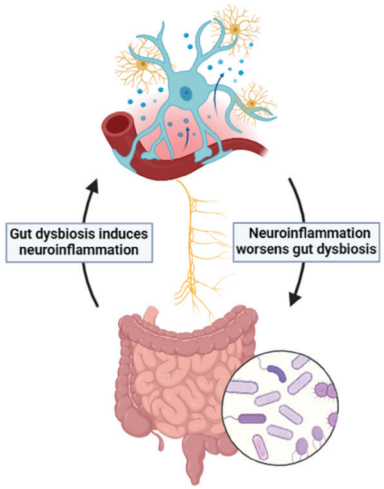

Figure 1: Model of the gut gut-brain axis, a communication between the CNS and the ENS. Gut dysbiosis causes neuroinflammation, which in turn worsens dysbiosis (causing gut inflammation). This cycle illustrates the constant exchanges between the dysregulated gut and the inflamed brain, mediated by the vagus nerve.

On the other hand, a "second brain", known as the enteric nervous system (ENS), is in the gastrointestinal tract. The communication between the CNS and the ENS, known as the gut-brain axis, is facilitated by the vagus nerve, transmitting sensory signals from the gut to the brain (**Figure 1**).[1]

This mutual exchange, allowing a two-way communication between the CNS and the ENS, oversees the body's balance and links the emotional and cognitive regions of the brain with various intestinal functions like immune response, gut permeability, reflexes, and hormone signaling. The gut's microbiome, among various factors, significantly influences this connection.

Acting as an integral part of the gastrointestinal tract, the gut microbiome distinguishes between beneficial organisms, harmful pathogens, and others. Recent research has been bringing to light the gut microbiome's pivotal role in this bidirectional relationship.[2] However, this research paper aims to take it a step further by studying the effect of gut microbiota dysbiosis on memory formation in children. To do so, it is crucial to understand what methodologies previous studies have used to examine the impact of gut dysbiosis on memory formation in children. Studies of the existing common findings, as well as gaps, in the current literature on gut dysbiosis and memory formation in children will also be conducted.

Therein, two main questions arise: Are the findings on gut dysbiosis and its implications on memory formation in children similar throughout various demographic groups, taking into consideration age and socioeconomic status? Is there empirical evidence that supposes that there are therapeutic interventions like dietary changes and pre/probiotics that may improve the effects of gut dysbiosis on memory formation in children?

This research suggests that dysregulation in the gut microbiota can negatively affect memory formation in children. This dysregulation may be caused pharmaceutically by excess medications or dietarily through constant intake of fatty, sugary

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foods, low in nutrients that the microbiota in the gut requires.[3] It is also proposed that the findings on gut dysbiosis and its implications on memory formation in children vary throughout various demographic groups taking into consideration age and socioeconomic status.[4] Finally, it is hypothesized that therapeutic interventions like dietary changes, pre/probiotics will improve gut dysbiosis and therefore improve its negative effects on memory formation in children.[5]

By conducting this literature review, the aim is to provide a thorough understanding of the current state of research on the effect of gut dysbiosis on memory formation in children, highlighting its significance and identifying pathways for future investigations. Moreover, understanding the role of gut dysbios is in cognitive development can inform clinical practices and interventions aimed at promoting cognitive health in children.[6,7] The findings could influence dietary guidelines and public health strategies to enhance gut health and cognitive development in children.

Antibiotics-Induced Gut Dysbiosis

Gut dysbiosis induced by antibiotics in children:

The gut microbiome is well-known to be unique and diverse but also very sensitive and vulnerable to changes in the gut.[8] Recent studies have shown that the gut microbiome's richness, diversity, and taxonomic composition can be significantly altered by antibiotic intake. This disruption in the gut microbiota has been shown to negatively impact cognitive functions in both adults and children.[9]

In fact, a recent study grouping three investigations of gut richness in children between the ages of 0 and 18 found that children who received antibiotics had microbiota richness that was substantially lower than that of children who were not exposed to antibiotics in all three investigations.[9] However, the pediatric gut microbiome's reduction in richness was resolved in a few months to a few years, depending on the antibiotic taken: it took one year after penicillin consumption and up to two years after macrolides consumption.

The same study also analyzed pediatric gut microbiome diversity and summarized the data of 8 investigations around the world. While alpha diversity analyses the variety of species on a single sample, beta diversity does so on multiple samples. The average alpha diversity of the gut measured by the Shannon index was significantly different according to the geographical location. While the initial average alpha diversity in Eurasian countries was 3, that of African countries was 15. However, meta-analyses of 4 randomized control tests (RCTs) studying azithromycin's impact on the pediatric gut microbiome revealed that its consumption was linked to reduced alpha diversity by 0.86 on average (**Figure 2**).

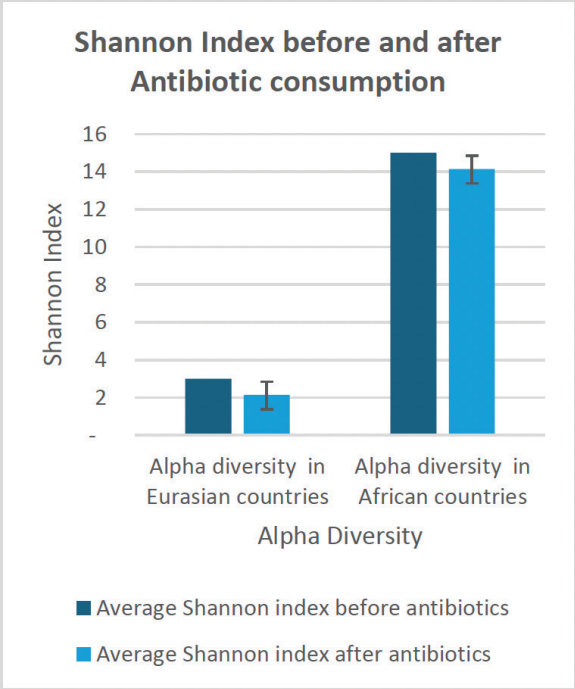

Figure 2: Antibiotic consumption reduced alpha diversity by 0.86 in the Shannon Index.

$$Shannon\ Index\ (H') = -\Sigma(p_i * \ln(p_i))$$

The Shannon Index (H') represents the species diversity index and is calculated by dividing pi, the percentage of individuals (i) of a specific species detected by the total number of individuals detected.

On the other hand, 2 out of 3 investigations in the study reported a significant reduction in beta diversity, suggesting a substantial change in the types of species in the microbiome as well. Overall, six of the eight investigations reporting on species diversity suggested a strong correlation between the usage of antibiotics and a decline in species diversity.

The study also noted the changes in taxonomic composition in disrupted pediatric gut microbiomes caused by antibiotic exposure and studied in 10 different investigations. Antibiotic use has been proven to reduce the number of beneficial bacteria in the pediatric gut, like *Bifidobacteria and Lactobacilli* (probiotic supplements). Moreover, it has decreased the number of *Clostridium clusters IV and XIVa*, bacteria which play a big role in the gut microbiome and the immune system. On the other hand, antibiotic treatment was associated with an increase in *Bacteroidetes* and *Proteobacteria* like *E. coli*, species which have been implicated in serious infections. Overall, evidence suggests that antibiotic-induced gut dysbiosis causes unhealthy alterations in the microbiome's diversity, richness, and taxonomic composition.[9]

Cognitive impairment induced by antibiotics:

Numerous research studies also reveal that antibiotics induce cognitive impairment and suggest that it is caused by antibiotic-induced gut dysbiosis (**Figure 9**).[10] In this study, germ-free (GF) mice were separated into three groups: group A, group B, and group C. A specific antibiotic mix was made to deplete their gut microbiota and was administered for 10 days. Group A was prepared to go through an open field test,

an elevated maze test, a tail suspension test, and a novel object recognition test (NORT) (**Figure 3**). Group B was subjected to the Barnes Maze (BM) test (**Figure 4**) and went through training for 2 days. Group C was treated with antibiotics but was not accustomed to any behavioral tests.

Figure 3: Novel Object Recognition Test (NORT). The mouse is exposed to certain objects during training trials. During test trials, one object is replaced with an unfamiliar one and time spent with novel object is recorded.

The GF mice performing the NORT were tasked with exploring two objects placed at close sides of the central area for 5 minutes. One hour later, they were exposed once more to one familiar object and one novel object. The time of exploration and behavior were filmed by a video camera and analyzed with the VideoMot 2 software. Mice who explored the objects for less than 5 seconds were excluded. Familiar and unfamiliar objects were chosen alternately between trials to prevent spatial and object bias.

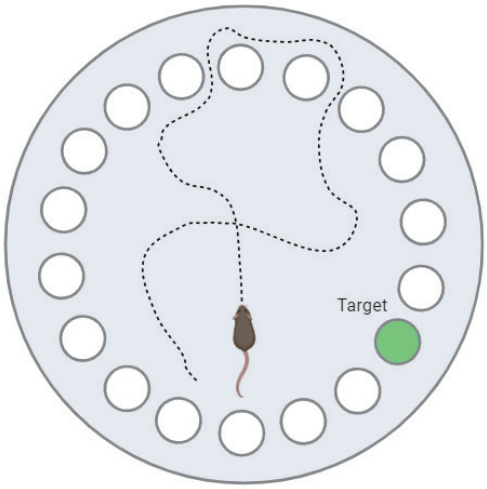

Figure 4: Barnes Maze (BM) test. The mouse is trained to memorize the specific position of the target hole with an escape cage attached to it. During test trials, the escape cage is removed, and the mouse must find the target hole. This test is performed to test its spatial memory.

On the other hand, GF mice were subjected to the maze for three successive days to get accustomed to it. An escape cage was attached to the target hole in the training sessions but detached during the probe session. During the training, the mice learned the specific position of the hole and were tested on their spatial memory during the probe session. Their movements were tracked for 2 minutes by a video camera and analyzed with the VideoMot 2 software. The location of the escape cage was switched after every three mice to prevent spatial or visual cue bias.

The results show that the microbiome was significantly altered by antibiotic treatment, which decreased bacterial diversity and load. Since GF mice have insufficient memory, the NORT was used to assess non-spatial memory, while the BM test was used to assess spatial learning and memory in a different group of animals, following antibiotic treatment.[11] The memory index of mice treated with antibiotics was considerably lower than that of vehicle-treated mice (not given antibiotics), suggesting a disruption in the memory for novel object identification. The results of the BM test showed that the antibiotic therapy did not affect spatial learning or memory. Moreover, as well as revealing the alteration of metabolic profiles in the colon and plasma of the mice, the study concluded that antibiotic-induced dysbiosis influences specific types of learning and memory but does not cause neurotoxicity. Evidence suggests that antibiotic use impairs object recognition but not spatial memory. To conclude, research has proven that antibiotics can induce gut dysbiosis, which influences cognition. However, this study was done with adult mice, and not young ones. More research is needed to understand the gut microbiota's role in this antibiotic-related long-term consequence, with a focus on pediatric gut microbiomes.

Nevertheless, recent research has revealed that long-term antibiotic exposure in childhood causes cognitive impairment in adulthood, suggesting that the previous results with the GF mice may apply to children as well. Similarly, a study assembled 474 infants who had been administered antibiotics in their first 24 months (about 2 years) of life.[12,13] At 11 years of age, 342 of them (72%) had a neurocognitive assessment to determine the effects of early consumption of antibiotics. In fact, antibiotic exposure during the first six months of life had caused significant impairments in the overall cognitive and verbal comprehension abilities of the children, as well as an increased risk of metacognition, executive function, impulsivity, hyperactivity, attention-deficit hyperactivity disorder, anxiety, and emotional disorders.

Research has proven multiple times that antibiotics affect cognition. When taken excessively during infancy and childhood, the consequences are long-term. More research is needed to fully understand the specific cognitive impairments that may result from each type of antibiotic, as well as their duration, more specifically in pediatric antibiotic-induced dysbiosis.

Probiotics against gut dysbiosis and cognitive impairment:

The gut microbiota is composed of both beneficial and pathogenic bacteria that communicate to the brain through the vagus nerve.[2] Gut dysbiosis occurs when pathogenic bacteria overpopulate the gut, suppressing and dominating the beneficial ones. To counter this imbalance, research suggests consuming probiotics like *Lactobacilli* or *Bifidobacteria*, which have long been proven to have a positive influence on gut microbiota.[14] Specifically, recent studies have researched their exact implications on gut dysbiosis, in hopes that it may reverse antibiotic-induced dysbiosis, as well as provide more insight on cognition.

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One study assembled male Swiss albino mice and split them into 4 groups, each group comprised of 6 animals. They were housed in a controlled temperature (around 21˚C) with an alternating cycle of light and dark every 12 hours, *ad libitum* to food and water.[15] The first group was the control group (who only received the vehicle, normal saline). While the second group only received antibiotics, the third was administered with probiotics as well. Finally, the fourth group only received probiotics. After receiving the dosages, a qPCR (quantitative polymerase chain reaction) was performed through a collection of the mice's fresh feces to study their bacterial 16S rRNA. The mice were challenged with multiple behavioral experiments, like an Elevated plus maze (EPM) (**Figure 5**), a Passive avoidance test (PAT) (**Figure 6**), a Morris water maze (MWM) (**Figure 7**), and a novel object recognition test (NORT) (**Figure 3**).

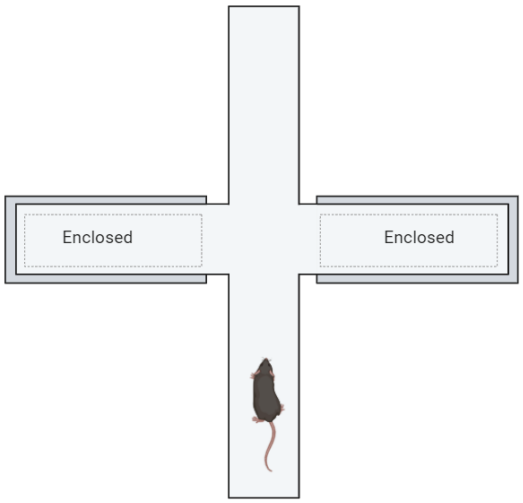

Figure 5: Elevated plus maze (EPM). With its back to the center, the mouse was positioned at one of the open arm's edges. Transfer latency (TL) is the amount of time it takes an animal to move from the end of an open arm into one of its closed arms, four paws within the closed arm.

Prior to Day 1 of the EPM test, the mice spent 120 seconds (about 2 minutes) exploring the maze. The study excluded the animals who displayed a transfer latency (TL) of more than 120 seconds on Day 1.

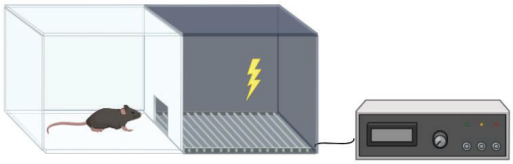

Figure 6: Passive avoidance test (PAT). When the mouse crosses to the dark side of the chamber, it receives an aversive stimulus (shock) through the floor. On test trials, time to cross to the dark chamber is recorded.

The PAT was conducted in a two-chamber box connected by an open gate, one chamber being lit and the other being dark. The animal was permitted to explore both compartments on the first day. After being placed in the illuminated chamber, the animal set foot in the dark chamber the next day and experienced a moderate foot shock measuring between 0.2–0.4 mA during 1 s. The mouse was excluded from the study if it took more than sixty seconds to enter the dark chamber. After three days without shock treatment on the grid floor, the memory recall of the included mice was assessed, with a maximum duration of 300 s.

Figure 7: Morris water maze (MWM). Tests a mouse's ability to use visual cues to locate a hidden underwater platform. Swimming is recorded and tracked via an overhead camera.

The opposite quadrant of the platform, or the most remote position, was the starting point. The animal trials lasted 120 seconds for four successive days and enabled the mice to mount on the platform. Animals were permitted to stay on the platform for up to 30 seconds. The study excluded the animals that were unable to mount on the platform in less than 120 seconds. The probing trial took place on the fifth day, during which the animals were given 120 seconds to swim without the platform. Noldus Technology's computer-based image analysis system captured videos of the probing trial, allowing them to determine the escape latencies and the amount of time spent in each quadrant.

During the NORT, the mouse was permitted to move around the rectangular open plastic box on the first day of habituation. The next day, the mouse was permitted to move around the same arena containing 2 similar objects (A+A) to get accustomed to it. The animal was removed from the study if it did not investigate any of the objects in the arena. On test day, the animal was once more permitted to explore the arena but was given two distinct objects (A + B); A is the previous object, and B is the new object. Preference Index (PI), which is the ratio of the amount of time spent on test day exploring the new object to the amount of time spent exploring both objects, was used to measure cognitive function. A preference index of more than 50% suggests a preference for a novel object, while one of less than 50% indicates a preference for a familiar object. A 50% preference index means that neither of the two items has been chosen.

The results of the study suggest that the use of antibiotics dramatically ($p < 0.001$) decreased the amounts of DNA in *Lactobacillus, Bifidobacterium*, and *Firmicutes* compared to control. Moreover, the antibiotic group had considerably reduced levels of *Clostridium* ($p < 0.01$) in comparison to the control group. In fact, during the MWM test, the antibiotic group spent less time in the target quadrant, which was enhanced by probiotic treatment. The longest path to reach the target

quadrant was also taken by the mice who had been exposed to antibiotics. This was significantly improved in mice who had also been exposed to probiotics. These results were similar across all tests. In mice treated with antibiotics, probiotic administration resulted in the replenishment of all four gut microorganisms: *Lactobacillus, Firmicutes, Clostridium*, and *Bifidobacterium* ($p < 0.001$). Probiotic administration helps reverse previously mentioned consequences and prevents gut dysbiosis-associated memory impairment in mice by restoring the intestinal microbiota and protecting hippocampal neurons.

Western Diet-Induced Gut Dysbiosis

Western diet-induced gut dysbiosis linked to cognitive impairment:

While it is understandable that antibiotics can induce gut dysbiosis, it is a lot less known that an unhealthy diet, high in fat and sugars like the Western diet (WD), can cause the same disruption.[3]

Research suggests that a WD, unrelated to obesity, has an adverse effect on hippocampal function. For example, even though the animals' body weights were comparable to those of regular chow-fed controls, hippocampal-dependent impairments in spatial memory have been documented after just 3 or 9 days of WD consumption. High fructose diets, like WDs, can affect mice's hippocampal-dependent learning and memory even in the absence of obesity.

To study the individual influences of the WD's macronutrients, research has studied two different types of diets. It found that a high-fat, low-carb diet (72% kcal from fat) lowers the levels of the probiotic *Bifidobacteria*, causing inflammation in the gut.[16] On the other hand, levels of *Bifidobacteria* were not affected by a low-fat chow diet supplemented with a 65% fructose solution. However, recent research data showed that *Bifidobacteria* were elevated following free access to the sugar solutions (along with chow and water) that mimic commonly consumed sugar-sweetened beverages, compared to controls that were not given sugar. This suggests that the concentration of carbohydrates is a determining factor in sugar-induced gut microbiome alterations.

Researchers have revealed that WD causes alterations in the gut microbiome, which contribute to WD-mediated cognitive impairments, as well as neuroinflammation.[16] This justifies the link between unhealthy diets and Alzheimer's disease, strokes, or even psychological disorders like bipolar disorder.

Furthermore, WD affects not only the gut microbiota but also the brain directly (**Figure 9**). When food is consumed, its nutrients travel from the gut into the bloodstream, ultimately reaching the brain. These nutrients play a vital role in brain development, cognitive function, and even emotional well-being, especially in children. Hence, it is especially pivotal for the pediatric gut to respect the food pyramid (**Figure 8**).

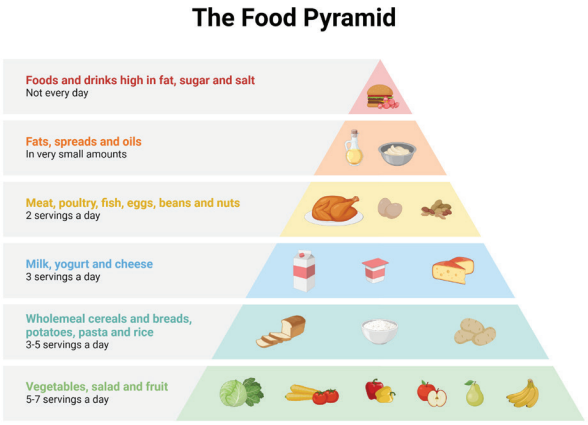

Figure 8: The food pyramid. Respecting the food pyramid is crucial to having a healthy diet, promoting beneficial gut microbes. Inversely, having a diet high in fat and sugar like the WD worsens gut dysbiosis and induces cognitive impairment.

Favoring nutrient-rich foods can significantly enhance intelligence and promote mental, cognitive, and emotional health. Moreover, maintaining a balanced diet has been shown to increase gray matter in the brain, which correlates with higher cognitive abilities.

Beyond digestion, recent research has highlighted the gut microbiome's ability to produce neurotransmitters, which regulate mental and emotional health. In fact, an astonishing 95% of serotonin—the mood-regulating neurotransmitter—is synthesized in the gut.[17] Disruptions in the gut microbiome can influence mood disorders like anxiety and depression. Therefore, prioritizing a nutritious diet not only improves gut health but also ensures optimal brain function. This is especially crucial in children, who have developing brains and bodies, as well as a sensitive gut microbiome.

High fiber diets against gut dysbiosis and cognitive impairment:

The first step to improving gut microbiome composition is to have a nutritious and balanced diet by respecting the food pyramid. Not doing so will not only worsen gut dysbiosis but also lead to neuroinflammation, a precursor to numerous neurodevelopmental (ND) diseases. This was clearly showcased with the WD, which was proven to alter gut microbiome composition, leading to cognitive impairment and gut inflammation.

To tackle gut dysbiosis, recent research recommends high fiber diets, highlighting their anti-inflammatory properties, their capacity to maintain gut microbiota equilibrium, and their link to a lower risk of several inflammatory disorders, including obesity, colon cancer, and cardiovascular disease.[6,18] In fact, a diet containing 24.3 mg of fiber per day reduced the risk of Crohn's disease, a gastrointestinal disorder linked to gut dysbiosis, by 40% in prospective research. The greatest reductions in risk were attributed to fiber derived from fruit sources. Furthermore, high dietary fiber was linked to a decreased risk of Crohn's disease in a case-control study involving 130 individuals.

In another one of Sun *et al.*'s study investigations, researchers who recruited 2,924 middle-aged participants discovered a

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negative correlation between the participants' baseline weight and their intake of dietary fiber after adjusting calorie intake.[6] Moreover, eating more dietary fiber and consuming less total and saturated fat were linked to weight loss after a year. Thus, high-fiber diets furthermore offer a viable treatment approach to prevent diabetes in high-risk populations. More research must be conducted to understand this link.

Later research has gathered dietary fiber deficiency (FD) mice to mimic low fiber intake in humans.[19] The study tested their object location memory, as well as their temporal order memory. The results suggested that mice's hippocampal synaptic ultrastructure was damaged. It also identified a rapidly differentiating microbiota change 7 days before the development of cognitive impairment. Indeed, the mice were found to have gut microbiota dysbiosis, with a reduction in *Bacteroidetes* and an increase in *Proteobacteria*, substantially associated with cognitive deficits. The paper concluded that fiber-deprived diets lead to cognitive impairment in mice. However, this must be further investigated in children.

Research has suggested that cognitive impairment may, at least in part, share the same origin (i.e., gut dysbiosis) as many gastrointestinal disorders and neurodegenerative diseases. Consequently, this data might suggest that a high-fiber diet is a viable treatment approach to prevent cognitive decline.

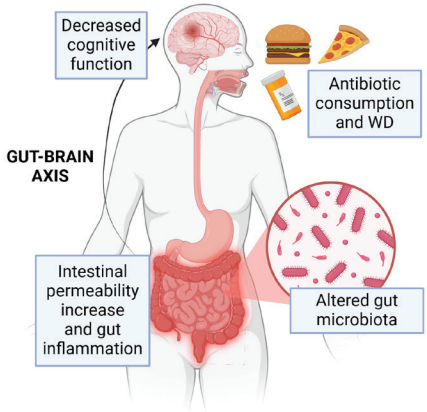

Figure 9: Antibiotic consumption and WD on the gut-brain axis. Gut dysbiosis induced by antibiotic consumption and the WD alters the gut microbiota, causing intestinal inflammation and cognitive impairment. To prevent this, probiotics and a high-fiber diet have been shown to improve the gut microbiome.

■ Healthy Gut Microbiome: A Solution to Cognitive Impairment

It has long been suggested that cognitive impairment is associated with gut dysbiosis.[20] Inversely, it is possible to infer that having a healthy gut microbiome improves cognition. Therefore, improving the gut microbiome in gut dysbiosis might offer a solution to its consequent cognitive impairment.

Previously, this paper has suggested consuming probiotics, as well as high fiber diets. A pertinent study also offers two other strategies to improve the gut microbiome.[6]

Fecal microbiota transplantation (FMT):

Fecal microbiota transplantation (FMT) is the transplantation of feces from a "healthy" donor into the intestinal tract of a recipient usually struggling with dysbiosis to restore their microbial composition.

In fact, FMT has proven to be rather effective in achieving this. In one randomized controlled investigation, patients with ulcerative colitis were either given autologous fecal microbiota (control) for three weeks or underwent FMT using feces from healthy donors. Thirty percent of patients who got FMT from healthy donors and twenty percent of the controls had achieved significant improvement, or even cure. Results showed that the diversity of the patients' fecal microbiome has also increased.

There has been a rising amount of research advocating for the application of FMT to specific diseases that have been linked to gut dysbiosis, like autism disorder (ASD) or Alzheimer's disease (AD).[21,22] A recent research study revealed that FMT showed potential in improving AD symptoms in elderly people.[22] The implementation of FMT as a treatment to manage cognitive impairment appears promising, despite the lack of evidence from trials involving humans.

Indeed, an investigation in the paper studied two types of mice: Senescence-accelerated mouse prone 8 (SAMP8) mice, who show aging-related cognitive impairment and are often used as models in AD investigations, as well as Senescence-accelerated mouse resistant 1 (SAMR1) mice, who show regular aging characteristics. Although both these models have an accentuated cellular aging (senescence), only SAMP8 mice show signs of cognitive impairment.

During the investigation, gut microbiota was transferred from both SAMP8 mice and SAMR1 mice (case group) into GF mice (control group). After receiving the fecal transplants from SAMR1 mice, GF mice with reduced cognitive skills demonstrated improvements in behavior, spatial learning, and memory function, as well as improved microbiota alpha- and beta-diversity indices.[22] However, there was no improvement of cognitive function and an altered gut microbiota composition in GF mice who have received FMT from SAMP8 mice. Indeed, the study has revealed that SAMP8 mice showed abnormal gut microbiota composition and experienced AD symptoms, suggesting there might be a causal link between gut microbiota composition and cognitive function. Nonetheless, as shown with SAMR1 mice whose gut microbiota successfully improved GF mice's cognition, FMT could be a promising therapeutic intervention to address age-related cognitive impairment, among others.

However, recent studies have also suggested that FMT may have adverse effects (AE) on the patients. Indeed, a recent study analyzing the individual results of 9 high-quality studies revealed that out of 388 patients who had received FMT, 124 of them experienced at least one symptom of AE.[23] The vast majority of the symptoms were mild and mainly included abdominal pain at 5.9%, bloating at 5.2%, worsening of colitis, nausea, and vomiting. On the other hand, 11 of the 388 patients had experienced at least one symptom of severe AE, the reported rates ranging from 0 to 7.3%, and its most common symptom being *C. difficile* infection at 0.8%. Moreover, the method of delivery was also shown to correlate with the rate of AE symptoms: for instance, therapy through capsules or nasoduodenal tubes increased the chances of experiencing AE.

Although no deaths were attributed to FMT across all 9 studies analyzed, there are still numerous safety concerns regarding the use of FMT and its possible transmission of infectious diseases. In fact, despite being relatively safe, a few complications in FMT were noted in the study.[22] However, overall, FMT's benefits seem to outweigh its AEs.

Although FMT seems to be an efficient solution against gut dysbiosis and memory impairment, more research must be conducted on FMT's role in cognition before making an official claim.

Physical Exercise:

Although sleep has already been proven to be linked to gut dysbiosis and cognitive impairment, another less obvious factor also comes into play in influencing gut dysbiosis.[24] Indeed, a recent study also demonstrated that exercise influences the gut microbiota's functional balance and composition.[6] Nevertheless, little is known about the exact processes through which exercise affects the microbiota. Initial research has indicated that exercise enhances gut microbiota.

The research, which used GF mice as a model, demonstrated that wheel running exercise training has been shown in several studies employing rats as subjects to have a multitude of positive impacts on the gut microbiome, such as increased microbial diversity, reduced inflammation, and elevated antioxidant enzymes in intestinal lymphocytes.

According to the study, professional rugby players' microbiotas were more diverse than those of age-matched controls. More research in this area is required, including aging people, larger cohorts, and more types of exercise. Exercising has been demonstrated to be an effective strategy to maintain cognitive function in both healthy and diseased settings. It has even been found to protect against neurodegenerative disorders and cognitive decline. Exercise training also raised the volume of the hippocampus, which is essential for learning and memory.

Whether specific gut bacteria influence the positive benefits of exercise on brain neurogenesis and cognitive performance is still unknown. However, despite the lack of direct data supporting its beneficial effects on ameliorating cognitive impairment, research shows exercise is still a viable therapy method for late-life cognitive impairment. The influence of exercise on gut dysbiosis has yet to be studied in children.

■ Other Factors Influencing The Gut Microbiome

Eating healthy meals and opting for natural remedies rather than antibiotics is an excellent way to keep the gut microbiome healthy. However, recent studies have suggested that multiple other hidden factors can influence the gut microbiome's composition. Earlier, age, antibiotics, and probiotics were mentioned. However, recently, new factors influencing the gut microbiome's composition have been brought to light.

Socioeconomic status:

A recent paper has revealed a new factor that influences the gut microbiome: socioeconomic status (SES).[25] The study was a multiethnic prospective study, conducted in the United States. It gathered stool samples from 825 participants from various age groups, races/ethnicities, and diverse backgrounds. The stool samples were collected to undergo 16S rRNA gene sequencing to study the gut microbiota compositions of the different participants. Participants with unknown data were excluded from the study. To classify the participants' data, the study assigned the occupational socioeconomic index (OSEI), ranging from 0 to 100. This index considers an individual's occupation-related prestige, income, and level of education.

The results of the study showed a positive correlation between gut microbiome diversity and composition and lower SES. Numerous bacterial taxa associated with poor socioeconomic status were found, particularly in the genus *Catenibacterum* and *Prevotellacopri*. These results show how influential SES is as a factor of the gut microbiome. Indeed, although there was a strong correlation between SES and race/ethnicity, the link between low SES and microbiota composition was unaffected by the separation and adjustment of the data for race/ethnicity. Moreover, the study has highlighted a positive relationship between gut microbiome diversity and structure and lower SES. These factors should be considered when studying gut microbiomes and memory formation in children. More research should also be conducted to understand how to improve the lower gut microbial diversity in high SES populations and how age affects this influence.

Artificial additives in food:

Nowadays, artificial food additives' impact on gut microbiota in both healthy individuals and inflammatory bowel disease (IBD) patients has drawn a lot of interest. In fact, new research indicates that artificial food additives and bacteria may interact, potentially affecting host gut health.

In fact, a recent study has revealed the influence of food additives on the development of IBD through gut dysbiosis.[26] Artificial sweeteners, emulsifiers, food colorants, and preservatives are all artificial food additives that have been proven to negatively alter the gut microbiota's composition and its functions. In fact, additives have been proven to promote pro-inflammatory bacteria like *E. coli* or *Proteobacteria*, as well as reduce the number of beneficial bacteria like *Lactobacillus*. This dysregulation improves gut permeability, leading to gut inflammation and creating IBDs like Crohn's disease or ulcerative colitis (UC).

These artificial additives are often found in children's candies and can be consumed excessively, having a detrimental impact on the child's gut.[27] These could be consumed, but only in extreme moderation, to avoid gut dysbiosis and consequently, cognitive impairment. Nonetheless, natural food additives like stevia, soy lecithin, and natural antioxidants have been proven to benefit the gut microbiota's composition and its functions.[26] Indeed, these natural additives have shown to increase the number of beneficial bacteria like *Akkermancia* and *Lactobacillus*, as well as decrease the pro-inflammatory bacteria like *E. coli* and *Salmonella*. Eating natural food is crucial to having a healthy and balanced gut microbiome, therefore promoting optimal cognitive health.

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Mother dysbiosis, method of birth, and infant feeding:

There is clinical evidence of mother-infant transfer of gut microbiota. In fact, 50% of the microbes in the infant gut were inherited from the mother.[28] Maternal dysbiosis has been shown to negatively impact pregnancy. In fact, a study has shown that maternal dysbiosis led to intestinal permeability and bacterial translocation, inducing malabsorption in the fetus, which could have long-term consequences on the child's development, including cognitive deficiencies.[28] However, more research must be conducted to better understand how maternal dysbiosis is associated with adverse pregnancy outcomes.

Moreover, the method of birth has been shown to exert a significant influence on the child's gut microbiome. The study showed that children who had been delivered through Caesarian section showed a significant decrease in beneficial bacteria, like *Bifidobacteria* and *Bacteroidetes*, compared to vaginally born infants.[29] The decrease in these bacteria causes diminished capacity to metabolize carbohydrates, like the oligosaccharides in breast milk. Antibiotic use has also been shown to disturb the early gut microbiota in the newborn. However, probiotic supplementation has demonstrated its capacity to restore a more healthy and balanced gut microbiome.

Furthermore, the method of feeding has been proven to influence the child's gut microbiome.[30] Indeed, recent research, which has gathered multiple newborn infants both breast-fed and formula-fed, found that children who were formula-fed had a significant increase in harmful bacteria like *E. coli* and *Clostridium (C.) difficile* among others. On the other hand, children who were breastfed showed a significant increase in beneficial bacteria, like *Lactobacillus, Enterococcus*, and *Bifidobacterium*, as well as a decrease in harmful bacteria like *Enterobacteria* and *C. difficile*.[28] Antibiotic consumption while breastfeeding has also been shown to disturb the child's gut microbiome; however, this can be improved by probiotic exposure.

To conclude, the pediatric gut microbiome may be altered if the infant's mother struggled with gut dysbiosis, if the infant was born through C-section or was formula-fed. More research must be conducted to determine the cognitive implications of this disruption.

Conclusion

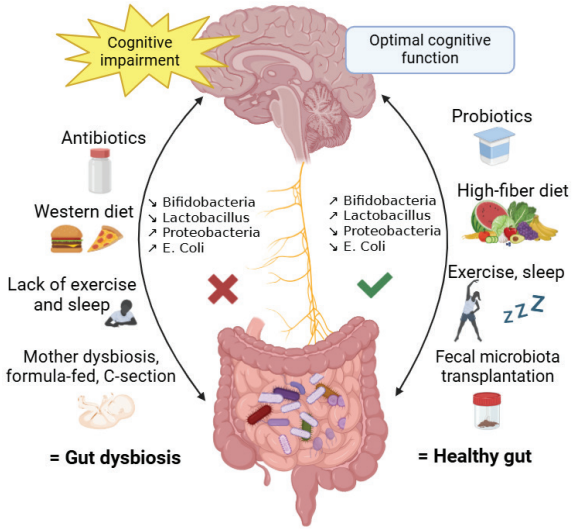

Figure 10: The gut microbiome's influence on cognition. An individual's lifestyle significantly influences gut microbiota composition. Factors such as early-life conditions, diet, exercise, and sleep shape the gut microbiome, in turn influencing cognition. Sufficient sleep, exercise, and nutrition promote a healthy gut microbiome and, therefore, optimal cognition. Meanwhile, taking probiotics or doing an FMT are great interventions to restore a healthy gut microbiome. Inversely, a poor lifestyle with inadequate nutrition, exercise, or sleep worsens gut microbiota compositions, leading to gut dysbiosis. Playing a crucial role in the gut-brain axis, an imbalanced gut microbiome may lead to cognitive impairment.

This literature review has brought to light the pivotal relationship between the gut microbiome and the brain. Indeed, a disruption in the gut microbiome's composition not only adversely impacts the gut's function but also adversely impacts cognition. Numerous factors that negatively influence the gut microbiome have been identified and are all associated with an increase in pro-inflammatory bacteria like *C. difficile* and *Proteobacteria*, as well as a decrease in beneficial bacteria like *Lactobacillus, Bifidobacterium*, and *Firmicutes*. Whether it was antibiotic-induced or western diet-induced, disturbance of gut microbiome composition in every study has led to cognitive impairment, mainly in the hippocampus, responsible for learning and memory. However, the specific type of memory that is affected because of gut dysbiosis remains unknown. One of the studies concluded that antibiotic-induced dysbiosis impairs object recognition but not spatial memory.[10] More research must be conducted to understand whether this outcome is universal in all types of gut dysbiosis-mediated cognitive impairments or simply specific to antibiotic-induced gut dysbiosis in children. This paper also revealed that the effects of gut dysbiosis on memory formation were consistent across different demographic groups, as opposed to the paper's hypothesis. However, low SES was discovered to be associated with a more diverse gut microbiome. Considering that low SES has been linked to an increased risk of Alzheimer's, this outcome should be further studied to understand the diverse gut microbiota's influence on this neurodegenerative disease.[31] Moreover, it is recommended to further study the gap in microbial diversity between high and low SES. This may help develop potential

treatments aimed at improving low gut microbial diversity in high SES populations.

Moreover, this study identified therapeutic interventions like probiotic intake or high fiber diets to improve gut dysbiosis, suggesting that improving the gut microbiome in gut dysbiosis might offer a solution to its consequent cognitive impairment. This hypothesis must be further studied to fully understand the extent to which therapeutic interventions may be effective in improving memory formation in children. Overall, having a healthy gut microbiome has proven to improve cognition and may prove to be an effective long-term solution against neurodevelopmental diseases (**Figure 10**).

These findings highlight the gut microbiome's significance in multiple neurocognitive functions, identifying ways for future interventions. However, although this paper delves deep into gut dysbiosis and its effect on cognition, especially in youth, more research must be done to clearly understand the extent to which therapeutic interventions may be effective in improving memory formation in children, as numerous scientific questions arise.

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