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Corresponding author mail id: vellingr@med.umich.edu

The Microbiome in Mental Health: Potential Contribution of Gut Microbiota in Disease and Pharmacotherapy Management

Authors:

Stephanie A. Flowers[1], Vicki L. Ellingrod[1,2]

[1]College of Pharmacy, Clinical Social and Administrative Sciences, University of Michigan

[2]University of Michigan, School of Medicine, Department of Psychiatry

Address for correspondence:

Vicki L. Ellingrod
428 Church Street Rm #2053
Ann Arbor, Michigan 48109
Office: 734-936-1914

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Abstract

The gut microbiome is composed of approximately 10^{13}–10^{14} microbial cells and viruses that exist in a symbiotic, bidirectional communicative relationship with the host. Bacterial functions in the gut have an important role in healthy host metabolic function, and dysbiosis can contribute to the pathology of many medical conditions. Alterations in the relationship between gut microbiota and host have gained some attention in mental health, as new evidence supports the association of gut bacteria to cognitive and emotional processes. Of interest, illnesses such as major depressive disorder are disproportionately prevalent in patients with gastrointestinal illnesses such as inflammatory bowel disease, which pathologically has been strongly linked to microbiome function. Not only is the microbiome associated with the disease itself, but it may also influence the effectiveness or adverse effects associated with pharmacologic agents used to treat these disorders. This field of study may also provide new insights on how dietary agents may help manage mental illness both directly as well as though their influence on the therapeutic and adverse effects of psychotropic agents.

The human microbiome is primarily composed of 10-100 trillion bacterial symbionts that are commensal to our gut, mucosal surfaces, and skin.[1] These microbes greatly outnumber our somatic and germ cells by an estimated 10-fold.[1] Aside from variation in our genomic DNA, we understand that the collective genomic content of our gastrointestinal microbiome profiles also

contributes to human diversity[1,2]. Although the gut microbiome actually consists of a variety of microorganisms, such as commensal fungi, viruses, protozoa, and parasites, the vast majority of work focuses on bacterial colonizers and will be the focus of this review. The bacterial component of gut microbiota is composed of more than 1000 phylotypes (organisms classified based on evolutionary relationships), predominantly obligate anaerobes, with *Firmicutes* and *Bacteroidetes* representing more than 90% of the total microbiota[3]. Gut microbiota structure and function (the metagenome) is influenced by a variety of factors, including host physiology, diet, antimicrobials medications, infections, and environment.

Although microbiome research is still developing, there is also a growing amount of evidence to support the effect of microorganisms on cognitive and emotional processes. This review summarizes the role of the microbiome on mental illness, focusing on the interaction of the microbiome and pharmacologic management of psychiatric disease.

Microbiome in the Gut-Brain Axis

The gut-brain axis is a term that defines the bidirectional communication between an individual's microbiome and brain, and has become a topic of interest in psychiatry and neuroscience. Communication from the gut to brain and the brain to gut can occur by neural, hormonal, or immunologic mechanisms. The ubiquitous presence of neuroendocrine hormones in both mammalian and nonmammalian systems has been recognized for decades. Bacterially produced neuroactive compounds include catecholamines, such as norepinephrine and dopamine, and γ-aminobutyric acid (GABA), histamine, serotonin, and acetylcholine, which have known roles in a majority of mental illnesses as well as in the mechanisms of action of psychiatric drugs[4]. Remarkably, the complete identical biosynthetic pathway for catecholamines was found in bacteria, which led to the hypothesis that mammalian cell-to-cell signaling systems, such as neuroendocrine pathways, are derived from late horizontal gene transfer from bacteria[5]. Not only do certain species of endogenous bacteria produce these chemicals, but some bacteria possess receptors to these neuroactive compounds, which suggests that these compounds not only facilitate interbacterial communication but also mediate communication from the host[6]. This intersection of neurobiology and microbiology has been termed microbial endocrinology.

Gut-brain communication can be mediated in part through enteric, vagal, and central nervous pathways[7]. The enteric nervous system (ENS) is embedded into the lining of the intestinal tract from the esophagus to the colon and governs the function of the gastrointestinal system.

Despite considerable innervation from the autonomic nervous system, it operates largely independently of the central nervous system (CNS) and is sometimes referred to as the "second brain"[7]. Neurochemicals produced by gut microbiota from the food we eat can directly interact with receptors found on components of the ENS and can influence the brain via ENS-CNS communication through the various pathways [8].

The microbiome plays a critical part in the development of the immune response of the intestinal endothelium and the blood-brain barrier (BBB) system, as shown by work in germ-free mice. Compared to their conventionally housed counterpart, germ-free mice have stunted development of gut-associated lymphoid tissue, which is critical in pathogen recognition[9]. Germ-free mice have also exhibited increased BBB permeability compared to conventionally raised mice[10]. Intestinal and BBB integrity can be restored when germ-free mice are colonized with intestinal microflora. Psychiatric disorders have been linked to the immune system, and an emerging concept is that gut bacteria may be able to influence the emotional state of the host [11]. It is thought that a commonality between psychiatric illness and the gut may reside in inflammatory pathways. Indeed, high rates of comorbid depression have been found in patients with inflammatory disease states such as inflammatory bowel disease and rheumatoid arthritis[12,13].

Understanding the Gut-to-Brain Connection Through Lipids

Short-chain fatty acids (SCFAs) are the major metabolic products of intestinal bacteria derived from the fermentation of carbohydrates and proteins in the gut[14]. The main SCFAs produced in the gut are acetic acid, propionic acid, and butyric acid, which come from dietary intake[15]. SCFAs interact with the human body by a number of different mechanisms, including mediation of colonic epithelial cell growth, hepatic control of lipids and carbohydrates, gene expression, and energy sources for a wide array of tissues. Both propionic acid and butyric acid have been shown to be ligands for receptors involved in host energy homeostasis and inflammatory responses[16]. SCFAs can cross the BBB and might be environmental factors that contribute to neurodevelopment disorders such as autism spectrum disorders[17]. Recent work has highlighted the role of SCFAs and their regulation of immune responses by their effects on T cells, neutrophils, and colonocytes. Importantly, SCFAs have been shown to induce both effector and interleukin-10 T-regulatory cells, depending on the cytokine condition and immunologic context [18,19].

Bile acids are not only a known contributor to drug pharmacokinetics but are also a regulator of gut microbiome composition[20]. Formed in the liver, bile acids account for the majority of cholesterol turnover in the body. Bile acids form micelles in bile and are excreted in the small intestine after eating, where they are an essential component required for the absorption of lipophilic vitamins, fat, and drugs. The gut microbiome is capable of producing secondary bile acids, such as deoxycholic acid and lithocholic acid, that affect host metabolic processes, drug metabolism, and immune response[21,22]. Bile acids mediate these processes through the activation of receptors such as the farnesoid X, pregnane X, vitamin D (VDR), and TGR5 receptors[23,24]. Activation of the VDR exhibits wide range of immunomodulatory effects, and VDR ligands have been shown to reduce messenger RNA (mRNA) expression and decrease plasma concentrations of proinflammatory cytokines[2425]. Bile acids also have antimicrobial properties despite the microbiome's critical role in their biotransformation; thus, a dynamic equilibrium exists between the microbiome and the bile acid pool[26].

Cometabolism of Drugs by Host and Gut Bacteria

The pharmacokinetics of orally administrated drugs can be complicated and dependent on measures such as the chemical properties and environmental risk parameters specific for each drug. Knowledge of how human genetics affect drug pharmacokinetics and pharmacodynamics has further advanced our understanding of inter-individual variations in drug efficacy and adverse effects, but much variation remains unexplained. An important but sometimes overlooked contributor to drug metabolism is the gut microbiota, which expands the metabolic processes of these compounds beyond that of mammalian encoded enzymes.

Microbiome-mediated reactions in the gut tend to be dominated by reduction or hydrolysis reactions whereas mammalian metabolism shows a greater propensity for oxidation and conjugation[27]. Gut microbiota have been shown to participate in the reductive metabolism of psychotropic medications such as the benzodiazepine clonazepam[28]. Risperidone, an atypical antipsychotic, has been shown in postmortem studies to undergo gut-mediated isoxazole scission,[29] and studies with levodopa, a mainstay in the treatment for Parkinson's disease, show that the presence of *Helicobacter pylori* is associated with decreased plasma levels of the drug[30]. Although the pharmacokinetics of these medications may, in part, be altered by the microbiome, there are currently no defined clinical consequences of these occurrences. The gut microbiota can also indirectly contribute to xenobiotic metabolism by altering gene expression of hepatic enzymes that aid in the metabolism and detoxification of drugs outside of the gut.

Studies in colonized and germ-free rats (rats cultivated with no intestinal microbiota) showed that the microbiome affects hepatic concentration of both phase I and phase II metabolizing enzymes, which are responsible for transformation of the majority of prescribed medications [31,32].

Microbiome, Inflammation, and Mood

Changes in proinflammatory and cell-mediated immune cytokines have been thoroughly documented in psychiatric diseases such as major depressive disorder (MDD). In fact, in addition to genetic and environmental factors, a robust association has been defined for MDD, immune response, and inflammation[33,34]. Evidence suggests that antidepressants such as the tricyclic antidpessants and selective serotonin reuptake inhibitors (SSRIs) may function to normalize cytokine levels, and this may be an additional therapeutic mechanism secondary to their effect on neurotransmitters[33,35]. Several studies have examined the effects of antidepressants on bacterial endotoxin lipopolysaccharide (LPS)-induced inflammation and depressive symptoms in animals. In rodents, pretreatment with SSRIs (fluoxetine or paroxetine) or serotonin-norepinephrine reuptake inhibitors (venlafaxine and duloxetine) reduced LPS-induced inflammation and depressive-like behaviors[36].

Few studies have examined whether an increased gastrointestinal permeability with an increased translocation of LPS from gram-negative bacteria may play a role in the pathophysiology of MDD and other mental illnesses. One study in humans examined levels of serum antibodies against LPS of gram-negative enterobacteria and found higher levels in patients with MDD than in controls[37]. Alterations in gut epithelial permeability in patients with autism and schizophrenia has been described but without conclusive results[38]. In animals, acute and chronic stress has been shown to lead to increased gut permeability and bacterial translocation[39,40]. In these studies, the therapeutic benefits, such as reduced stress-induced corticosterone level, anxiety, and depression-related behaviors, were obtained through the administration of probiotics. The therapeutic benefits of adjunct therapy with minocycline and doxycycline have been explored in both animal and human studies for MDD and schizophrenia[41-43]. Minocycline has antioxidant, anti-inflammatory, and neuroprotective properties that are not related to its antimicrobial properties but mirror many of the deficits observed in MDD[44,45].

Microbiome, Obesity, and Cardiovascular Disease in the Mental Health Population

Longitudinal studies following the introduction of atypical antipsychotics antipsychotics(AAPs) have noted the growing contribution of cardiac and metabolic disease to increased mortality in subjects with schizophrenia.[46] Recent data suggest that the standardized mortality ratio for cardiac disease in these subjects is increasing compared with the general population[47,48]. Due to the wealth of data that links changes in the microbiome to obesity and metabolic syndrome, the role of the microbiome in AAP–associated metabolic risk is currently being investigated in animal models.

A study of olanzapine use in rats demonstrated that treatment had significant effects on a number of physiologic, inflammatory, and microbial parameters and that many, but not all, were more pronounced in females compared with males[49]. Specific microbiome alterations in olanzapine-treated female rats included dose-dependent increased levels of *Firmecutes*, decreased levels of *Bacteriodetes* species, and overall decreased biodiversity. These observations were replicated in male rats but only at higher doses. In a follow-up study performed in female rats, coadministration of antibiotics attenuated the physiologic and inflammatory effects of olanzapine use[50]. A recent study in germ-free mice determined that gut bacteria were not only necessary but sufficient for olanzapine-mediated weight gain[51]. As seen in previous studies, colonized mice treated with olanzapine showed a shift in gut microbiota toward an "obesogenic bacterial profile".[52] Finally, in an in vitro model, olanzapine was determined to have antimicrobial activity against enteric bacterial strains.[51] In all, these studies make a strong case for the translation of these types of studies to humans.

Personalized Management of Gut Microbiota

Currently, interest in exploring probiotics as a component of nutrition-based health is widespread. Probiotics are currently defined as a dietary supplement containing live bacterial cultures that is taken orally in adequate quantities to exert a health benefit. Although many bacteria are advertised as probiotics, data show that the in vivo effects of different species vary greatly, and few have been thoroughly investigated. Derived benefits from probiotic microorganisms are due to a number of different actions, including conferring protection against pathogenic organisms and modulation of the immune response, and the actions of microbial-derived metabolic products[53]. Evidence that using probiotics to affect human behavior is limited, but there are data that support its use as an adjuvant treatment in mental health.

Desbonnet et al. assessed potential benefits of the probiotic *Bifidobacterium infantis* compared with the SSRI citalopram on mood using a rat maternal separation model.[54] In this study,

maternally separated rats were chronically treated with *Bifidobacterium infantis* or citalopram. Assessments made were motivational state, as measured by a forced swim test, cytokine concentrations in whole blood samples, monoamine levels in the brain, and central and peripheral hypothalamic-pituitary-adrenal axis measures. For the control group of nontreated rats, maternal separation reduced swim behavior (indicating a depressed-like behavior) and decreased mobility as demonstrated by the forced swim test. Decreased norepinephrine levels were measured in the brain in addition to greater proinflammatory cytokine and amygdala corticotropin-releasing factor mRNA levels. Probiotic treatment resulted in improvement of mood deficiencies in addition to normalization of cytokine levels and basal norepinephrine levels, which was comparable to the effects of citalopram.

Another study by Bravo et al. investigated the impact of *Lactobacillus rhamnosus* on behavior and central GABA receptors in mice.[40] Probiotic-treated mice exhibited reduced anxiety symptoms and altered cerebral expression of both GABA type A and GABA type B receptors compared with mice treated with inactive broth. A subset of animals underwent a vagotomy and was treated with either the probiotic or inactive broth. Vagtoimized mice treated with a probiotic did not show a decrease in anxiety indicating that the vagus may mediate behavioral and neurochemical effects of *L. rhamnosus*.

Table 1 provides a summary of preclinical and clinical studies examining microbiomes in animals or humans with behavioral and psychological disorders.

Perspective and Future: Impact of Host Microbiome on Personalized Medicine

Advances in next-generation sequencing and culture-independent approaches to study the microbiome have led to a new understanding of the microbiome's involvement on host physiology and disease. The most common method of studying microbiome biodiversity and structure is by sequencing hypervariable regions of the gene encoding the small ribosomal subunit known as 16S[66]. As many of the anaerobic species that inhabit the gut are not culturable, we may find that composition data may not be sufficient to define the role of the microbiome in health and disease. Perhaps even more insightful, culture-independent methods such as shotgun sequencing of the metagenome are now employed to study both the composition and the functionality of processes occurring in the gut[67].

Conclusion

Consideration of the human gut microbial composition and function will be a necessary part of future personalized medicine strategies. There is a great potential in examining the microbiome to develop diagnostic markers of disease and to take advantage of therapeutic strategies that will maximize the benefice of a healthy gut structure. Currently, most data describing the importance of the microbiome in psychiatric illness and pharmacologic management are from ex vivo or animal preclinical models. Biological validation of these methods on large human cohorts will be necessary to demonstrate the strength and clinical utility of these types of predictors and therapeutic management of disease.

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Table 1. Preclinical and Clinical Studies Examining Microbiomes in Animals or Humans with Behavioral and Psychological Disorders

Reference	Model	Probiotic Intervention or Other Method	Conclusions
Preclinical studies			
	Germ-free		
Neufeld et al. (55)	mouse (female)	Comparison of germ-free vs SPF mice	Basal behavior for germ-free mice vs SPF mice was interpreted as anxiolytic; increased BDNF mRNA in hippocampus of germ-free animals
Goehler et al. (56)	mouse	*Camphylobacter jejuni*	Increased anxiety-like behavior and increased markers of activation within the limbic structures in the brain
Bravo et al. (40)	mouse	*Lactobacillus rhamnosus*	Induced region-dependent alterations in GABA mRNA in the brain and reduced stress-induced corticosterone level and anxiety- and depression-related behavior that was not seen in vagotimized mice
Steinberg et al. (57)	mouse	*Lactobacillus acidophilus* L36 or *Lactobacillus salivarius* L38	L36 increased the expression of Th2 cytokines (IL-5, IL-6 and TGF-β1) and Th17 (IL-17a, TNF-α and IL-6) inflammatory response
	Conventional		
Zareie et al. (58)	rat	*Lactobacillus helveticus* and *Lactobacillus rhamnosus*	Intervention prevented chronic stress-induced intestinal abnormalities
Desbonnet et al. (54)	rat	*Bifidobacterium infantis*	Decreased depressive-like behavior in maternal separation model
Ait-Belgnaoui et al. (59)	rat (female)	*Lactobacillus farciminis*	Treatment attenuated the HPA response to acute stress
Clinical studies			
Tillisch et al. (60)	human (female)	FMPP; *Bifidobacterium animalis* , *Streptococcus thermophiles*, *Lactobacillus bulgaricus*, and *Lactococcus lacti*	Intervention affected activity of brain regions that control central processing of emotion and sensation
Benton et al. (61)	human	*Lactobacillus casei*	Improved mood
Messaoudi et al. (62)	human and rat	*Lactobacillus helveticus* and *Bifidobacterium longum*	Beneficial effects on anxiety and depression and showed reduced urinary levels of cortisol
Schmidt et al. (63)	human	Prebiotics	Intervention associated with lower cortisol levels at awakening and improved attention to positive stimuli compared with negative stimuli in an emotional categorization task and in an emotional recognition task

Rao et al. (64)	human	*Lactobacillus casei*	Decreased anxiety in patients with chronic fatigue syndrome
Tomasik et al. (65)	humans with schizophrenia	*Lactobacillus rhamnosus* GG and *Bifidobacterium lactis* Bb12.	14 weeks of probiotic add-on treatment significantly reduced levels of vWF and increased levels of MCP-1, BDNF, RANTES, and MIP-1 beta with borderline significance (p= 0.08)

SPF = specific pathogen-free; BDNF = brain-derived neurotrophic factor; mRNA = messenger RNA; GABA=γ-aminobutyric acid; Th = T helper; IL = interleukin; TGF = transforming growth factor; TNF- α = tumor necrosis factor α; HPA = hypothalamic-pituitary-adrenal; FMPP = fermented milk product with probiotic; prebiotics = oliogosaccharides that can promote growth of beneficial commensal bacteria; vWF = von Willebrand factor; MCP-1 = monocyte chemotactic protein-1; RANTES = a cytokine that is a member of the IL-8 superfamily of cytokines; MIP-1= macrophage inflammatory protein-1.

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