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Review Article

# Role of The Gut Microbiota in Mental Health

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## Abstract

The human gastrointestinal tract contains distinct microbial communities that differ in composition and function depending on several factors such as age, body location, ethnicity, geography, etc. There is evidence of the bidirectional interaction of the gut microbiota-brain axis and its role in mental health. In this mini review we attempt to summarize and comment on some relevant studies evaluating the role of the gut microbiota in mental health in humans.

**Keywords:** Gut Microbiota; Stress; Depression; Anxiety; Bipolar Disorder

## Introduction

It is estimated that more than 100 trillion microbes, both eukaryotic and prokaryotic, live in symbiosis with humans. It is known that the human body contains approximately 1000 different bacterial species, in such a way that the intestinal microbiota is considered as an organ [1,2] that contains 150 times more genes than those of the human genome [3]. Factors such as age, sex, race, diet, and body location influence the type of symbiotic microbes and their function [4]. Commensal bacteria settle in the host shortly after birth and progressively develop in a complex and variable ecosystem as the host grows [5]. Association studies have shown that the gut microbiota is related to some chronic degenerative diseases [6,7], including mental illnesses [8,9]. This review focuses on the relationship between the microbiota and mental and psychological illnesses.

## Main Text

There is evidence that brain function can be influenced by the gut microbiota through nervous, endocrine and immune pathways [8,10,11]. The mechanisms that relate the microbiota to human health and disease situations are the following:

a) The microbiota has the potential to increase the energy efficiency of food [12], increase nutrient harvesting [13-15] and modify appetite signaling [16,17]. The microbiota contains genes with greater metabolic diversity than human genes and confers unique enzymes and specific biochemical pathways to humans [14]. Some examples of the metabolic processes of the microbiota, which benefit the host, are those that participate in the acquisition of nutrients or in the metabolism of xenobiotics, the metabolism of undigested carbohydrates and the biosynthesis of vitamins [15, 18].

b) The human gut microbiota provides a physical barrier that confers host protection against foreign pathogens through competitive exclusion and the production of antimicrobial substances [19-21].

c) The development of the intestinal mucosa and the host's immune system is directly influenced by the microbiota [22-24]. The intestinal epithelium strongly participates in innate immunity. Endocrine cells and stem cells at the base of the intestinal crypts give rise to enterocytes, goblet cells, Paneth

cells and enteroendocrine cells. Enterocytes and Paneth cells (PC) produce different molecules such as: antimicrobial peptides, alpha-defensins, lysozyme C, phospholipases, type C lectin, and islet-derived regenerating 3-gamma [25] , which are important in keeping pathogens under control. In addition, goblet cells secrete mucins that lubricate and protect the intestinal epithelial surface, in addition to participating as antigen presenting cells (APC) delivering luminal antigens to CD103+ dendritic cells (DC), which promote the development of regulatory T cells (Tregs ) [26]. Other data supporting the effect of the microbiota on the immune system is that germ-free animals have abnormalities in the count of different types of immune cells, deficits in local and systemic lymphoid structures, malformed spleen and lymph nodes, and altered levels. of cytokines [24]. The microbiota appears to modulate immunity by promoting the maturation of immune cells and thus the normal development of immune functions [23].

## Mental Diseases and Microbiota

Here is a brief summary of the evidence that relates the intestinal microbiota with different mental illnesses:

**a) Depression:** Depression is a mental illness that is considered the main cause of disability and is a major contributor to the burden of disease all over the world. The prevalence of depression throughout life ranges from 20% to 25% in women and 7% to 12% in men. Depression explains approximately 50% of psychiatric consultations and 12% of all hospital admissions [27]. Accumulating evidence suggests that gut microbiota play an important role in the pathogenesis of neuropsychiatric diseases including major depressive disorder (MDD). A study of 36 MDD patients showed that those with MDD had an overrepresentation of phylum Actinobacteria and Firmicutes and the genus Bifidobacterium and Blautia compared to controls [28]. In contrast, another study in China reported that Firmicutes were the most significantly decreased phylum in the MDD samples compared to healthy controls [29]. A metaproteomic study in 10 patients found different bacterial protein signatures in MDD compared with controls, with differences in proteins belonging to glucose and amino acid metabolism. Considering the merits of this profile, the authors concluded that Firmicutes, Actinobacteria and Lachnospiraceae were more abundant in MDD, whereas Bacteroidetes and Proteobacteria were less abundant, in MDD compared to controls [30]. It has been proposed that short chain fatty acids (SCFAs), which are produced during fermentation of non-digestible polysaccharides, are regulatory compounds with the potential to influence inflammatory, as well as emotional state and cognition through the gut–brain axis. In this regard a study reported lower fecal levels of the bacterial metabolites SCFAs acetate and propionic acid, but higher isocaproic acid concentrations in depressed compared to non-depressed Polish women [31]. In a cohort study including 1054 subjects, fecal Dialister and Coprococcus spp. were depleted in depression and using a module-based analytical framework, they also identified the microbial synthesis potential of the dopamine metabolite 3,4-dihydroxyphenylacetic acid as correlating positively with mental quality of life and indicated a potential role of microbial γ-aminobutyric acid production in depression [32]. In another cohort study in the UK, 40 participants from the general population completed self-report questionnaires for depression, self-judgement, over-identification and affective and cognitive empathy. Faecal and blood samples were taken to assay microbiota (Bifidobacterium; Lactobacillus spp.) and pro-inflammatory molecules, they found that the fecal predominance of Lactobacillus spp. was directly related to positive self-judgment but only indirectly to cognitive depression and lower affective empathy [33].

**b) Anxiety:** Throughout their life 15-20% of people will experience an episode of depression or anxiety and therefore are among the top 10 cases of the global burden of disease. In addition to the relationship between IBS and mental illness, the composition of the gut microbiota in individuals with anxiety or depression is known to differ from that of healthy controls. Studies in mice showed that intestinal infections or chemical-induced colitis caused an increase in anxiety-related behavior patterns. Fecal transplants of anxious-type mice to a more resilient strain increase anxiety-like behaviors in the resilient strain and vice versa. Probiotic supplementation has also shown promise, with a reduction in anxiety and depression reported in many human and animal studies. In the comparisons of microbial changes in humans with generalized anxiety disorder against healthy controls, very few changes have been found, however, a decrease in commensal bacteria is observed, similar to cases of depression [34]. Bacteria of the microbiota produce neurotransmitters similar to those found in the central nervous system of animals such as γ-aminobutyric acid (GABA), acetylcholine, dopamine, serotonin, and norepinephrine [35-39]. GABA, acetylcholine, and norepinephrine are also immunomodulators [40,41]. In addition, short-chain fatty acids (SCFA) such as butyrate decrease the intestinal inflammatory process, [42] improve the integrity of the intestinal epithelial barrier [43], stimulate the secretion of 5-hydroxytryptamine from intestinal enterochromaffin cells and activate to free fatty acid receptors that have a direct anti-inflammatory effect on the activation of microglia [44]. Biotin and niacin produced by the gut microbiota are immunomodulatory, and deficiency could contribute to gut and systemic inflammation [42,45].

**c) Bipolar disorder:** Bipolar disorder (BD) is a serious psychological illness characterized by changes in mood and

energy [1]. The prevalence of BD, worldwide, is 1% and is independent of nationality, socioeconomic status or ethnicity, it is an important source of disability and is associated with drug abuse and cardiovascular problems [46]. The etiology of BD is not fully understood. There is increasing evidence supporting the presence of a link between gastrointestinal pathologies and psychological illnesses. For example, there is a comorbidity rate of irritable bowel syndrome (IBS) with psychiatric disorders that ranges from 54% to 94% [46]. A meta-analysis consisting of 177,117 IBS patients and 192,092 healthy controls showed that the prevalence of BD was significantly increased in the IBS population compared to healthy volunteers (OR = 2.48, p <0.001) [47]. In one study, the subgroup of IBS patients, who had had traumatic experiences in early life, was associated with a different gut microbiota composition and differences in brain morphology compared to healthy volunteers [48]. It appears that intestinal inflammation causes a "leaky gut" phenotype that generates the escape into circulation of the gram-negative associated lipopolysaccharide that in turn produces both central and systemic inflammatory immune responses while selecting the survival of specific bacterial species that can tolerate the response. host immune [49-51]. BD patients often show low-grade peripheral inflammation with a further increase in pro-inflammatory cytokine levels during mood episodes [52]. Patients with schizophrenia and BD have been shown to exhibit higher levels of serum antibodies against fungal organisms such as Saccharomyces cerevisiae and Candida albicans, as well as soluble CD14 (sCD14), a protein marker of bacterial translocation [53-57]. Other supporting data are that the use of antipsychotic medications or diet products can attenuate this leaky gut phenotype [53,58]. However, this and other theories that delineate inflammatory mechanisms remain highly nonspecific for psychological illness.

**d) Stress:** There is evidence that stress affects neuro-immuno-endocrine pathways. Even exposure to acute stress alters the relative proportions of the main phyla of the microbiota, and when researchers deliberately alter the microbiota, the stress response is modified, anxiety-like behavior is generated, and the hypothalamic-pituitary-adrenal axis (HPA) set point changes [59] . In addition, in animal models of stress due to mild and chronic social defeat, they significantly change the intestinal microbiota. These changes are associated with changes in the concentration of some metabolites produced by the intestinal microbiota and in the immune signaling pathways, which suggests that these components may be important in stress-related clinical conditions, including depression [59] . In a rat model, prenatal stress (PNS) induced an exaggerated response of the HPA axis, increased blood pressure, and impaired cognitive function. In addition, an increase in the variability of the baseline respiratory rate and an abnormal response of the rate to hypoxic and hypercapnic insults was observed, which shows that there is an alteration in respiratory control. PNS also affected neurodevelopment and decreased the density of innervation of the distal colon and increased the colonic secretory response to catecholamine stimulation. Finally, the SNP induced lasting alterations in the composition of the intestinal microbiota, which consisted of a decrease in the number of bacteria in the Lactobacillus genus and an increase in the genera of Oscillibacter, Anaerotruncus and Peptococcus generates [60].

**e) Suicide:** One of the main causes of suicidal ideation is the presence of a pre-existing major depressive disorder (MDD) [61]. There is evidence obtained from animal models that relates MDD and suicidal ideation with the gut microbiota [62]. The most plausible theory that explains this association is that the gut microbiota modulates brain development, function and behavior by recruiting the same neuroimmune, neuroendocrine and neural pathways of the brain-gut axis that are dysfunctional in MDD [63]. Specifically, abnormalities in the serotonergic system have been widely implicated in suicidal behavior and suicide. For example, a strong association between low concentrations of 5-hydroxyindoleacetic acid (a way of measuring serotonin) and increased expression of 5HT2A receptors on platelets has been reported with suicidal behavior [64].

## Interest conflict

The authors declare that we have no conflict of interest

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## Conclusion

There is a growing body of information that establishes the bidirectional relationship between the gut microbiota-brain axis and mental health. In general, the studies reviewed provide support for the relevance of communication between the gut microbiota and the brain and its association with mood disorders in both animals and humans at different stages of life. This generates new research perspectives aimed at discovering interventions that modify the microbiota trying to improve the mental health of patients.

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