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The Co-Relation Between The Nervous System And Gut Health

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Abstract:
The human Gastrointestinal tract (GUT), also called the Alimentary canal, is the human digestive system, which has a simple and elaborative process involving several micro-organisms and processes in its course. The nervous system is a complex architecture of the human body which regulates the whole body and in-turn is regulated by the changes in the body. The inter-relationship between the GI tract and the nervous system is of utmost importance as it is one of the major systems in the body that decides the overall health of an individual. The relationship between the GUT and the Nervous System is called the "Gut-Brain Axis". The Gut-Brain Axis is so called as it refers to the bio-chemical signaling between the GUT and the nervous system in maintaining the normal function of the system. The human GUT consists of micro-flora which regulates the digestive and absorbing functions in the GI tract and when nervous system is influenced by the microflora it is termed as Microbiota-gut-brain Axis (MBG or BGM). The Gut-Brain Axis consists of the Central Nervous System, the Neuro-endocrine System, the Neuro-immune System which includes the Hypothalamic-Pituitary-Adrenal Axis (HPA), the sympathetic and para-sympathetic systems of the autonomic nervous system and the Vagus nerve. It was previously identified that altered emotional state and prolonged stress can change the composition of gut microbiome, but it has become more evident that communication between gut microbiome and central nervous system is bidirectional. The existence of a healthy and diverse gut microbiota appears to be imperative not only for normal gastrointestinal function, but may also influence a variety of systemic and mental processes. There are various mechanisms that imply some degree of access of either the microorganism itself or its products to the deeper layers of the gut, in turn activating a numerous factors. A primal connection exists between our brain and our gut. We often talk about a "gut feeling" and are told to "trust our gut instinct" when making a difficult decision. This mind-gut connection is not just metaphorical. Our brain and gut are connected by an extensive network of millions of neurons and a highway of chemicals and hormones that constantly provide feedback about how hungry we are, whether or not we're experiencing stress, or if we've ingested a disease-causing microbe. This information superhighway is called the brain-gut axis and it provides constant updates on the state of affairs at your two ends. That sinking feeling in the pit of your stomach after looking at your post-holiday credit card bill is a vivid example of the brain-gut connection at work. You're stressed and your gut knows it immediately. There are hundreds of millions of neurons connecting the brain to the enteric nervous system, thus it is often referred to as body second brain. This vast web of connections monitors the entire digestive tract from the esophagus to the anus. The enteric nervous system is so extensive that it can operate as an independent entity without input from our central nervous system, although they are in regular communication. While our "second" brain cannot compose a symphony or paint a masterpiece the way the brain in our skull can, it does perform an important role in managing the workings of our inner tube. The network of neurons in the gut is as plentiful and complex as the network of neurons in our spinal cord, which may seem overly complex just to keep track of digestion. Why is our gut the only organ in our body that needs its own "brain"? Is it just to manage the process of digestion? Or could it be that one job of our second brain is to listen in on the trillions of microbes residing in the gut? It is believed that The Good Gut is Taking Control of the Weight, Mood and Long-Term Health and therefore the wellness of gut is absolutely imperative for good health and mental wellbeing.

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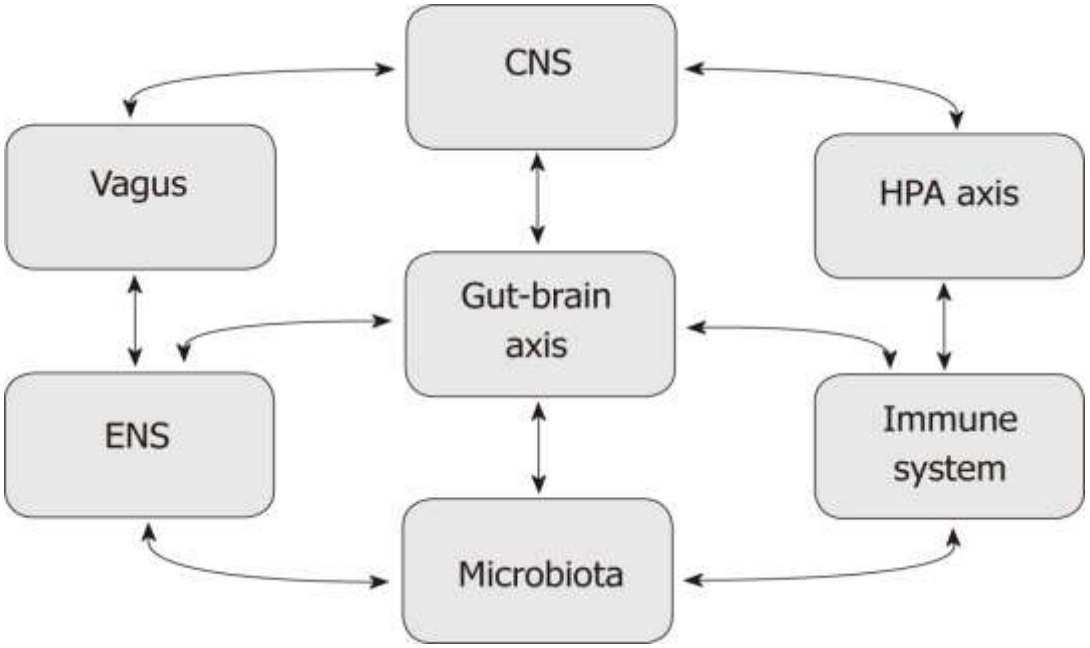
I. Background

How are the gut and brain connected?

The intestines and brain are connected physically and chemically and also microbes. Changes in the gut can affect the brain. Estimates suggest that you have roughly 30 trillion human cells and 40 trillion bacteria. Each of these bacteria can produce different substances that can affect the brain. These include short-chain fatty acids, neurotransmitters, and amino acids .Gut bacteria can also influence the brain and central nervous system by controlling inflammation and hormone production.Vagus nerve, a large nerve in the central nervous system, sends signals between the intestines and brain. Also, Operations of the enteric nervous system are overseen by the brain and central nervous system via the sympathetic and parasympathetic branches of the autonomic nervous system. The autonomic nervous system is tasked with the job of regulating the speed at which food transits through the gut, the secretion of acid in our stomach, and the production of mucus on the intestinal lining.



Brain-gut axis is a two way communication channel between the enteric nervous system and the central nervous system via vagus nerve. It is proved that the connection does exist between the brain and the gut but the question arises, does the microbiome in your intestine vastly effect you're thinking and nervous system? Yes, in a big way. Simply inside your intestine resides the good and the bad bacteria. These bacteria can affect anywhere from mood to obesity levels, Both bacteria's control over the nervous system that indirectly has an effect over various cascades both chemical as well as physiological in the body, right up to your brain. Overabundance of bad bacteria causes psychologicalproblem like depression, anxiety and OCD. Good bacteria on the other hand help in wellbeing and relaxation by nervous stimulation and GABBA release. Our food has a crucial role in maintaining the ratio between the good and the bad bacteria. It is believed, "What you eat shapes who you are".

Initially scientists believed that gut microbiome couldn't affect our brain because of the presence of the Blood Brain Barrier.Brains blood vessels are structured so they are packed super close together in a way that keeps your brains immune system basically separated from the rest of your body. But recent breakthroughs are challenging the previous assumptions and it's more lodging towards the establishment of brain - gut axis.

Brain derived neurotrophic factor(BNDF) is a seat for learning, memory and higher order thinking. There are numerous researches based on the gut brain axis. Studies proved that BDNF factor was predominantly more in germ mice than germ free mice. Even in one study, scientist found out exposing germ free mice to microbiome of other mice could influence their behavior. Also, they observed an increase in the BDNF protein. It meant that the microbiome had a direct effect over the brain area. It is established over the course of researches that connection persists and microbiome does affect the brains wellbeing. It is also proved how microbes can affect or regulate the chemical levels of the body and somehow despite the blood brain barrier these chemicals can affect the brain. A second route of relation between mental health and gut is via serotonin .Serotonin, which is well known for influencing the mood the drugs. There are many drugs prescribed for

depression and anxiety alters Serotonin levels. But it turns out majority of serotonin isn't made in the brain, about 80% of it is made in the gut and the microbes there can affect how much serotonin is produced.

A third route of microbes to influence brain is via immune system which can have a huge effect over the brain. Microbiome can affect cytokines that are proteins produced by immune cells and some of those proteins like IL-6 are known to influence stress. Researchers also discovered that microbes can release molecules that affect the behavior of blood brain barrier, making it more or less permeable to outside molecule which can affect the coordination of our brain and vice versa. Impaired intestinal barrier function due to presence of pathogens and consequent increased gut permeability can lead to increased translocation of gut bacteria across the intestinal wall and into the mesenteric lymphoid tissue. Increased contact of the ENS or immune cells of the mucosa to bacteria can provoke an immune response that can lead to release of inflammatory cytokines which can lead to the activation of the vagus nerve and spinal afferent neurons. Inflammatory cytokines and the vagal system in turn can modulate the activity of the CNS and ENS. Moreover, increase in permeability of the gut can also increase the movement of metabolic products such as lipopolysaccharide (LPS) or neuro-active peptides created by the bacteria that can change the activity of the ENS and CNS. LPS can activate Toll-Like receptors that are present on epithelial cells, enteric neurons, sensory afferent neurons in the spine, and various cells in the brain, which modulates their activity and affects the function of both ENS and CNS. Thus, as is being increasingly recognized, gut permeability is perhaps the most important factor in initiating microbial interactions with the rest of the body. While studying the effect of bacterial products on nervous system, it was known theoretically that bacterial products can be absorbed into the blood stream and affect distant sites in the brain. Alternatively, or additionally, bacteria can interact with local elements in the gut such as nerves or endocrine cells that which in turn signal to the brain. Data suggest that a variety of biologically active products derived from gut microbiota like LPS can directly or indirectly influence the brain by activating Toll-like receptor 4 on microglial cells causing release of inflammatory cytokines by them within the CNS, or indirectly by inducing release of inflammatory cytokines from the GI tract. LPS can cause behavioral changes during an acute illness or cause a delayed change in mood after sickness. In patients with depression or chronic fatigue syndrome, IgA and IgM against LPS of gut bacteria are seen in their blood of, which suggests a probable role for LPS in the pathogenesis of these diseases.

Effects of Nervous system on Gut Health

As previously mentioned, the interaction between the gut and brain is bidirectional, the central nervous system can affect gut permeability and increased gut permeability in turn, can alter CNS function. It has been seen that stress can reduce water secretion and increase ion secretion in the intestine, and thus impair the physical protection of the epithelial layer and lamina propria against adhesion of harmful bacteria and chemicals. Activation of the hypothalamic-pituitary-adrenal (HPA) axis and increased production of corticotrophin-releasing factor (CRF), altered activation of the vagal system, mast cell activation, and release of certain cytokines such as IFN-γ, TNF-α, and IL-4 are suggested culprits in this interaction. Moreover, stress can change the function of mucosal-associated immune cells and cause increased antigenic and bacterial uptake. Various studies have shown that the composition of gut microbiota is changed in the face of acute or chronic stress, and this in turn can eventually change the function of intestinal barrier as explained above. There is limited data regarding the changes in intestinal barrier or GI physiology and the underlying mechanisms of it in neuropsychiatric disorders. It has been reported that the frequency of GI symptoms is increased in children with autism but the mechanism is not known.In patients with schizophrenia, there are increased intestinal permeability and change in intestinal function. Emotional stress and depression have been shown to increase prevalence of disorders of the digestive system.

A potential unifying mechanism through which these various processes can influence the activity of CNS is via vagal nerve activity. In animal models, administration of *Campylobacter jejuni* into the gut can induce anxiety like behavior. These animals presented with increased activity in vagal sensory nucleus and other areas in brain stem related to this nucleus.Furthermore, intraduodenal administration of a non-pathogenic bacterium, *Bifidobacteriumlongum*, is anxiolytic but also requires an intact vagus.The vagus nerve might also be involved in behavioral effects of microbial LPS. It is known that LPS can induce depressive-like and anxious behavior in animal models. Studies have shown that rat or mice that undergo vagotomy before exposure to LPS do not show the expected cytokine profile changes in the CNS or the same depressive or anxious behavior.However, the role of the vagus may be restricted to specific models or pathogenic processes.

Hypothalamic-pituitary-adrenal axis

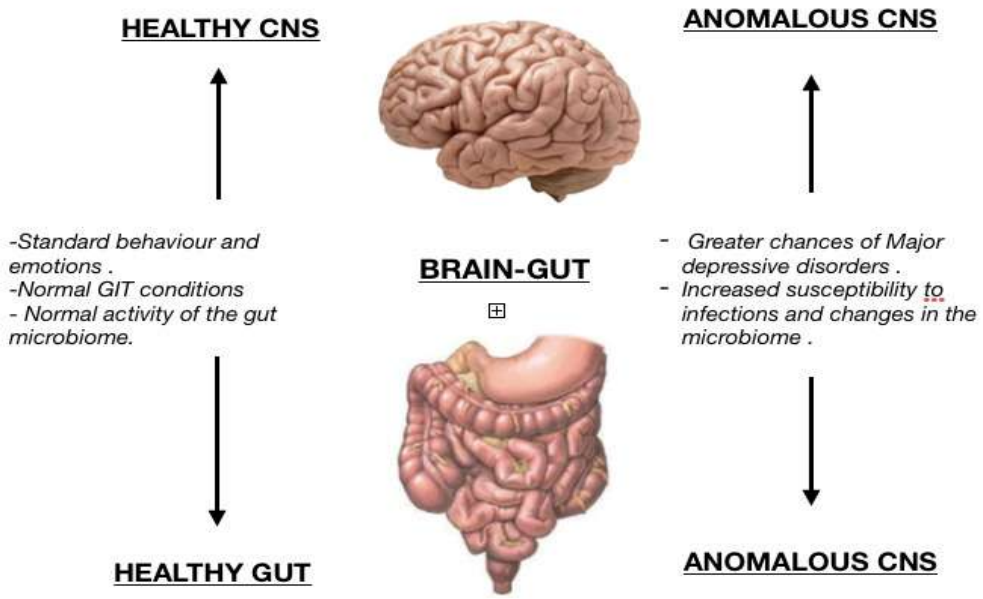
Hypothalamic-pituitary-adrenal axis, or HPA axis, is another mechanism by which the brain can communicate with the gut to help control digestion through the action of hormones. This circuitry of neurons, hormones, and chemical neurotransmitters not only sends messages to the brain about the status of our gut, it allows for the brain to directly impact the gut environment. The rate at which food is being moved and how

much mucus is lining the gut—both of which can be controlled by the central nervous system—have a direct impact on the environmental conditions the microbiota experiences.

What about the microbial side? When the microbiota adjusts to a change in diet or to a stress-induced decrease in gut transit time, is the brain made aware of this modification? Does the brain-gut axis run in one direction only, with all signals going from brain to gut, or are some signals going the other way? Is that voice in your head that is asking for a snack coming from your mind or is it emanating from the insatiable masses in your bowels?

Recent evidence indicates that not only is our brain "aware" of our gut microbes, but these bacteria can influence our perception of the world and alter our behavior. It is becoming clear that the influence of our microbiota reaches far beyond the gut to affect an aspect of our biology few would have predicted—our mind.

For example, the gut microbiota influences the body's level of the potent neurotransmitter serotonin, which regulates feelings of happiness. Some of the most prescribed drugs in the U.S. for treating anxiety and depression, like Prozac, Zoloft, and Paxil, work by modulating levels of serotonin. And serotonin is likely just one of a numerous biochemical messengers dictating our mood and behavior that the microbiota impacts.



The different aspects of the inter-connection have been studied by Timothy R. Sampson and Sarkis K. Mazmanian in 2015. The study revealed the influence of human GUT flora on the nervous system. The microbiota is responsible for the production of the metabolites to hormones and neurotransmitters influencing the metabolism or directly producing active metabolites itself. The symbiotic microbiotas have the capability to influence the systemic immune system which in-turn has an effect on the relationship of the immune system and the nervous system. Also the Enteric Nervous System (ENS) is directly connected with the Central Nervous System via Vagus Nerve providing a direct neuro-chemical pathway for the GI-microbiota to influence the nervous system. As mentioned earlier that the microbiota influences the hormones and the neurotransmitters, recolonizing of adult GF mice was done with complete microbiota showed the anxiety-like behavior and in SPF mice showed control of anxiety-like behavior. This can occur due to active and constant signaling between the GUT and the CNS. The GF mice also displayed lower levels of BDNF serotonin and specific 5-HT receptors in some parts of brain like Amygdala and Hippocampus. The levels of these molecules are not restored upon re-colonizing of the adult mice as there are certain phenotypes programed by the micro-flora during the development of the fetus. The study also revealed that there was an increased turn-over rate in GF mice of noradrenaline, dopamine and 5-HT in the striatum region of the brain. It is still unknown about the microbiota's permeability to BBB (blood brain barrier), but in GF mice, there is remarkable permeability seen in the BBB with microbiome. This increased permeability is due to the lowered integrity of the endothelial tight-junction proteins specially Occludin and Claudin-5 in absence of microbiome. The integrity of BBB can be restored by mono-colonizing with either Clostridium Tyrobutyricum or B. thetaiotaomicron. It is seen that these species produce SCFA's by fermentation of complex carbohydrates in the GUT which has significantly shown that the effect of SCFA butyrate in influencing the restoring of the BBB is remarkably sufficient. The microbially

produced SCFAs influences the endothelial cells that create BBB and increases the production of tight-junctions proteins that is Occludin and Claudin-5 which in-turn prevents the unwanted metabolites to pass the BBB. In absence of these SCFAs, there is lack of these proteins which in-turn reduces the integrity of the tight-junctions and thus permitting the entry of the undesired metabolites. This concludes that the metabolic signals from the GUT actively and constantly have an effect on the physiological status of the BBB. It has also been seen that the serum metabolites which does not crosses the BBB parenchyma can potentially cross the BBB depending on the status of the microbiota, providing the environment to the GUT microbes to regulate the concentrations of the metabolites which directly controls the nervous system.

Gut bacteria are priority to proper immune system development and maintenance. Studies show that any alteration in the concentration or presence or absence of any microbe can alter the process and promote inflammation. Any microbial products may influence entero-endocrine cells, which line the gut and release hormones and peptides. Some of those cells contribute in regulation of digestion and control insulin production, but also release the neurotransmitter serotonin, which travels through the body. Holobiome discovered that bacteria which were present in rat's digestive system produced GABA, which may increase GABA levels in the brain. And it found that rats who produced increased levels of GABA, were seen with reduced learned helplessness—a symptom of depression. At Holobiome, Strandwitz, Gilbert and his colleagues have identified and ranked 30 promising GABA-producing bacteria. The study will go into human trial in 2021 after ethical clearance.

Gut linkage with mental health

Major Depressive Disorder (MDD)

To find the correlation between depression and gut microbiota, a study was performed on human subjects with depression, which showed no significant difference in the composition of gut microbiota between depressed patients and a control group. However, another recent study examined the composition of fecal microbiota in 46 patients with depression and 30 healthy controls, and reported significant differences with higher population of Bacteroidetes, Proteobacteria, and Actinobacteria, and lower population of Frimicutes in patients with depression. Evidence that suggests a role of gut microbiota in the pathogenesis of depression is from studies that have shown certain probiotics can lessen depressive symptoms in rodent models. Treatment of these rats with probiotics containing B. infantis was seen to reduce the mood disturbance and correct the abnormalities in the concentration of norepinephrine in the brain. In a model of depression post myocardial infarction, treatment with probiotics including L. helveticus and B. longum has been reported to reduce the depression, seemingly by reducing the pro-inflammatory cytokines and gut permeability. Certain antibiotics such as minocycline have been shown to be effective in treatment of depression. Their mechanism of action is not clearly understood. The epidemiological researchers have also found out the remarkable connections between the GUT and the nervous system as people with irritable bowel disease are also depressed, people on Autism spectrum also have digestive problems and the people with Parkinson's are prone to have constipation. Researches have also shown increase in depression with people taking antibiotics and not with anti-viral or anti-fungal where GUT flora was unharmed.

In another study, Cryan, Dinan, and Gerard Clarke thought that the amino acid tryptophan, which is produced by some gut bacteria, could have a very important connection in the regulation of the GUT-Brain Axis. Microbes or the body's own cells have the potential to convert tryptophan into serotonin, a neurotransmitter involved in depression and other psychiatric disorders. Cells also turn tryptophan into kynurenine, which further reacts to form products that can be harmful to neurons. Any changes in the microbiota will lead to production of such unwanted harmful substances which are toxic to the neurons. Research has shown that people with depression convert tryptophan into kynurenine more readily than getting converted to serotonin

Another study conducted by scientists of Harvard University, Kevin Eggan in 2020, identified the connection between GUT-Brain in the neuro-degenerative disease ALS (Amyotropic lateral sclerosis) in diseased mice. This study states that in mice with ALS genetic mutation, if the GUT flora was changed using anti-biotics or fecal transplants, it could prevent or improve disease symptoms.In conclusion, alteration in the composition of the gut microbiome can potentially lead to increased intestinal permeability and impair the function of the intestinal barrier. Subsequently, neuro-active compounds and metabolites can gain access to the areas within the central nervous system that regulate cognition and emotional responses. Deregulated inflammatory response, promoted by harmful microbiota, can activate the vagal system and impact neuropsychological functions. The effect of gut microbiota on several aspects of CNS function is increasingly supported by growing number of experimental data. The mechanism of this influence is complex and involves multiple direct and indirect pathways. Increased gut permeability appears to be the foundation of the microbiome-gut-brain interaction. This offers a pathway for gut bacteria and their metabolic products to access the immune system, ENS, the blood stream, and centripetal neural pathways. It is a debilitating psychiatric

illness & is the leading cause of disability globally and is associated with ~800,000 suicide deaths annually. One novel area of investigation related to MDD pathophysiology is the gut microbiome.The gut microbiota is considered so necessary and so integrated into host function that some describe this population as an overlooked organ. Beyond the breakdown of otherwise indigestible food substances and production of micronutrients, gut microbiota affect the hypothalamic-pituitary-adrenal axis (HPA), produce neurologically active substances such as gamma-aminobutyric acid (GABA) and short-chain fatty acids (SCFAs), and influence the immune system and gut barrier.

Parkinson's disease

Studies suggests Parkinson's had lower levels of *Prevotellaceae* and people with Parkinson's who had higher levels of *Enterobacteriaceae* had more clinically severe symptoms .the authors of the study drew no conclusions about whether gut flora changes were driving the disease or vice versa.A new study has added further evidence to the connection between the Parkinson's disease and the gut microflora. It states that there might be a reason why patients of Parkinson's complain of constipation before the symptoms arise. This study in mice has shown that the toxic Alpha-synuclein that builds up in the nerve endings of the patients can influence brain neurons in a matter of time. The study also shows that the patients having Alpha-synuclein in their brain also had it in their gut.

Autism

Around 70% of people with autism also have gastrointestinal problems, and autism is often diagnosed at the time that the gut flora becomes established, indicating that there may be a connection between autism and gut flora.

Anxiety and mood disorders

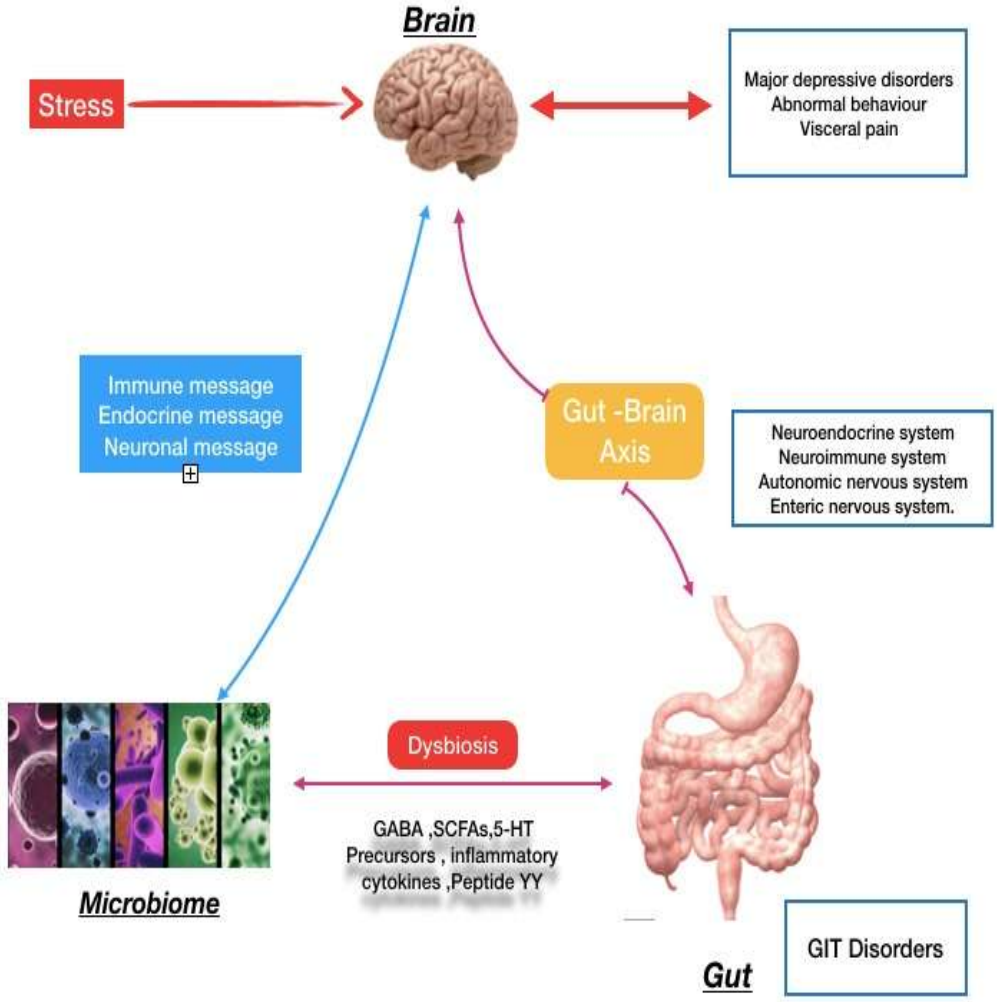
People with anxiety and mood disorders tend to have gastrointestinal problems; small studies have been conducted to compare the gut flora of people with major depressive disorder and healthy people, but those studies have had contradictory results. Additionally, there is a link between the gut microbiome, mood disorders and anxiety, and sleep. The microbial composition of the gut microbiome changes depending on the time of day, meaning that throughout the day, the gut is exposed to varying metabolites produced by the microbe's active during that time. These time-dependent microbial changes are associated with differences in the transcription of circadian clock genes involved in circadian rhythm. One mouse study showed that altering clock gene transcription by disrupting circadian rhythm, such as through sleep deprivation, potentially has a direct effect on the composition of the gut microbiome. Another study found that mice that could not produce the CLOCK protein, made by a clock gene, were more likely to develop depression. Stress and sleep disturbances can lead to greater gut mucosal permeability via activation of the HPA axis. This in turn causes immune inflammatory responses that contribute to the development of illnesses that cause depression and anxiety.

Probiotics, Prebiotics and the Gut-Brain Axis

Probiotics are live microorganisms, usually bacteria. When you consume enough of them, they provide a specific health benefit. Probiotics are "life-promoting" organisms — the word "probiotic" is derived from the Latin words "pro," meaning to promote, and "biotic," meaning life. Probiotics that affect the brain are also called psychobiotics. Both probiotics and prebiotics have been shown to reduce levels of anxiety, stress and depression few groups of foods are specifically beneficial for the gut-brain axis.

A recent study of people with irritable bowel syndrome and mild-to-moderate anxiety or depression found that taking a probiotic called Bifidobacterium longum NCC3001 for six weeks significantly improved symptoms.Another study found that taking a prebiotic called galactooligosaccharides for three weeks significantly reduced the amount of stress hormone in the body, called cortisol.

- Omega-3 fats: Studies in humans and animals show that omega-3s can increase good bacteria in the gut and reduce risk of brain disorders.
- Fermented foods: Fermented foods have been shown to alter brain activity.
- High-fiber foods: Prebiotics can reduce stress hormone in humans.
- Polyphenol-rich foods: They are plant chemicals that are digested by your gut bacteria. Polyphenols increase healthy guts bacteria and may improve cognition.
- Tryptophan-rich foods: Tryptophan is an amino acid that is converted into the neurotransmitter serotoninOmega-3 fatty acids, fermented foods, probiotics and other polyphenol-rich foods may improve your gut health, which may benefit the gut-brain axis.



II. Conclusion

There are more than a 750 million prescription in the world for anti-depressants in a year. The astounding fact is even with the tremendous amount of knowledge about the varsity of the microbiome and its connection with the nervous system fails to be recognized by most practitioners. As diet is usually not part of their treatment protocol. A nervous system is highly influenced by what and when you eat and what are you feeding your gut microbiome- kind of like second brain. It can influence everything from mood to obesity levels and could be a major factor in health epidemic. Giving probiotics after traumatic brain injury may reduce the rate of infections and length of time the person needs to stay in intensive care. People according to recent survey are on anti-depressants around 9% in UK and over 10% in USA.

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