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# BIFACIAL PERSUASION AND INTERACTION OF GUT BIOME WITH DEPRESSION AND OTHER AFFECTIVE (MOOD) DISORDERS

Gastroenterology

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## ABSTRACT

Intestinal Gut flora and Mental health are compound structures. Recent studies show that gut microbiota and mental health are in bidirectional interaction and influence each other. Consequently, this era is witnessing an exponential growth in studies aiming to understand this interaction. Studies conclude that some microorganisms like *Lactobacillus* spp. employ vagus nerve for affecting mental health. *Escherichia* spp., *Bacillus* spp. etc. produce various neurometabolites or fermented products i.e. Dopamine, propionate etc. Others affect the HPA axis or cause inflammation affecting the CNS. Polysaccharides of intestinal microorganisms can also play a role by entering and affecting intestinal cells. These anomalies can be rectified by probiotic formulations or Fecal transplantation pills of beneficial species like *Lactobacillus* spp., *Oscillibacter* spp. etc. Dietary modifications are also helpful. The purpose of this article is to be a collection and interpretation of findings of prevalent and peripheral studies linking mood disorders with gut microbiota.

## KEYWORDS

Mood disorders, Gut flora, Probiotics

## INTRODUCTION

### 1.1. Mental Disorders

Mental illnesses are anomalies in health conditions pertaining alterations in cognitive processes, emotion or behavior (or a combination of these). They are peculiarized by periods of depression, sometimes alternating with periods of elevated mood. People suffering from mood disorders experience severe or chronic mood states that disrupt their day-to-day functioning.[1] According to the Diagnostic and Statistical Manual of mental disorders (DSM), mood disorders are chiefly classified into 2 primary categories, namely Bipolar disorder and Depressive disorders.[2] which include various subtypes such as unipolar depression, mania, major depression and bipolar disorder. Unipolar disorder is diagnosed when only one extreme mood (depressed condition) is experienced. Bipolar disorder refers to when two alternating states of extreme moods of depression and mania are experienced. Depression is a serious communal illness that has a negative effect on a person's feelings, thinking and behavior. It is often comorbid with low self-esteem, low energy, and pain without a clear cause. Diametrically opposite disorder of depression is Mania, which is marked by periods of great excitement or euphoria, delusions, and over activity.

### 1.2. Gut Microbiota

The gastrointestinal tract of humans is paved with various communities of microorganisms. These microorganisms account for a total of approximately 100 trillion cells. Their quantity is estimated to be 10 times the somatic and germ cells of a human body.[3,4] In terms of the gene set, gut microbial genome is roughly 150 times larger than the human's genome.[5] Human colon serves as a dwelling to majority of the microorganisms where densities may approximate to $10^{11}$–$10^{12}$ cells/ml, the highest registered for any microbial habitat.[6] The multitude functions carried out by these dwellers influence the human's physiology to a large extent. They carry out numerous essential processes such as breakdown, processing and regulation of nutrients, fats etc. and provide protection against pathogens.[7] Due to this, the gut flora is even considered as a forgotten organ by many scientists.[8] When their equilibrium is disturbed, they may even act as causative agents for various diseases.[9] Intestinal flora houses Gram positive and Gram negative microorganisms. Vastly, it contains two major phyla, namely Bacteroidetes and Firmicutes. It even contains other microorganisms such as *Escherichia coli*, *Klebsiella pneumoniae*, *Serratia marcescens*, *Campylobacter, Dialister*, *Staphylococcus* etc.[10] Out of them, some are beneficial which are known as probiotics while others may cause harmful effects, such as *Helicobacter pylori.*

#### 1.2.1 Probiotics

A probiotic is a live microorganism which can be ingested in adequate amounts to treat various illnesses including psychiatric illness as they produce health benefits.[11] Various microorganisms such as *Lactobacillus, Bifidobacterium* etc. possess probiotic qualities and have proven to be useful in elevating a person's mood.[12]

### 2. Mechanisms by which Gut microbiota affect organism's mood

Since ages, an idea revolved that infections somehow were followed by mood disorders. But only recently, scientists were able to "work" over this hypothesis rather than just pondering over it. Thereafter, umpteen number of studies were undertaken and conclusions were drawn. Scientists finally stumbled upon the conclusion that microbiota does play a role in the modulation of mental health[13] and cause mental disorders.[14] This raised an important question as to, "How does the gut flora and an organism's mood influence each other?". To grasp the understanding of the employed pathways, intensive and extensive research commenced. Studies showed that gut and the brain are closely connected[15] and are interlinked in a complex communication system which helps in maintaining the equilibrium of the gut flora.[16]

### 3. Gut flora affects the Mood

Analytical studies showed that humans, when "infected" with an infection at any stage of life, are prone to acquiring a mental disorder. A recent study demonstrated the bivariate relation between an infection acquired at an early life in youth and the increased cases of mental disorders including major depression and anxiety disorder.[17] A population-based nationwide study was carried out, which showed that the subsequent development of mood disorder increased after infection, which accounted for a total increase in the risk by 62%.[18] Due to similar studies, the fact that somehow mood disorders are related to inter-body infections, including gastrointestinal infections caused by the alterations in the gut flora or by accidental consumption and subsequent insertion of a pathogenic microorganism into the gut flora, is now well established. Some scientists and studies established this fact directly, that the gut microbiota plays a role in acquiring a mental disorder.[19] Other studies tried to substantiate the aforesaid conclusion via indirect means such as studying the correlation between anti-infective agents and the endangerment towards a mental disorder including mania.[20,21]

Generally, the mechanisms undertaken by the gut microbiota are inflammation, Hypothalamic–Pituitary–Adrenal axis (HPA) or disruption in neurotransmitter signaling.[22] The employed bidirectional influential mechanisms between brain and gut microbiota are represented in **figure 1.**

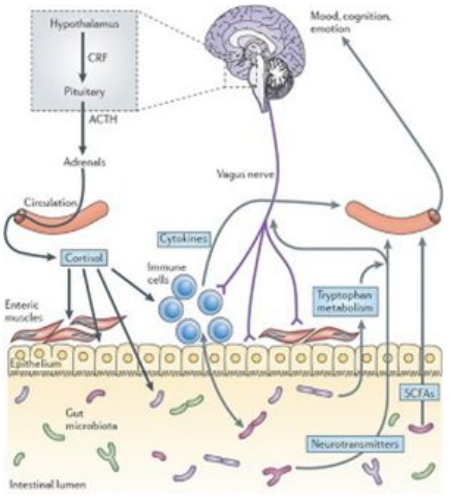


**Figure 1: Employed bidirectional influential mechanisms between brain and gut biota.**

**Sources: Cryan and Dinan[67]**

### 3.1. HPA axis

Hypothalamic-pituitary-adrenal (HPA) axis is a complex of pathways of feedbacks and interactions among the three endocrine glands: hypothalamus, pituitary and adrenal gland. HPA axis plays the role of central figure while giving responses towards stressors and its dysfunction may give rise to depressive episodes.[23,24] This disruption could've been brought-forth by microorganisms as they remain in an unmediated direct link with the HPA axis. This result was proven by scientists who demonstrated the overstated response of adrenocorticotrophin (ACTH) and corticosterone (CORT) towards stress in specific pathogen-free (SPF) and germ-free (GF) mice.[25]

### 3.2. Leaky gut

Sometimes, a condition called "leaky gut" develops which can be attributed to various reasons one being enterotoxins produced by *Clostridia perfringens*, an inhabitant of gut flora. The enterotoxins drastically increase the permeability of the intestinal wall.[26] Stress has also proved to be a factor which increases the permeability of the intestinal wall.[27] This increased permeability can serve as a potential pathway by which the microbiota can directly affect the host's mood by affecting the Central Nervous System (CNS) through the Enteric Nervous System (ENS) and the immune system.

### 3.3. Inflammation

Insertion of a pathogen may induce inflammation of the inner-lining of the intestine. This inflammation may serve as an activating agent of immune response which in-turn affects the CNS resulting in the alteration of the host's mood. Various studies established the linkage between depression and elevated levels of TNF, IL-6 and C-reactive protein. Proinflammatory cytokines such as IL-6, TNF etc. induce depressive symptoms.[28,29,30]

### 3.4. The Vagus nerve

The vagus nerve is the longest cranial nerve having the widest distribution in the body. It incorporates various fibers such as motor, sensory, somatic and visceral afferent. During the insertion of noninvasive pathogens into intestinal tract and/or cecum, the nuclei of brain stem quickly get activated. Studies show that the signals for this activation are carried out by the vagus nerve.[31,32] Recent studies carried out on animals have shown that gut flora can trigger the vagus nerve which carries out a critical role in mediating consequences on brain and behavior.[33] Another study evidently demonstrated that vagus nerve serves as a potential pathway for the modulation (decreased in this case) of depressive behavior by *Lactobacillus* spp.[34]

### 3.5. Metabolites by Microbiota

Intestinal Bacteria are responsible for the modulation of various host reactions by the production of certain metabolites like bile acids, choline and short chain fatty acids.[35] All these metabolites are critical for the host health. Even complex carbohydrates like deity fiber can be digested and eventually fermented in the colon into short chain fatty acids like n-butyrate, acetate and propionate that are known for their neuroactive properties.[36,37]

### 3.6 Neurometabolites by microbiota

Certain bacteria also have the capacity to generate numerous neurotic components like neurotransmitters and neuromodulators. These neurometabolites possess the ability to impact brain directly/indirectly. The list for the Neurometabolites produced by intestinal microorganisms is given in **table 1**.

**TABLE – 1 List of Neurometabolites produced by intestinal microorganisms**

| Microorganisms | Neurometabolites | Reference |
|---|---|---|
| ***Bacillus* spp.** | Noradrenalin, Norepinephrine, Dopamine | 63, 64 |
| ***Bifidobacterium* spp.** | GABA | 39, 63 |
| ***Candida* spp.** | Dopamine, Serotonin | 63 |
| ***Cornyebacterium* spp.** | Serotonin | 64 |
| ***Enterococcus* spp.** | Dopamine, Serotonin | 63, 64 |
| ***Escherichia* spp.** | Noradrenalin, Norepinephrine, Serotonin, Dopamine | 63, 64 |
| ***Lactobacillus* spp.** | GABA, acetylcholine | 39, 63 |
| ***Saccharomyces* spp.** | Noradrenalin, norepinephrine | 63, 64 |
| ***Serratia* spp.** | Dopamine | 64 |
| ***Streptococcus* spp.** | Dopamine, Serotonin | 63, 64 |

### 3.7 Polysaccharides of the Bacterial cell wall

Even the exterior coating of exocellular polysaccharide probiotic bacteria is directly responsible for various health developing effects. The bacterial cell walls and their components of intestinal microorganisms alter intestinal epithelial cells and functions and triggers them to release molecules which regulate neural signaling and act directly on primary afferent axons.[38]

## 4. Evidence Based Studies

An integrative outcome from a cluster of analogous studies carried out on mice is in a positive correlation with the central theme of this paper. Gamma-Aminobutyric acid (GABA) is an inhibitory (calming) neurotransmitter. It is essential for proper functioning of the brain. Valeric acid structurally resembles GABA. Studies show that GABA can be produced by microorganisms such as *Lactobacilli and Bifidobacterium* and Valeric acid can be produced by microorganisms such as *Oscillibacter*.[39,40] GABA, being a neurotransmitter, plays a role in the reduction of affective disorder such as depressive behavior through GABA signaling pathway by affecting the GABA receptors.[34] Valeric acid can potentially act upon the GABA receptors resulting in an analogous modulation of depressive behavior.[41]

Till date, there have been quite a handful of studies which link gut microbes with depression. A study was carried out to understand the effect of gut microbiota on depression produced by maternal separation in rats. The maternal separation caused a decrease in the noradrenaline content in the brain and increased the release of peripheral interleukin (IL)-6. It even increased mRNA levels of corticotrophin-releasing factor (CRF) in the amygdala cortex. A large majority of these abnormalities were nullified to a certain extent, after the consumption of *Bifidobacterium infantis.* This proves the gut microbiota can be useful in the normalization of the setback of behavioral deficits and it may even help in the normalization of noradrenaline levels in the brainstem.[42] The same group of scientist carried out another research few years prior to this one, examining the role of probiotics such as *Bifidobacteria infantis* as potential anti-depressants in rats.[43]

Another experiment showed that germ-free animals have elevated levels of Serotonin (5-hydroxytryptamine) and its main metabolite (5-hydroxyindoleacetic acid) as compared to conventionally microbe-colonized animals. Results prove that intestinal microorganisms can affect the brain and affective disorders.[44]

### 4.1. Studies involving transference of fecal microbiota from depressed patients to healthy subjects

#### 4.1.1 Study by Kelly Jr et al.

They studied the fecal microbiota of patients suffering from depression

and found numerous anomalies and disruptions. Scientists then performed fecal microbiota transplantation, taking samples from these depressed patients and transferring them into microbiota-deficient rat subjects via oral gavage. Behavioral and physiological changes characteristic to depression were noted following the transplantation. Alterations in tryptophan metabolism which is a characteristic of anxiety-like behavior was also observed. This established the possibility of the causal role of gut microbiota in the development of depression.[45]

#### 4.1.2 Study by Zheng et al.

They substantiated that the absence of gut microbiota can lead to a decrease in depression-like behavior using germ-free (GF) mice. Along with this, they performed microbiota transplantation from depressed patients to GF mice and proved that certain microorganism can cause depression by comparing it with the transference of microbiota from healthy patients to GF mice, who didn't show signs of depression or any such characteristic behavior changes.[46]

### 4.2 Anomalies in normal gut biota in depressed patients

Several correlations and over/under-presentation of certain microorganisms have been noted by various studies involving depression. Data representing the anomalies in the density levels of various gut microorganisms while suffering from depression are given in **Table 2**.

### 4.3 Probiotics and depression

#### 4.3.1 Depression due to Lipopolysaccharide

Studies have shown that the 'endotoxin' or 'Lipopolysaccharide' can translocate from the Gram negative enterobacteria towards the inner lining of the intestine. It was shown that this endotoxin plays a role in inducing depressive-like behavior, especially in mice.[47] Extensive work has been carried out by a group of scientist on this very subject and they were able to substantiate that this maneuver of LPS in inducing depression wasn't constricted to mere mice but to humans as well.[48] They noted an increased level of IgA and IgM in depressed patients, directed towards these Gram negative inhabitants, which concluded that microbiota plays a role in altering the prevalent robust state of mind.[49] An analogous study with diametric disorder was executed which affirmed that the translocation of gut biota through the intestinal barrier ensues a role in giving rise to bipolar disorder.[50]

**TABLE – 2 Anomalies in normal gut biota in depressed patients**

| Microorganism | Density Levels | References |
|---|---|---|
| ***Anaerofilum* spp.** | Increased | 46 |
| ***Actinobacteria* spp.** | Increased | 47 |
| ***Bacteroidales* spp.** | Decreased | 65 |
| ***Bacteroidetes* spp.** | Increased | 66 |
| ***Bacteroidetes* spp.** | Decreased | 47 |
| ***Dialister* spp.** | Decreased | 46 |
| ***Eggerthella* spp.** | Increased | 46 |
| ***Firmicutes* spp.** | Decreased | 66 |
| ***Firmicutes* spp.** | Some members: increased Other member: decreased | 47 |
| ***Gelria* spp.** | Increased | 46 |
| ***Lachnospiraceae* spp.** | Increased | 65 |
| ***Paraprevotella* spp.** | Increased | 46 |
| ***Prevotella* spp.** | Decreased | 46 |
| ***Proteobacteria* spp.** | Increased | 66 |
| ***Thermoanaerobacteriaceae* spp.** | Increased | 46 |
| ***Turicibacter* spp.** | Increased | 46 |

#### 4.3.2 Probiotic Formulation in treating depression

To inspect whether alterations in gut microbiota by adding probiotics can affect the depression caused by various reasons; a group of scientists used a probiotic formulation (PF) of *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 for the reduction of depression induced due to myocardial infraction in mice. Even though the mechanical relation between depression and myocardial infraction (MI) is suppositional, inflammation could be the key factor regulating the relationship as, many scientists believe that depression is an inflammatory disease.[51] *L. helveticus* R0052 and *B. longum* R0175 were successful in reducing the depression symptoms in the test subjects. The study provided us with the first positive outcome of the effect of probiotic formulation on post-MI depression[12]. Another study was carried out on mice test subjects using *L. rhamnosus* which proved to reduce anxiety and depressive behavior by altering the levels of GABA in prefrontal cortex and amygdala (decreased level of $GABA_{A\alpha2}$) and in hippocampus (increased GABAAα2).[34]

Similar study using the same formulation of *L. helveticus* R0052 and *B. longum* R0175 as a daily dose for 30 days was undertaken to assess its effect on everyday life events of humans volunteers. Probiotic formulation-treated subjects had a lower global severity index of the HSCL-90 over time as compared to the control subjects due to lower values for depression, somatization etc.[52]

### 4.4 Comorbidity of depression and anxiety

Intrinsically, anxiety is not a part of mood disorders. However, it has been reported by various studies that anxiety could be a comorbid disorder in an individual suffering from unipolar mood disorder.[53] As a result, many scientists carried out studies contemplating anxiety as the presence of some kind of mood disorder. One such decade-long study showed that disequilibrium in the gut microbiota brought forth by *Helicobacter pylori* infection and Small Intestinal Bacterial Overgrowth (SIBO) resulted in the acquisition of anxiety along with depression.[54] Another study with connatural supposition supported these findings by measuring the mental state of patients coming for intestinal endoscopy for various reasons including *Helicobacter pylori* infection.[55]

### 4.5 Anti-infective agents and the endangerment towards a mental disorder

A handful of scientists tried to view the scenario through a novel perspective. They worked upon finding the correlation between exposure to anti-infective agents and the consequent risk of developing a mood disorder. A large-scale population based case-control study which continued for almost two decades by Lurie et al. found that recurrent treatment with a single antibiotic course is associated with a higher risk for depression for all antibiotic groups including penicillin and quinolones.[56]

Köhler and his group carried out a population based study in Denmark and they concluded that infections of all types including gut when treated with anti-infective agents, increase the chances of affective disorder and schizophrenia.[20]

Yolken and his group worked upon antibiotic prescriptions and mania. They compared the rates of antibiotic prescription in individuals using logistic regression models and found that individuals hospitalized because of acute mania had a considerably magnified rate of recent antimicrobial prescription.[21]

## 5. Depression precedes Mania

It is evidently proven that Major Depressive Disorder oftentimes antedates the initial onset of mania.[57] Therefore, most of the solutions are being provided to tackle depression but they can also be extrapolated for the treatment/ prevention of the onset of mania.

## 6. SOLUTIONS

### 6.1 Probiotics and pre-existing inter-body substances

For the implementation of probiotics as promoters of robust mental state, we need beneficial microorganisms which can produce healthy metabolites and neuromodulators or they must be able to utilize a preexisting substance which can as act as a precursor for the synthesis of neuromodulators. A study was carried out in which 91 intestinally derived microorganisms were grown on MSG medium (Monosodium glutamate) and production of GABA from MSG was measured. Results showed that strains of *Bifidobacterium* and *Lactobacillus brevis* DPC6108 were the most efficient stains, giving a conversion output of 90%.[39]

### 6.2 Probiotics and mechanical Pathways

Gut microbiota can cause inflammation of the small intestine and colon (enterocolitis). Employment of certain beneficial strains of bacteria such as *Lactobacillus helveticus* R0052 will prevent the invasion of inflammation-causing bacteria such as *Campylobacter jejuni* on our intestinal cells.[58] Thus, if inflammation of the intestine is not occurring, subsequent chances of acquiring a mood disorder will reduce.

### 6.3 Probiotics and Cytokines

Yet another possible method would be the addition of probiotics in our intestine which can reduce or suppress the production of

proinflammatory cytokines such as IL-8, TNF etc. as, the inhibitory effects of probiotics on inflammatory cytokines may influence the mood and may ultimately influence MDD.[59] This method was evidently employed by a group of scientists who were successful in showing the modulated (in this case, decreased) secretion of proinflammatory cytokines by certain *Lactobacillus* strains.[60]

### 6.4 Fecal microbiota transplantation (FMT)

Despite its sporadic use in the ancient times, this method was standardized by Ben Eiseman in 1958. FTM includes the transference of fecal microbiota from a healthy donor to a subject by injecting filtrate of stools. FMT has given prominent results in the treatment of various disease such as Crohn's disease. It even opens doors to the possibility of transferring beneficial product-producing microorganisms (such as *Lactobacilli, Bifidobacterium* and *Oscillibacter* which produce GABA and valeric acid) into patient suffering from affective disorder. Fecal pills, processed from stool of healthy donor (containing microorganisms) are orally supplied to patient. Fecal pills are gaining popularity as they have proven to be cost effective and they reduce the risk associated with invasive delivery methods.[61]

### 6.5 Dietary modifications

It has been duly noted that people suffering from various disorders (including mood disorders) have a deficiency of essential vitamins, minerals and omega-3 fatty acids. It has been scientifically proven that a regular intake of essential nutrients often reduces the symptoms of patients. Supplements that contains amino acids get converted to neurotransmitters which may ease bipolar and depressive disorder. Food like fish oil can be used to treat depression and bipolar disorder as it contains omega-3 fatty acids.[62]

## Conclusion

The mental well-being of human body is highly dependent upon the kind of microorganisms residing inside its gut. Alteration in the normal gut microbiota may result in the alterations in the host's health. Along with providing the host with beneficial products like micronutrients, some microorganisms have the ability to modulate the host's behavior and mental condition. Modulations in the mood happen due to certain metabolites and neurometabolites produced by the gut flora or by the activation of the inflammatory system or HPA axis of the host. Exocellular polysaccharides produced by certain microorganisms have also been proved to be such modulators of the host's mood. The endgame of these labyrinthian mechanisms is the ontogenesis of mood disorders. The anomalies in the mood or the developed mood disorders can be treated/prevented by various methods which include the consumption of probiotics. Other treatment methods include dietary modifications and fecal microbiota transplantation (and fecal pills) which are getting popularized and have proven to be promising.

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