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Influence of Microbiota on the Central Nervous System, and Emerging Treatments Affecting the Gut-Brain Axis

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Abstract

The human body is host to trillions of bacteria, with roughly 100 million located in the gastrointestinal (GI) tract, which includes over 500 species of bacteria. This is collectively referred to as the "Human Gut Microbiota", the human gut microbiota develops and change over time and is affected by multiple factors. Alterations of these factors have been found to affect more than just gut health. The gut microbiota has been implicated in neurogenerative and neuropsychiatric disorders. Emerging research is highlighting the roles of probiotics, diet, and other treatments in improving various neurologic and neuropsychiatric health disorders.

Keywords: Microbiota; Probiotics; Neuropsychiatric disorders, Neurodegenerative disorders

Introduction

Development of microbiota in different stages of the human life cycle

The human body is host to trillions of bacteria, with roughly 100 million located in the gastrointestinal (GI) tract, which includes over 500 species of bacteria [1,2].This is collectively referred to as the "Human Gut Microbiota", with the whole human genome being called "Human Microbiome" [1]. Microbiota and microbiome can be used interchangeably to describe the microorganisms that live in association with humans. The human microbiome is a relatively new area of research, which requires in depth investigations to uncover more information about this exciting yet mysterious field. The gut microbiota is emerging as a main player influencing overall human health [2].

The basic composition of the gut microbiota is established during the early stages of life, and continues to change and diversify throughout the lifespan [2]. Under normal physiologic conditions the gut microbiota is involved in various processes to maintain homeostasis; including food metabolism, gut motility and secretion, host fat storage, immune function, emotional response to visceral stimuli, and even regulation of brain physiology and behavior [3,4].

The fetal gastrointestinal tract is sterile prior to birth, with microbial colonization initially occurring at the time of delivery [2]. This is a result of various external stimuli; including: environment, diet, mode of delivery, and early introduction of antibiotics [1,5]. In vaginal delivery, the GI tract is mostly colonized by *Bifidobacteria*, as well as *Lactobacilli, Bacteroides, Proteobacteria*, and *Actinobacteria*. In contrast, infants delivered via cesarean section have been found to have more *E.coli*, and *Clostridia* species in the gut microbiome, and fewer *Bacteroides* and *bifidobacteria* [2,6]. Additionally, infants fed with breast milk possess a microbiota dominated by *Bifidobacteria* and *Lactobacillus*; while formula fed infants typically show a more diverse microbiota including *Bacteroidetes, Clostridia, Bifidobacteria, staphylococci, Eneterobacteriaceae*, and *Streptococci* [2,3,6]. Interestingly, when infants placed on a formula diet take prebiotics, the number of *Bifidobacteria* and *Lactobacillus* species are increased, and there are reduced *Clostridium, Enterococcus* and *E.coli* [2,3]. A shift in diet from a primarily breast milk and/or formula diet to more solid foods results in an increase in the *Bacteroidetes* to *Firmicutes* ratio, with a reduction in *Proteobacteria* and *Bifidobacteria* [3].

The composition of the microbiota varies drastically from young, healthy adults to elderly individuals due to multiple factors including nutrition, deterioration of digestion and dentition, intestinal transit time, stress, and lifestyle. Due to the changes in gut physiology and morphology found in elderly individuals, the gut microbiota diversity and composition are also affected. The level of *Bifidobacteria* and *Bacteroides* species is reduced with age, as well as an associated increase in the *Clostridium, Enterobacteria, Ruminococcus*, and *Lactobacilli* species.

Microbiota classification

Bacteria in the gut microbiota can be classified as potentially beneficial bacteria and potentially harmful bacteria, which can be seen in Tables 1 and 2.

External influences on gut microbiota composition

Prebiotics are non-digestible food ingredients that are not digested by the host, but metabolized by gut bacteria. They promote the growth of beneficial gut microorganisms that improve host health and wellness [2,7]. Probiotics are the beneficial gut microorganisms (bacterial or yeast) that are administered to the host to confer health benefits [2,7]. Growing evidence from animal studies support a role of the gut microbiome in modulating emotional behavior. Some of the studies have shown prebiotics and probiotics have influence in the gut brain axis to influence emotional behaviors. They are called psychobiotics [2,6]. Common probiotics include *Propionibacterium*, *Bifidobacterium* and *Lactobacillus*, as well as specific yeasts; and have been implicated in having beneficial effects on anxiety and depressive-like behavior in animal studies [2,7].

Diet composition also affects gut microbiota composition. Changes in diet, even within a short duration, can drastically alter the gut microbiota. Current research is being done on the effects of Mediterranean diet versus Western diet on the microbiome and

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Potentially Beneficial Bacteria	Role in Gut Health
Bifidobacterium	Decrease Obesity, aid in digestion, antitumor activity and enteric epithelial barrier function)
Lactobaccillus	Aid in digestion, antitumor activity and enteric epithelial barrier function
Eubacterium	Production of short chain fatty acids, source of energy and Modulating mucosal immune responses
Fusobacterium	Production of short chain fatty acids, source of energy and Modulating mucosal immune responses
***Campylobacter* jejuni**	Potential tumor marker

Table 1: Potentially beneficial bacteria and their potential role in gut health.

Potentially Harmful Bacteria	Impact on Gut Health
Clostridia	Production of enterotoxin and leaky gut syndrome
E. coli	Cause of gastroenteritis and urinary tract infections
Proteus	Toxin production
Staphylococcus	Toxin production
Pseudomonas	Toxin production

Table 2: Potentially harmful bacteria and their potential impact on gut health.

associated symptoms of dysregulation. The Western diet is richer in fats, salt, and sugar as compared to a Mediterranean diet. The Mediterranean diet consists of whole grains, legumes, nuts, vegetables and fruits, with moderate consumption of fish and poultry and low consumption of meat. The western diet leads to increased *Firmicutes* and decreased *Bifidobacteria, Bacteroides* and *Prevotella* that result in the decreased production of short chain fatty acids e.g, butyrate, acetate, and propionate and leads to increased anxiety and depression. Conversely, the Mediterranean diet increases the number of *Bifidobacteria*, *Bacteroides* and *Prevotella* and decreases *Proteobacteria* and *Firmicutes* phyla in the gut microbiome; resulting in increased production of short chain fatty acids that are anti-inflammatory and improve mood [3].

Microbiota-Gut-Brain Axis

Recent animal studies have shown a significant relationship between the nervous system, the gastrointestinal tract, and the gut microbiome [6]. There is increasing evidence of interaction between the gastrointestinal microbiota, the gut, and the central nervous system (CNS), termed the Microbiome-Gut-Brain Axis (GBA) [8]. Initial studies in humans support the existence of a bi-directional relationship between the complex world of microbiota in the intestine and brain structure and function [7].

Mechanism of bidirectional communication in gut brain axis

The bi-directional communication between the gut microbiota and CNS is mediated through the autonomic nervous system (ANS), endocrine mechanisms, the immune system, and the bacterial metabolites/intermediates [3,4,6]. Some of these intermediates interact directly with enteroendocrine cells, enterochromaffin cells, and the mucosal immune system; and are able to cross the intestinal and blood brain barriers [6]. During normal physiological circumstances the GBA influences digestive processes, GI homeostasis, immune function, perception and emotional response to visceral stimuli as well as multiple effects on brain development, overall mood, and cognitive functions [1,4]. Dysregulation of the GBA has been implicated in the development and perpetuation of various gastrointestinal and CNS diseases; including gut motility issues, gut inflammation, chronic abdominal pain disorders (IBS, IBD), Parkinson's Disease, Alzheimer Disease, autism, anxiety, and clinical depression [1,2,4].

The presence of food particles in the GI tract stimulate the afferent nerve fibers that carry information to the subcortical and cortical centers of the brain; including the cerebral cortex, cingulate gyrus, and insular regions. Efferent fibers are then stimulated to carry motor signals affecting the smooth muscle of the gut [3]. The Vagus nerve is the main pathway of the parasympathetic aspect of the ANS and mediates the effects of gut microbiota on various neurophysiological functions [3]. The gut microbiota synthesizes a large number of neurotransmitter metabolites and plays a role in the development of multiple neuroactive molecules including serotonin, melatonin, acetylcholine, catecholamine, histamine and gamma-aminobutyric acid [3]. Enteroendocrine Cells are the specialized cell of the GI tract, located in close proximity to the gut microbiota that sense, produce, and release peptides used in production of several hormones, such as cholecystokinin and short chain fatty acids (acetate, propionate, and butyrate), which stimulate the afferent fibers of the Vagus nerve [3].

Metabolites derived from gut microbiota are present in the gut lumen and can be absorbed into the circulatory system by passive or active mechanisms. Sometimes the epithelial barrier in the gut is breached, resulting in what is termed a "leaky gut". This phenomenon occurs when inflammation in the gut causes loosening of the intercellular junctions, allowing for materials and bacteria to pass between cells in the intestines and into the circulatory system affecting the CNS [3].

The immune system also has a role in maintaining homeostasis between the gut microbiota and gut, as well as between the gut microbiota and the brain. The gut microbiota release potent promotors of the innate immune system, such as Lipopolysaccharide and peptidoglycan, that can be translocated from the gut to the peripheral immune system and activated. Microbiota has also been found to affect microglial phenotypes. The use of antibiotics in animals has been found to change the microbiota, resulting in aberrant microglial phenotypes [3].

Influence of Microbiota on CNS Diseases and Novel Treatments

Understanding the pathogenesis of disease is vital to effectively treating it. Research is currently evaluating the role of the gut microbiota in the pathogenesis of many CNS disorders. This research is continuously leading to new discoveries related to the GBA and providing clues to potential treatments. A role for probiotics, as well as other treatments related to the GBA, is becoming evident related to many CNS disorders. Further research into this topic will allow for better and more cost-effective treatments for many diseases.

Neurogenerative disorders

Parkinson's disease (PD): PD is a neurodegenerative disorder with both motor and non- motor symptoms. Recent studies suggest that

intestinal dysfunction is a non-motor symptom of Parkinson's Disease with a prevalence of 70-80% [4,9,10,11]. Constipation is the most prominent GI symptom and has been found to precede development of motor symptoms by as many as 87% of PD patients [11,12].

Role of gut microbiome in PD has been reported in many research studies. Fecal microbiota from PD patients showed higher counts of *Enterobacteriaceae, Lactobacilliceae* and reduced levels of *Prevotellaceae* [9]. *Enterobacteriaceae* has been positively correlated with the severity of postural instability and gait. Ghrelin, a gut hormone that is involved in the maintenance and protection of normal nigrostriatal dopamine function has been reported to be impaired in PD patients due to decreased *Prevotella* and increased *Lactobacilli* [13,14]. Reduced *Prevotellaceae* is also associated with diminished levels of neuroactive short chain fatty acids (SCFA), which contribute to gastrointestinal dysmotility in PD patients [15].

A randomized, double-blind, placebo-controlled study comparing probiotic supplementation with placebo demonstrated improvement of the MDS-UPDRS rating score for PD in the treatment group ($p=0.01$). The same study also found reduced C-reactive protein levels ($p<0.001$) and improvement in insulin sensitivity ($p=0.01$) in the treatment group [16]. This study followed sixty participants for twelve weeks.

Current data on the use of probiotics to treat PD symptoms is limited, but Tamtaji et al found evidence that probiotic supplementation improves symptoms in PD [16]. Based on this study; probiotics should be tried along with current PD treatments to improve symptoms. Further studies are needed to examine cost effectiveness and long-term effects of probiotic use in PD.

Alzheimer's disease (AD): AD is the most frequent cause of dementia characterized by progressive decline in cognitive function. The key feature of the disease is deposition of amyloid beta followed by formation of plaques and neurofibrillary tangles composed of hyperphosphorylated tau protein. The gut microbiota is a significant source of amyloids [17]. The best studied bacterial amyloid is curli, produced by *Escherichia* coli. Although bacterial amyloids differ from the CNS amyloids in their primary structure, they share similarities in their tertiary structure. The exposure to bacterial amyloid proteins in the gut may cause priming of the immune system, consequently enhancing immune response to endogenous production of neuronal amyloid in the brain [18]. Certain dietary nutrients, such as phenols, have been shown to promote amyloid β (Aβ) clearance, as well as inhibit tau aggregation/tangles [17]. Gut microorganisms may translocate from the GI tract through microfold cells overlaying the Peyer's patches of the gut and into the blood and other tissues, known as atopobiosis, which may contribute to local and systemic inflammation which impairs the blood-brain barrier and promotes neuroinflammation, neural injury and ultimately neurodegeneration [19].

Postmortem studies in human brain have demonstrated pathogens like *Chlamydophila pneumoniae, Borrelia burgdorferi*, and other spirochetes, as well as Herpes Simplex Virus Type 1 (HSV1) in patients with AD [20,21]. This has led to ongoing research involving bacterial translocation. Kowalski and Mulak support the beneficial use of probiotics as treatment for AD and have found that using probiotics enhances intestinal epithelial integrity, protects against barrier disruption, reduces the pro-inflammatory response, and inhibits initiation and propagation of neuro-inflammation and neurodegeneration. This article noted beneficial effects of food-based therapy, including high intake of plant-based foods, antioxidants, soy beans, nuts, and omega-3 polyunsaturated fatty acids in decreasing AD symptoms [20]. AD is associated with increased biomarkers of oxidative stress and inflammation [22]. A randomized, double-blind, controlled trial investigated the use of probiotics on mental status exams and inflammatory markers in sixty participants found significant improvements in mini mental status exams ($p<0.001$), serum C-reactive protein ($p<0.001$), and beta cell function ($p=0.001$) [23]. The probiotic used in this study was a mixture of *Lactobacillus bifidum* and *Lactobacillus fermentun.*

Based on current research, there is evidence to support using probiotics to improve symptoms in AD patients. Additionally, there is support for a healthy diet consisting of a high intake of plant-based food and reduced intake of refined sugars [20].

Neuropsychiatric disorders

Mood disorders: Mood disorders are associated with altered serotonin activity. Tryptophan is the sole precursor of peripherally and centrally produced serotonin. Gut microbiome play a major role in the production of both tryptophan and serotonin, thus plays a major role in development of mood disorders [24]. In a study involving germ free mice with increased tryptophan and low serotonin, introduction of tryptophan metabolizing microbiota (*Clostridium, Burkholderia, Streptomyces, Pseudomonas,* and *Bacillus*) resulted in positive effect on anxiety and depressive behaviors due to the decreased tryptophan and increased serotonin levels in their body. However, there was no effect on vagotomised mice, confirming that gut communicates to brain through vagus nerve [24].

Depression: A double blind, randomized control clinical trial testing effects of probiotics and prebiotics in depression was performed by Kazemi et al using the Beck Depression Inventory score (BDI) as the primary endpoint. This study found that probiotics significantly improved BDI compared to both placebo and prebiotic groups. No difference was found comparing prebiotics alone to placebo [25]. A meta-analysis performed by Huang *et al* of five randomized controlled trials investigating probiotic supplementation and various depression rating scales showed that probiotics significantly improved depression scale scoring. Probiotics were shown to improve depressive behaviors in both healthy participants and those with major depressive disorder [(MDD) ($p=0.03$)]. These findings were consistent in participants under age 60, but no significant effect was noted on participants over 65 years of age [26]. The studies included showed that probiotics decreased the number of pathogenic gastrointestinal microorganisms, reduced GI discomfort (diarrhea, constipation, and bloating), enhanced the immune system, and protected the body from oxidative damage. *Bifidobacterium infantis* has been shown to reduce depression and elevated Hypothalamic Pituitary Adrenal Axis response when used in rats. A study performed by Abildgaard et al found decreased depressive behaviors in rats when treated with probiotics compared to placebo independent of diet. Physiological findings of this study included altering cytokine production to lower amounts of IL-6 and TNF and to tryptophan metabolism [27].

Huang *et al* performed a meta-analysis showing an increase in tryptophan levels related to probiotic supplementation [26].A larger meta-analysis utilizing 10 clinical trials comparing the use of a probiotic to placebo effects on mood was performed by Ng *et al* In this study patients with depression were found to have significant improvements in mood with probiotic supplementation ($p=0.029$), but no significant difference was seen in healthy individuals [28]. Zheng et al demonstrated that fecal transplants from depressed patients to rats alter tryptophan metabolism and lead to depressive behaviors in

rats [29]. Probiotics have been tested and are able to restore normal behaviors in affected rats [29]. Probiotic use in conjunction with SSRI use in humans was tested in a randomized controlled study by Rudzki et al. This study found that the test group had improved cognitive performance and decreased kynurenine concentration when compared to a control group using only SSRI and placebo to treat MDD. *Lactobacillus plantarum 299v* was in the probiotic tested [30].

Current data supports the use of probiotics, but not prebiotics, to improve mood in patients with MDD. Further research is needed to examine the possibility of fecal transplant as a treatment for depression in humans.

Anxiety: González-Arancibia et al found in animal studies that stress early in life leads to long term elevated corticosterone levels and increased anxiety-like behaviors into adulthood; along with intestinal dysbiosis and increased intestinal permeability [31]. Kim and Shin described decreased levels of waking cortisol in patients taking probiotics [32]. Multiple animal studies have shown *Lactobacillus* supplementation to reduce corticosterone levels and anxiety; and restore both serotonin and norepinephrine levels [32]. Kim and Shin indicated that probiotic use in humans improve memory and learning in patients with diagnosed anxiety [32].

Based on current research, there is strong evidence supporting the use of probiotics in patients suffering from diagnosed anxiety, when used in conjunction with traditional anxiety management methods. Further studies are needed to compare the use of probiotics alone to current anxiety treatments.

Bipolar disorder: Bipolar Disorder (BD) has been found to be associated with alterations in the gut microbiome, which subsequently lead to increased intestinal permeability [33]. A review of current research by Genedi,et al reviewed two recent studies showing probiotic supplementation in patients with bipolar disorder decreases the rate of re-hospitalization and improves cognitive function [33]. Current research is limited, though there is evidence to support a role for probiotics in treatment of bipolar disorder.

Autism spectrum disorder (ASD)

Patients diagnosed with ASD suffer from a range of GI symptoms including diarrhea, constipation, abdominal pain and GERD. A review article by Doenyas describes a greater number of GI symptoms in people with ASD than comparison groups; and severity of GI symptoms is correlated with severity of ASD symptoms [34,35]. ASD patients have a larger amount of *Clostridium* bacteria in their GI tracts than normal patients [32,34,35]. Clostridia can produce propionic acid in the gut – which disrupt the production of neurotransmitters. Propionic acid is found to cause autism- like symptoms in rats, including repetitive movements, unusual motor symptoms and atypical social interactions. Studies have also shown that beneficial bacteria like *Bifidobacterium* are decreased in autistic patients [36].

Doenyas's review article describes improved ASD symptoms and behaviors in patients age 5-9 years old when taking probiotics over a three-month period. Similarly, Doenyas describes a decrease in ASD symptoms in children ranging in age from 3-16 years old with supplementation of *Lactobacillus rhamnosus* [34]. Improvement in memory and learning in ASD patients when supplemented with probiotics was also noted. Microbiota transfer therapy was found to reduce GI symptoms in ASD patients by as much as 80% and also improved ASD symptoms [34]. A review article by Jenkins *et al* also suggests fecal microbiota transplants reduce ASD symptoms [24].

While more research is needed to determine the most effective treatments for ASD, there is sufficient evidence supporting the use of probiotics, particularly containing *Lactobacillus* species, as part of a treatment plan for ASD patients. A role for fecal microbiota transfer therapy (FMT) is also apparent, but more studies are necessary to provide guidelines for FMT.

Schizophrenia (SCZ)

People with SCZ are found to have increased GI inflammation based on measures of bacterial translocation. Several unique bacterial taxa- *Veillonellaceae* and *Lachnospiraceae*- were associated with SCZ severity. Patients with SCZ were found to have less diverse microbes as compared to healthy controls. When the SCZ microbiota were transferred to a germ-free mice, they were found to have increased glutamine, decreased glutamate and increased GABA, in areas of the brain related to memory, neuron repair and executive functioning, which were all impacted in patients with SCZ [37]. Schizophrenia is often associated with anxiety and depressive symptoms, along with multiple GI issues, including constipation [32,33].

A review of current research by Genedi et al reviewed four recent studies showing probiotic supplementation in patients with schizophrenia had an anxiolytic and anti-depressive effect, as well as improving GI symptoms. This review found no significant improvement in positive or negative schizophrenic symptoms outside of depression, anxiety, and bowel issues [33]. Based on current research, patients with schizophrenia with concurrent depression, anxiety, or GI symptoms may benefit from probiotic supplementation. Further research needs to be performed to determine optimal dosing and composition of probiotics.

Microbiota Influence in GI Disorders

Recently, altered microbiota has been proposed as one of the causes for Irritable Bowel Syndrome (IBS). Antibiotic use for extra intestinal infection or recent infection like gastroenteritis can alter the gut microbiota. IBS is associated with increased harmful bacteria including *Enterobacteriaceae*, *Lactobacillaceae* and *Bacteroides*. Presence of *Enterobacteriaceae* reflects prior intestinal infections in these patients. *Lactobacillus* is responsible for the bloating symptoms in patients with IBS. *Bacteroides* species can produce toxins causing intestinal inflammation and dysmotility, causing abdominal pain and diarrhea. Protective bacterial group present in patients with IBS include group of uncultured Clostridiales I, which helps maintain gut mucosal health [38].

In a pilot study by Pinto-Sanchez et al the probiotic *Bifidobacterium longum NCC3001* was tested to treat depressive symptoms in patients with IBS compared to a placebo. The treatment group was found to have improvements in depressive scores and have improved quality of life. Functional MRI was used to evaluate response to emotional stimuli in the amygdala, and fronto-limbic regions of the brain in the study. The treatment group had decreased response to negative emotional stimuli. No difference was noted in fecal microbiota profile or serum markers of inflammation [39-41].

This pilot study supports the use probiotics to improve quality of life in patients with IBS. Larger studies are necessary to confirm these findings and expand on probiotic options.

Conclusion

As per our review, it was noted that improving microbiota composition helped to improve various symptoms in PD, AD, mood

disorders, schizophrenia, and IBS. Probiotics and diet were found to alter microbiota composition. Further studies are necessary to look at the effect of microbiota on neuropsychiatric disorders. The alteration of microbiota has potential as a cheap and efficient treatment for multiple neuropsychiatric disorders.

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