Adiel C. Rios, Pawan Kumar Maurya, Mariana Pedrini, Maiara Zeni-Graiff, Elson Asevedo, Rodrigo B. Mansur, Andrea Wieck, Rodrigo Grassi-Oliveira, Roger S. McIntyre, Mirian A.F. Hayashi and Elisa Brietzke*

Microbiota abnormalities and the therapeutic potential of probiotics in the treatment of mood disorders

DOI 10.1515/revneuro-2017-0001
Received January 5, 2017; accepted March 8, 2017; previously published online May 8, 2017

Abstract: Major depressive disorder (MDD) and bipolar disorder (BD) are among the leading causes of burden and disability worldwide. Despite intensified research efforts to improve the treatment options and remission rates in mood disorders, no disease modifying treatment exists for these disorders. Accumulating evidence implicates the involvement of the gut microbiota in processes relevant to etiopathology of central nervous system-based disorders. The objective of this article was to critically evaluate the evidence supporting the link between gastrointestinal microbiota and mood disorders and to discuss the potential benefits of using probiotics in the treatment of MDD and BD. The concept of psychobiotics, which is bacterial-based interventions with mental health benefit, is emerging in the field. On the other hand, while probiotics might potentially represent a significant advance, specific roles of microbiota in the pathophysiology of mood disorders still need further investigation along with intervention studies.

Keywords: bipolar disorder; major depression disorder; microbiome; microbiota; mood disorders; probiotics.

***Corresponding author: Elisa Brietzke,** Research Group in Molecular and Behavioral Neuroscience of Bipolar Disorder, Federal University of São Paulo (UNIFESP), São Paulo, Brazil, e-mail: elisabrietzke@hotmail.com
Adiel C. Rios, Mariana Pedrini, Maiara Zeni-Graiff and Elson Asevedo: Research Group in Molecular and Behavioral Neuroscience of Bipolar Disorder, Federal University of São Paulo (UNIFESP), São Paulo, Brazil
Pawan Kumar Maurya: Research Group in Molecular and Behavioral Neuroscience of Bipolar Disorder, Federal University of São Paulo (UNIFESP), São Paulo, Brazil; and Centre for Medical Biotechnology, Amity Institute of Biotechnology, Amity University Uttar Pradesh, Noida, India
Rodrigo B. Mansur and Roger S. McIntyre: Mood Disorders and Psychopharmacology Unit (MDPU), University Health Network (UHN), University of Toronto, Toronto, Canada
Andrea Wieck: Laboratory of Immunosenescence, Institute of Biomedical Research, Pontifical Catholic University of the Rio Grande do Sul (PUCRS), Porto Alegre, Brazil
Rodrigo Grassi-Oliveira: Cognitive Neuroscience Research Group (GNCD), Postgraduate Program in Psychology, PUCRS, Porto Alegre, Brazil
Mirian A.F. Hayashi: Department of Pharmacology, Federal University of São Paulo (UNIFESP), São Paulo, Brazil

Introduction

Major depressive disorder (MDD) and bipolar disorder (BD) are mood disorders and are among the leading causes of burden and disability worldwide (Collins et al., 2011). Notwithstanding the progress in drug development, most individuals receiving treatment for a mood disorder do not achieve full symptomatic remission and functional recovery. Moreover, a substantial proportion of patients are not able to tolerate existing medicines (Leclerc et al., 2013; Tondo et al., 2014). Despite the intensified research efforts to improve the treatment options for mood disorders, no disease modifying treatments are currently available (Soczynska et al., 2009; Alsaif et al., 2013). The guideline-guided pharmacological treatments were not developed based on disease pathophysiology, and their impact in the neurobiology of those conditions remains incompletely understood (Dodd et al., 2013; Mansur et al., 2013).

Although MDD and BD have been considered as mental disorders or brain disorders, a robust body of evidence has indicated recently that mood disorder pathophysiology may involve multiple organs and systems (Czepielewski et al., 2013; Noto et al., 2014; Rizzo et al., 2014; Maurya et al., 2016). Mood disorders have repeatedly been associated with increased medical burden, especially cardiovascular conditions, metabolic syndrome, and cancer (Perron et al., 2009; Crump et al., 2013). Recent evidence also suggests that immune-inflammatory, oxidative stress, and metabolic mechanisms are directly involved in

mood disorder pathophysiology. For example, peripheral mediators of inflammatory dysregulation have been consistently reported during mood episodes and euthymia in both MDD and BD (Brietzke et al., 2011; Modabbernia et al., 2013; Cattaneo et al., 2015).

Regarding possible systemic factors, microbiota has currently attracted interest in psychiatry. Microbiota is a term used to characterize an ensemble of microorganisms that is present in one environment (Tralau et al., 2015). Human beings have groups of bacteria in several parts of the body, such as skin, mouth, vagina, and gut or gastrointestinal (GI) tract (Barbara et al., 2008; Rook et al., 2014). Microbiota in the digestive tube is diverse and includes at least 1000 different species that together expresses more than 3 million genes. In fact, there are more bacteria in the gut (about 10^{14} bacterial organisms) than somatic cells of the human body. Colonization of the GI tract begins at birth and continues in early postnatal phase and remains throughout the life (Alverdy et al., 2014) with a recognized role in the development and shaping up the immune system (Smith et al., 2007; Fetissov and Déchelotte, 2011).

One third of the digestive microbiota is common to most people, and two thirds are specific to the individual. The microbial genomes (microbiome) encode essential proteins/enzymes necessary for metabolic functions that humans have not evolved wholly on their own, including the ability to extract energy and nutrients from general diet (Bercik et al., 2011). Imbalances in GI microbiota have been referred as dysbiosis, which has been linked to several health problems such as allergies, obesity, and diabetes (Sun and Chang, 2014; Biedermann and Rogler, 2015). In other words, the human being and gut microbiota symbiotic relationship facilitates nutrient uptake and metabolism, also providing the necessary and inaccessible nutrients, for instance, the essential amino acids that cannot be synthesized by the organism and are needed for the synthesis of neurotransmitters such as serotonin (e.g. tryptophan) (O'Mahony et al., 2014).

Accumulating evidence has indeed indicated that the gut microbiota's roles are involved in processes beyond those related to digestion, and it has been shown to be relevant to brain formation and function. Therefore, it is possible that microbiota abnormalities also play roles in the pathophysiology of central nervous system (CNS) illnesses (Borre et al., 2014). Nonetheless, a large collection of animal studies has revealed the diversity of the interaction between CNS and gut microbiota. The possibility of a bidirectional relationship between gut microbiota and brain has long been recognized and is thought to occur mainly through the autonomic nervous, enteric nervous, and immune systems (Foster and McVey Neufeld, 2013). The foregoing observations have supported a series of hypotheses on the modulatory effects of variations in the microbiome, microbiota-derived products, exogenous antibiotics, and probiotics, as well as on neuro-immune and neuro-psychiatric disorders (Wang and Kasper, 2014).

The objectives of this study were to critically evaluate the evidence(s) for a putative link between microbiota and mood disorders and discuss the hypothesis of a potential usefulness of probiotics in the treatment of MDD and BD.

Microbiota and the CNS

In 1907, Eli Metchnikoff, a Nobel prize winner, suggested that 'the dependence of intestinal microbes on food makes it possible to adopt measures to modify the flora in our bodies and to replace the harmful microbes by useful microbes'. Metchnikoff proposed the hypothesis that the aging results from the proteolytic activity of putrefactive microbes producing toxic substances in the large bowel (Sharma et al., 2014). Proteolytic bacteria such as Clostridia, which are part of the normal gut microbiota, produce toxic substances including phenols, indols, and ammonia from the digestion of proteins (Hughes et al., 2000). According to Metchnikoff, these compounds were responsible for what he named as 'intestinal auto-intoxication', which has the ability to cause several physical changes, including those associated with aging (Bested et al., 2013).

Among the multiple putative effects of microbiota in the body, several studies have shown an association between gut microbiota and brain development and behavior (Cryan and O'Mahony, 2011; Diaz Heijtz et al., 2011). Studies with germ-free mice suggested that these animals had a higher hypothalamus-pituitary-adrenal (HPA) axis responsivity to stress (Sudo et al., 2004), as well as behavioral changes, such as repetitive behaviors that were considered to mimic symptoms of autism (Desbonnet et al., 2014). Diaz Heijtz et al. (2011) demonstrated that colonization of germ-free mice early in life, but not in adults, could normalize several behavioral alterations, such as anxiety-like and motor activity abnormalities, as also recently reviewed by Ianiro et al. (2014). This evidence supports the gut microbiota contribution to a kind of developmental programming, in a 'window of vulnerability' within which the gut microbiota can influence physiological functions, with

potential lifelong consequences. In addition, changes in gut microbiota could lead to long-term modifications of synaptic transmission affecting motor control and anxiety-like behavior in adult life. The perinatal period appears to be critical for this type of developmental programming, due to the ability of the gut microbiota to modulate some systems such as the HPA axis, which occur after germ-free mice are exposed to gut microbiota in early postnatal development stage (i.e. before 6 weeks of age) (Dominguez-Bello et al., 2010; Diaz Heijtz et al., 2011). There are also similar data implicating microbiota-induced behavioral changes as being partially mediated by an increased turnover of monoamines and of synaptic-related protein expression in the striatum, such as synaptophysin (Bravo et al., 2012). The finding that germ-free animals display behavioral changes has been consistently replicated by multiple research groups using different mice strains (Ley et al., 2008; Diaz Heijtz et al., 2011). Using another approach, Bercik et al. (2011) have shown that NIH Swiss mice that received a mixture of antibiotics presented increased anxiety-like behavior, measured using a step-down test, which was reverted by restoring commensal microbiota (Bercik et al., 2011). Moreover, germ-free NIH Swiss mice that were colonized with microbiota from Balb/C, which has naturally a more anxious behavior, displayed anxiety-like behavior, characterized by diminished exploratory behavior (Bercik et al., 2011).

The influence of gut microbiota on brain function also introduces the possibility of a new relevant modulator for cognitive functions with potential to be explored and widely exploited. There are few studies assessing the impact of microbiota on cognitive performance. One of the first, conducted by Gareau et al. (2011), evaluated the new memories formation in mice infected with the Gram-negative pathogenic bacterium *Citrobacter rodentium*. Infected mice that were submitted to stress conditions presented deficits of nonspatial memory even after the resolution of the infection. Interestingly, pretreatment with probiotics was capable of preventing the cognitive deficit, partly by restoring the hippocampal brain-derived neurotrophic factor (BDNF) and c-Fos expression (Gareau et al., 2011).

The exact mechanism(s) involved in the brain function modulation by microbiota is not completely understood, and possibly several pathways are involved depending on the individual, the pathogen, and the interaction between them. For example, Goehler et al. (2005) suggested that infectious microorganisms such as *Campylobacter jejuni* initially communicate with the brain via peripheral sensory nerves. While in late stages, communication is via immune activation mediators, such as cytokines (Goehler et al., 2005).

The main pathways of microbiota influence in CNS are summarized below.

Autonomic nervous system

To test the hypothesis that local infection in the gut activates vagal sensory neurons Goehler et al. (2005) conducted an experiment with mice aiming to assess expression of the neuronal activation marker c-Fos in neurons in the vagal sensory ganglia and in the primary sensory relay nucleus for the vagus, the nucleus of the solitary tract (nTS). The mice were treated orally either with saline or live *C. jejuni*. Oral inoculation with *C. jejuni* led to a significant increase in c-Fos expression in neurons bilaterally in the vagal ganglia, in the absence of elevated levels of circulating proinflammatory cytokines. *Campylobacter jejuni* treatment activated neurons in the nTS, as well as in brain regions associated with primary viscerosensory pathways and the central autonomic network.

Immune system

Mood disorders are recognized in some circumstances as inflammatory conditions, as there is robust evidence for increases in proinflammatory cytokines in both MDD and BD (Brietzke et al., 2011; Modabbernia et al., 2013; Duffy et al., 2014; Noto et al., 2014). Nevertheless, the origin of inflammation in these psychiatric disorders is not well understood. Current theories include a multiplicity of possible pathways such as genetic variation in cytokines genes (Brietzke and Kapczinski, 2008; Cerri et al., 2010; Rafiei et al., 2013), immune reprograming caused by *Toxoplasma gondii* infection (Hamdani et al., 2013), disruptions in blood-brain (Patel and Frey, 2015), premature aging of the immune system (Noto et al., 2014), HPA axis activation caused by stress (Wieck et al., 2014), presence of general medical comorbidities (Mansur et al., 2015), also secondary to circadian rhythm alteration, autoantibodies against brain proteins (Steiner and Bogerts, 2015), and diet-generated humoral immune activation (Severance et al., 2010).

The translocation of commensal microbiota across the GI barrier has been largely recognized as a stimulus for a persistent state of low-grade immune activation and has been considered a candidate from the long list of factors involved in persistent inflammatory activation in mood disorders. Indeed, in nonpsychiatric conditions,

both observational and experimental evidence indicates that microbiota can modulate the immune response, changing the clinical expression of the disease (Severance et al., 2015). Lukens et al. (2014) showed in an animal model that diet can modulate the microbiota (high-fat diet induces a decrease in prevotella), which in turn offered protection against inflammatory bone disease. In addition, there are consistent evidence that changes in microbiota have effects on Crohn's disease and other inflammatory bowel diseases (Morgan et al., 2012; Gevers et al., 2014; Severance et al., 2014) in rheumatoid arthritis (Wu et al., 2010; Scher and Abramson, 2011), type I diabetes (Kriegel et al., 2011; Suez et al., 2014), and allergic diseases (Hong et al., 2010; Nakayama et al., 2011; Pérez-Losada et al., 2015).

Microbiota and mood disorders

Although discussions on the hypothesis of a microbiome influence in the development of mood disorders in the last few years have advanced, limited experimental studies that directly address this issue can be found.

Animal studies

One possible strategy to study the link between mood and microbiota in animals is the induction of depressive-like behaviors to observe the effects on microbiota. Park et al. (2013) induced depressive-like behavior in female C57BL/6 mice through bilateral olfactory bulbectomy and compared with a nontreated group. They demonstrated significant differences in microbial profile of stool samples between the experimental and sham operated mice groups (Park et al., 2013). In addition, Barseghyan et al. (2013) induced depressive-like behavior through chronic variable physical stress (e.g. forced swimming, ether, restraint, cold, orthostatic shock, and food deprivation) in early adolescent Wistar rats and compared their microbial composition in the gut, blood, and brain with that of control rats. The experimental group showed significantly higher number of *Candida albicans* and *Staphylococcus aureus* in gut at the same time the numbers of Lactobacilli and Bifidobacteria were reduced, and the number of *Escherichia coli* dropped significantly. The authors speculate that stress-induced depressive behaviors in the animals could be attributed to the enhanced growth of such opportunistic and pathogenic bacteria and fungi such as *S. aureus* and *C. albicans* in the digestive tract, which may markedly decrease the number of the beneficial bacteria in gut. Clinical cultures of *C. albicans* can cause desquamation of small fragments like peptidoglycan layers of cell wall, total destruction of Lactobacilli cytoplasmic contents, and growth, reducing the number of beneficial bacteria in the gut flora (Barseghyan et al., 2013).

Another promising preclinical strategy to evaluate the impact of the microbiome-gut-brain-axis in the development of CNS illnesses involves the use of germ-free animals. Neufeld et al. (2011) compared the performance of germ-free mice with that of control animals on elevated plus maze. Germ-free animals exhibited anxiety-like behaviors and changes in transcription of genes involved in anxiety-like behaviors. BDNF was also significantly up-regulated and the 5HT1A serotonin receptor subtype down-regulated in the dentate gyrus of the hippocampus of germ-free mice. The transcription of the gene encoding the NR2B subunit of the NMDA receptor was also down-regulated in the amygdala. Several other studies indicate that germ-free mice have abnormalities in stress response (Sudo et al., 2004), memory (Gareau et al., 2011), and social behavior (Desbonnet et al., 2014). Interestingly, recolonization of germ-free animals was not sufficient to reverse the neurotransmission alterations in adulthood, suggesting a long-term effect of microbiota changes during the post-natal developmental period (Borre et al., 2014). Studies with microbiota manipulation were also conducted to explore the possible reversal depressive-like behaviors. Pyndt et al. (2014) investigated whether gut microbiota would be the link between Western diet, with high saturated fat sugar intake, and depressive symptoms. They assigned 42 male BALB/cAnNTac mice for 13 weeks to one of three diets, namely a high-fat/no-sucrose, a high-sucrose/standard-low-fat, or a control diet, and evaluated the depressive-like behavior and microbiota composition, systemic low-grade inflammation, neuroinflammation, hippocampal level BDNF, and metabolic markers (Pyndt et al., 2014). Depressive-like behavior, such as less burrowing and decreased memory in the Morris water maze test, was found in mice under a high-fat diet, compared to control mice and mice under a high-sucrose diet, respectively. Interestingly, mice under a high-sucrose diet displayed significantly less anxiety to an open area challenge in the triple test compared to mice under high-fat diet, but they also had a trend for a decreased goal-oriented digging behavior compared to control mice. Behavioral changes were accompanied by a significant change in gray matter composition of mice fed with a high-fat diet (Collins et al., 2011).

Additionally, treatment with a probiotic formulation has been shown to reduce the HPA axis and the autonomic nervous system (ANS) activity in several ways.

Ait-Belgnaoui et al. (2014) have demonstrated that corticosterone, adrenaline, and noradrenaline plasma levels were not increased in chronically stressed mice that received the probiotic treatment. The probiotic formulation also influenced neurogenesis and gene expression, up-regulating the BDNF transcription and preventing stress-induced decrease in neuronal growth (Ait-Belgnaoui et al., 2014).

Human studies

Compelling indications of inflammatory dysregulation in MDD, accompanied by the induction of depressive symptoms by inflammatory cytokines and lipopolysacharides (LPS), opened a new line of investigation regarding the role of the Gram-negative bacteria in the pathophysiology of MDD. In this context, Maes et al. (2012a,b) found significantly higher values for serum concentration of immunoglobulin M (IgM) and immunoglobulin A against LPS of enterobacteria in patients with MDD compared to healthy controls, suggesting that increased translocation of Gram-negative bacteria may play a role in the activation of inflammatory pathways in MDD. Furthermore, higher levels of these immunoglobulins were associated with typical sickness behavior like fatigue and autonomic symptoms (Dantzer, 2009).

These findings were later replicated, supporting the evidence for an increased bacterial translocation (leaky gut). Moreover, serum levels of IgM against LPS of Gram-negative commensals bacteria were significantly higher in patients with chronic depression (Maes et al., 2012a,b). It is hypothesized that the loss of integrity of the intestinal barrier allows Gram-negative commensal enterobacteria to translocate into the *lamina propria* and the mesenteric lymph nodes activating the immune cells. Bacterial translocation may (a) occur secondary to systemic inflammation in MDD, intensifying and perpetuating the primary inflammatory response, once the commensals are translocated; or (b) be a primary trigger factor associated with the onset of depression in some vulnerable individuals. These findings suggest that, by causing progressive, intensifying immune pathways, translocated commensal bacteria from the gut may play a role in the pathophysiology of MDD (Maes et al., 2012a,b).

On a similar matter, Naseribafrouei et al. (2014) investigated the correlation between the human fecal microbiota and MDD. They compared gut microbiota composition between depressed patients (n = 37) and controls (n = 18), using 16S rRNA gene Illumina deep sequencing, and they found that at a high taxonomic level, an overrepresentation of the order Bacteroidales and underrepresentation of the Lachnospiraceae family was associated with MDD. On the other hand, at a low taxonomic level, the *Alistipes* and *Oscillibacter* strains were overrepresented in patients with MDD. Interestingly, *Alistipes* has been associated with both chronic fatigue syndrome and irritable bowel syndrome (IBS). Also, *Oscillibacter* produces a molecule (valeric acid) that is structurally similar to GABA, which was also shown to bind to GABA receptors (Naseribafrouei et al., 2014). The association between the depressive symptoms and gut microbiota composition was also shown in elderly population, with loss of community-associated microbiota being associated with several other markers of health deterioration (Noto et al., 2014).

Interestingly, many GI disorders demonstrate a high prevalence of psychiatric symptoms (Neufeld and Foster, 2009). IBS is the most common functional GI condition observed in patients who visit general practitioners for GI-related complaints. A high prevalence of psychiatric comorbidities, particularly anxiety and depressive disorders, has been reported in patients with IBS. A retrospective cohort study conducted between 2000 and 2005 evaluated the relationship between IBS and mental disorders. The IBS sample consisted of 4689 patients, and the comparison group comprised 18,756 matched controls without IBS. The risks for depressive disorders [hazard ratio (HR) = 2.71, 95% confidence interval (CI) = 2.30 to 3.19], anxiety disorders (HR = 2.89, 95% CI = 2.42 to 3.46), sleep disorders (HR = 2.47, 95% CI = 2.02 to 3.02), and BD (HR = 2.44, 95% CI = 1.34 to 4.46) were significantly higher in the IBS group than in the comparison group. In addition, the incidence of newly diagnosed depressive disorder, anxiety disorder, and sleep disorders remained significantly increased in all of the stratified follow-up durations (0–1, 1–5, ≥5 y) (Lee et al., 2015) (Figure 1).

The potential of probiotics in the treatment of mood disorders

The term ‘probiotics’ was first introduced to describe the organic and inorganic food supplements applied to restore health in patients suffering from malnutrition (FAO, 2001). Contrasting antibiotics, probiotics were defined as microbial derived factors that stimulate the growth of other microorganisms (FAO, 2001). In 1989, a novel definition for probiotics was suggested that has been widely used up to today: ‘A live microbial feed supplement which beneficially affects the host animal by improving its intestinal microbial balance’. In contrast, ‘prebiotics’ refers to

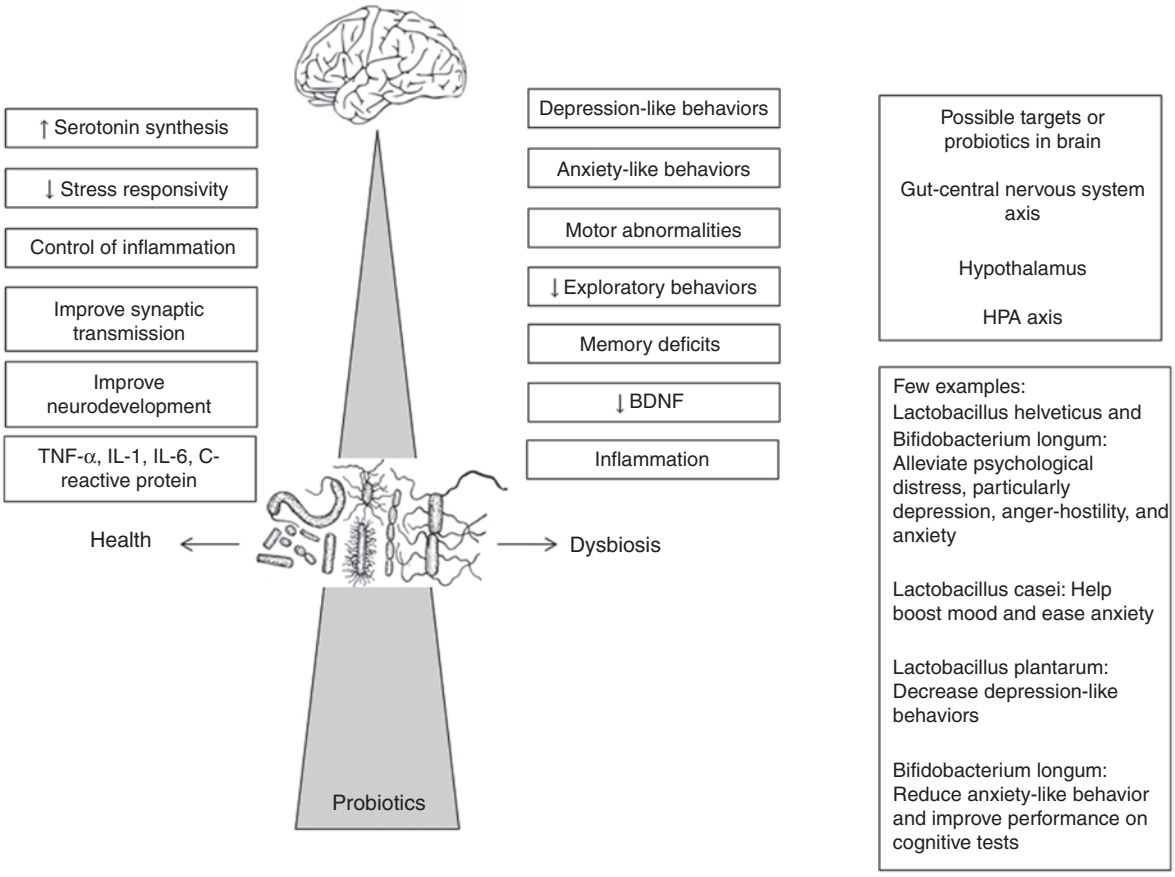

Figure 1: Schematic representation of gut-brain axis and microbiota in mood disorders.

chemicals, e.g. nondigestible fibers, that can facilitate proliferation or activity of bacteria in the GI trait (Schloss et al., 2014).

Probiotics are generally considered to be safe and are usually composed of bacteria that are already present in the digestive system. Probiotics are present in foods such as yogurt, and they are also available as dietary supplements. The mechanism of action of probiotics is exerted by one of the three means: (i) modulation of the content of gut microbiota, (ii) maintenance of the integrity of the gut barrier, or (iii) prevention of bacterial translocation and modulation of the local immune response by the gut-associated immune system (Teitelbaum and Walker, 2002).

Many clinical studies have suggested that probiotic therapy can help to treat many diseases and that it might delay the development of some pathologies, such as allergies in children (Azad et al., 2013), diarrhea, bacterial vaginosis, IBS, among others, although data are not very consistent and studies are still clearly limited (Toh et al., 2012; Hempel, 2014; Parma et al., 2014). Although probiotics are considered safe for most otherwise healthy individuals with mood disorders, short-term side effects may occur and generally include mild gas and bloating. But we should keep in mind that, at least in theory, probiotics could, in some susceptible individuals, promote overstimulation of immune system. On the other hand, in immune-deficient or immune-suppressed people, probiotics safety is not supported by evidence (Tralau et al., 2015).

Several actions of probiotics may represent opportunities for treatment of mood disorders.

Neurotrophic effects of probiotics

Mood disorders are well established as states of deficit in production and activity of neurotrophins, especially in the BDNF (Fernandes et al., 2011; Polyakova et al., 2015). In that sense, interventions that were able to increase BDNF might be potentially useful, a hypothesis corroborated by the effect of enhancement of the activity of this neurotrophin with several effective therapies for mood disorders, including antidepressants, lithium, and electroconvulsive therapy (Kodomari et al., 2009; Brunoni

et al., 2014; Duclot and Kabbaj, 2015). There is some evidence of a relationship between changes in microbiota and alterations in BDNF levels. For example, the oral administration of bifidobacterium to rats was associated with an increase in the hippocampal BDNF (Bercik et al., 2011; O'Sullivan et al., 2011). In addition, administration of antimicrobials that elevate the levels of intrinsic gut Lactobacilli also increases brain BDNF concentrations in mice (Bercik et al., 2011; Savignac et al., 2013). Administration of prebiotics also has been suggested to impact BDNF. One study reported that administration of fructo-oligosaccharides and galacto-oligosaccharides to rats increases hippocampal and peripheral BDNF (Savignac et al., 2013).

In a recent study, Liang et al. (2015) submitted adult specific pathogen free Sprague-Dawley rats to 21 days of restraint stress followed by behavioral testing (including the sucrose preference test, elevated-plus maze test, open-field test, object recognition test, and object placement test) and biochemical analysis. Supplemental *Lactobacillus helveticus NS8* was provided every day during stress until the end of experiment, and the selective serotonin reuptake inhibitor citalopram was used as a positive control. In this study, *L. helveticus NS8* improved chronic restraint stress-induced behavioral (anxiety and depression) and cognitive dysfunction, showing an effect similar to and stronger than that of citalopram. *Lactobacillus helveticus NS8* also resulted in higher hippocampal BDNF mRNA expression compared with the group of chronic stress rats that did not received the probiotic. Taken together, these data suggested a possible effect of prebiotics and probiotics on BDNF, mainly in the hippocampus, that could be potentially be useful in the treatment of mood disorders.

Immune effects of probiotics

Strong evidence has shown a contribution of microbiota in immune system, such as the development of gut-associated lymphoid tissues (GALTs), which are often recognized as the 'GI tract's immune system', a set of immune responses specific to prevention of invasion for pathogens (Hooper and Macpherson, 2010; Stecher and Hardt, 2011; Renz et al., 2012). A complex interaction between the host immune system and the presence of bacteria is necessary for intestinal homeostasis. An imbalance in this symbiotic relationship between the host and intestinal microbiota may be associated with increased diseases (Littman and Pamer, 2011).

Murine studies led to the observation that intestinal microbiota is necessary for the normal GALT maturation, including Peyer's patches, plasters crypt, and isolated lymphoid follicles (ILFS) (Gordon et al., 1966; Hamada et al., 2002; Bouskra et al., 2008). In germ-free mice, the development of Peyer plates seemed to suffer less influence of microbiota; however, the maturation of ILFS and crypts requires this stimulation. The incomplete development of these structures may lead to a change in several receptors responsible for identifying bacterial stimuli (Bouskra et al., 2008).

Probiotics have a well-demonstrate effect in enhancing local humoral immune responses and guarantee the integrity of the intestinal barrier (Isolauri et al., 1993). On the other hand, probiotics may help the immune system to down-regulate responses to nonpathogenic or even harmful bacteria, preventing hypersensitivity reactions (Sütas et al., 1996). The probiotic effects also seem to not be restricted to a local action. One study with the oral administration of *Lactobacillus rhamnosus* GG (ATCC 53103) has shown an effect in reducing the abnormally elevated fecal concentrations of tumor necrosis factor-alpha in patients with allergic conditions (Majarmaa and Isolauri, 1997). In addition, probiotic genes can also modulate host immune response. For example, in one study assessing 42 *Lactobacillus plantarum* strains, six genes with immunomodulatory properties were identified. Deletion of these genes in *L. plantarum* resulted in abolishing the capacity to stimulate production of interleukin-10 and interleukin-12 (van Hemert et al., 2010). In this sense, the modification of the bacterial genome may be a possible approach to improve the regulatory effects of probiotics.

Effects of probiotics in HPA activity

Exposure to psychological stress leads to activation of the HPA axis and causes altered intestinal barrier function, intestinal dysbiosis, and behavioral changes. A few set of studies assessed the effects of probiotic administration in the HPA axis. Gareau et al. (2007) demonstrated that probiotic administration to rats that were further submitted to maternal separation was able to prevent HPA axis activation, estimated by costicosterone levels. In the same way, Ait-Belgnaoui et al. (2014) observed that preexposure with probiotic formulation attenuated HPA axis and ANS activities in response to water avoidance test, a paradigm for chronic stress. In addition, probiotic pretreatment prevented the water avoidance stress-induced decrease in hippocampal neurogenesis and expression changes in hypothalamic genes involved in synaptic plasticity.

Implications for clinical practice and a research agenda

Although mood disorders are associated with changes in microbiota, very little is already known about how to extract any benefit from administration of probiotics. One of the limitations is the lack of a specific microbiota signature for MDD or BD. Moreover intra- and inter-individuals variation was very high on microbiota, and it is possible to identify deviant colonization using sophisticated bioinformatics tools.

A number of attempts to manipulate the microbiota have not produced identical results for every disease, most probably because the most effective interventions are not in adulthood, when the brain and the immunological system are already mature (Ianiro et al., 2014). In fact, constant antigenic stimulation shaping up the physiological immune response of the host is necessary to provide adequate formation of the CNS (Anderson et al., 2012). Abnormal expression and concentration of several neuropeptides in both CNS and periphery have been reported in eating disorders, major depression, and sleep disorders, suggesting that altered peptidergic signaling may be involved in their pathophysiology (Fetissov and Déchelotte, 2011). Moreover, reactive immunoglobulins against these neuropeptides have been identified in humans, and their levels or affinities were associated with neuropsychiatric conditions (Hsiao et al., 2013).

Gut microbiota possibly behave as a dynamic entity, influencing and being influenced by genetic factors both from bacteria and the host, age, food, environment, antigen exposition, and antibiotic exposition. For now, it is recommended that psychiatrists be aware of the patient's diet and be prepared to incorporate new tools from microbiology, genetics, and bioinformatics to research in mood disorders.

Acknowledgments: The authors acknowledge support from coordination of the Improvement of Higher Education Personnel (CAPES) and National Council of Technological and Scientific Development (CNPq), Brazil.

References

Ait-Belgnaoui, A., Durand, H., Cartier, C., Chaumaz, G., Eutamene, H., Ferrier, L., Houdeau, E., Fioramonti, J., Bueno, L., and Theodorou, V. (2012). Prevention of gut leakiness by a probiotic treatment leads to attenuated HPA response to an acute psychological stress in rats. Psychoneuroendocrinology *37*, 1885–1895.

Ait-Belgnaoui, A., Colom, A., Braniste, V., Ramalho, L., Marrot, A., Cartier, C., Houdeau, E., Theodorou, V., and Tompkins, T. (2014). Probiotic gut effect prevents the chronic psychological stress-induced brain activity abnormality in mice. Neurogastroenterol. Motil. *26*, 510–520.

Alsaif, M., Haenisch, F., Guest, P.C., Rahmoune, H., and Bahn, S. (2013). Challenges in drug target discovery in bipolar disorder. Expert Opin. Ther. Targets *17*, 565–577.

Alverdy, J., Gilbert, J., DeFazio, J.R., Sadowsky, M.J., Chang, E.B., Morowitz, M.J., and Teitelbaum, D.H. (2014). Proceedings of the 2013 A.S.P.E.N. Research workshop: the interface between nutrition and the gut microbiome: implications and applications for human health [corrected]. J. Parenter. Enteral Nutr. *38*, 167–178.

Anderson, I.M., Haddad, P.M., and Scott, J. (2012). Bipolar disorder. Br Med J. *345*, e8508.

Azad, M.B., Coneys, J.G., Kozyrskyj, A.L., Field, C.J., Ramsey, C.D., Becker, A.B., Friesen, C., Abou-Setta, A.M., and Zarychanski, R. (2013). Probiotic supplementation during pregnancy or infancy for the prevention of asthma and wheeze: systematic review and meta-analysis. Br. Med. J. *347*, f6471.

Barbara, G., Stanghellini, V., Cremon, C., De Giorgio, R., Gargano, L., Cogliandro, R., Pallotti, F., and Corinaldesi, R. (2008). Probiotics and irritable bowel syndrome: rationale and clinical evidence for their use. J. Clin. Gastroenterol. *42*, S214–S217.

Barseghyan, K.A., Alchujyan, N.K., Aghababova, A.A., Movsesyan, N.H., Avagyan, H.K., Movsesyan, H.A., Melkonyan, L.H., Hayrapetyan, H.L., Guevorkyan, A.G., and Kevorkian, G.A. (2013). Chronic stress-induced depression-like behavior of rats accompanied by microbial translocation the blood-brain barrier and persistent activation the inducible nitric oxide synthase in mitochondria of cortico-limbic brain. Eur. Chem. Bull. *2*, 373–382.

Bercik, P., Denou, E., Collins, J., Jackson, W., Lu, J., Jury, J., Deng, Y., Blennerhassett, P., Macri, J., McCoy, K.D., et al. (2011). The intestinal microbiota affect central levels of brain-derived neurotropic factor and behavior in mice. Gastroenterology *141*, 599–609.

Bested, A.C., Logan, A.C., and Selhub, E.M. (2013). Intestinal microbiota, probiotics and mental health: from Metchnikoff to modern advances: part I – autointoxication revisited. Gut Pathog. *5*, 5.

Biedermann, L. and Rogler, G. (2015). The intestinal microbiota: its role in health and disease. Eur. J. Pediatr. *174*, 151–167.

Borre, Y.E., O'Keeffe, G.W., Clarke, G., Stanton, C., Dinan, T.G., and Cryan, J.F. (2014). Microbiota and neurodevelopmental windows: implications for brain disorders. Trends Mol. Med. *20*, 509–518.

Bouskra, D., Brézillon, C., Bérard, M., Werts, C., Varona, R., Boneca, I.G., and Eberl, G. (2008). Lymphoid tissue genesis induced by commensals through NOD1 regulates intestinal homeostasis. Nature *456*, 507–510.

Bravo, J.A., Julio-Pieper, M., Forsythe, P., Kunze, W., Dinan, T.G., Bienenstock, J., and Cryan, J.F. (2012). Communication between gastrointestinal bacteria and the nervous system. Curr. Opin. Pharmacol. *12*, 667–672.

Brietzke, E. and Kapczinski, F. (2008). TNF-alpha as a molecular target in bipolar disorder. Prog. Neuropsychopharmacol. Biol. Psychiatry *32*, 1355–1361.

Brietzke, E., Stabellini, R., Grassi-Oliveira, R., and Lafer, B. (2011). Cytokines in bipolar disorder: recent findings, deleterious

effects but promise for future therapeutics. CNS Spectr. *16*, 157–168.

Brunoni, A.R., Baeken, C., Machado-Vieira, R., Gattaz, W.F., and Vanderhasselt, M.A. (2014). BDNF blood levels after electroconvulsive therapy in patients with mood disorders: a systematic review and meta-analysis. World J. Biol. Psychiatry *15*, 411–418.

Cattaneo, A., Macchi, F., Plazzotta, G., Veronica, B., Bocchio-Chiavetto, L., Riva, M.A., and Pariante, C. M. (2015). Inflammation and neuronal plasticity: a link between childhood trauma and depression pathogenesis. Front. Cell Neurosci. *9*, 40.

Cerri, A.P., Arosio, B., Viazzoli, C., Confalonieri, R., Vergani, C., and Annoni, G. (2010). The -308 (G/A) single nucleotide polymorphism in the TNF-α gene and the risk of major depression in the elderly. Int. J. Geriatr. Psychiatry *25*, 219–223.

Collins, P.Y., Patel, V., Joestl, S.S., March, D., Insel, T.R., Daar, A.S., and on behalf of the Scientific Advisory Board and the Executive Committee of the Grand Challenges on Global Mental Health (2011). Grand challenges in global mental health. Nature *475*, 27–30.

Crump, C., Sundquist, K., Winkleby, M.A., and Sundquist, J. (2013). Comorbidities and mortality in bipolar disorder: a Swedish national cohort study. J. Am. Med. Assoc. Psychiatry *70*, 931–939.

Cryan, J.F. and O'Mahony, S.M. (2011). The microbiome-gut-brain axis: from bowel to behavior. Neurogastroenterol Motil. *23*, 187–192.

Czepielewski, L., Daruy Filho, L., Brietzke, E., and Grassi-Oliveira, R. (2013). Bipolar disorder and metabolic syndrome: a systematic review. Rev. Bras. Psiquiatr. *35*, 88–93.

Dantzer, R. (2009). Cytokine, sickness behavior, and depression. Immunol. Allergy Clin. North Am. *29*, 247–264.

Desbonnet, L., Clarke, G., Shanahan, F., Dinan, T.G., and Cryan, J.F. (2014). Microbiota is essential for social development in the mouse. Mol. Psychiatry *19*, 146–148.

Diaz Heijtz, R., Wang, S., Anuar, F., Qian, Y., Björkholm, B., Samuelsson, A., Hibberd, M.L., Forssberg, H., and Pettersson, S. (2011). Normal gut microbiota modulates brain development and behavior. Proc. Natl. Acad. Sci. USA *108*, 3047–3052.

Dodd, S., Maes, M., Anderson, G., Dean, O.M., Moylan, S., and Berk, M. (2013). Putative neuroprotective agents in neuropsychiatric disorders. Prog. Neuropsychopharmacol. Biol. Psychiatry *42*, 135–145.

Dominguez-Bello, M.G., Costello, E.K., Contreras, M., Magris, M., Hidalgo, G., Fierer, N., and Knight, R. (2010). Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. Proc. Natl. Acad. Sci. USA *107*, 11971–11975.

Duclot, F. and Kabbaj, M. (2015). Epigenetic mechanisms underlying the role of brain-derived neurotrophic factor in depression and response to antidepressants. J. Exp. Biol. *218*, 21–31.

Duffy, A., Horrocks, J., Doucette, S., Keown-Stoneman, C., Grof, P., Andreazza, A., and Young, L.T. (2014). Immunological and neurotrophic markers of risk status and illness development in high-risk youth: understanding the neurobiological underpinnings of bipolar disorder. Int. J. Bipolar. Disord. *2*, 29.

FAO (Food and Agriculture Organization). (2001). Probiotics in food. Food Nutr. Pap. *85*, 71.

Fernandes, B.S., Gama, C.S., Ceresér, K.M., Yatham, L.N., Fries, G.R., Colpo, G., de Lucena, D., Kunz, M., Gomes, F.A., and Kapczinski, F. (2011). Brain-derived neurotrophic factor as a state-marker of mood episodes in bipolar disorders: a systematic review and meta-regression analysis. J. Psychiatr. Res. *45*, 995–1004.

Fetissov, S.O. and Déchelotte, P. (2011). The new link between gut-brain axis and neuropsychiatric disorders. Curr. Opin. Clin. Nutr. Metab. Care *14*, 477–482.

Foster, J.A. and McVey Neufeld, K.A. (2013). Gut-brain axis: how the microbiome influences anxiety and depression. Trends Neurosci. *36*, 305–312.

Gareau, M.G., Jury, J., Mac Queen, G., Sherman, P.M., and Perdue, M.H. (2007). Probiotic treatment of rat pups normalises corticosterone release and ameliorates colonic dysfunction induced by maternal separation. Gut *56*, 1522–1528.

Gareau, M.G., Wine, E., Rodrigues, D.M., Cho, J.H., Whary, M.T., Philpott, D.J., Macqueen, G., and Sherman, P.M. (2011). Bacterial infection causes stress-induced memory dysfunction in mice. Gut *60*, 307–317.

Gevers, D., Kugathasan, S., Denson, L.A., Vázquez-Baeza, Y., Van Treuren, W., Ren, B., Schwager, E., Knights, D., Song, S.J., Yassour, M., et al., (2014). The treatment-naive microbiome in new-onset Crohn's disease. Cell Host Microbe *15*, 382–392.

Goehler, L.E., Gaykema, R.P.A., Opitz, N., Reddaway, R., Badr, N., and Lyte, M. (2005). Activation in vagal afferents and central autonomic pathways: early responses to intestinal infection with *Campylobacter jejuni*. Brain Behav. Immun. *19*, 334–344.

Gordon, H.A., Bruckner-Kardoss, E., and Wostmann, B.S. (1966). Aging in germ-free mice: life tables and lesions observed at natural death. J. Gerontol. *21*, 380–387.

Hamada, H., Hiroi, T., Nishiyama, Y., Takahashi, H., Masunaga, Y., Hachimura, S., Kaminogawa, S., Takahashi-Iwanaga, H., Iwanaga, T., Kiyono, H., et al. (2002). Identification of multiple isolated lymphoid follicles on the antimesenteric wall of the mouse small intestine. J. Immunol. *168*, 57–64.

Hamdani, N., Daban-Huard, C., Lajnef, M., Richard, J.R., Delavest, M., Godin, O., Le Guen, E., Vederine, F.E., Lépine, J.P., Jamain, S., et al. (2013). Relationship between *Toxoplasma gondii* infection and bipolar disorder in a French sample. J. Affect. Disord. *148*, 444–448.

Hempel, S. (2014). Probiotics for diarrhoea. Indian J. Med. Res. *139*, 339–341.

Hong, P.Y., Lee, B.W., Aw, M., Shek, L.P.C., Yap, G.C., Chua, K.Y., and Liu, W.T. (2010). Comparative analysis of fecal microbiota in infants with and without eczema. PLoS One *5*, e9964.

Hooper, L.V. and Macpherson, A.J. (2010). Immune adaptations that maintain homeostasis with the intestinal microbiota. Nat. Rev. Immunol. *10*, 159–169.

Hsiao, E.Y., McBride, S.W., Hsien, S., Sharon, G., Hyde, E.R., McCue, T., Codelli, J.A., Chow, J., Reisman, S.E., Petrosino, J.F., et al. (2013). Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. Cell *155*, 1451–1463.

Hughes, R., Magee, E.A., and Bingham, S. (2000). Protein degradation in the large intestine: relevance to colorectal cancer. Curr. Issues Intest. Microbiol. *1*, 51–58.

Ianiro, G., Bibbò, S., Gasbarrini, A., and Cammarota, G. (2014). Therapeutic modulation of gut microbiota: current clinical applications and future perspectives. Curr. Drug Targets *15*, 762–770.

Isolauri, E., Majamaa, I.F., Arvola, T., Rantala, I., Virtanen, E., and Arvilommi, H. (1993). Lactobacillus casei strain GG reverses increased intestinal permeability induced by cow milk in suckling rats. Gastroenterology *105*, 1643–1650.

Kodomari, I., Wada, E., Nakamura, S., and Wada, K. (2009). Maternal supply of BDNF to mouse fetal brain through the placenta. Neurochem. Int. *54*, 95–98.

Kriegel, M.A., Sefik, E., Hill, J.A., Wu, H.J., Benoist, C., and Mathis, D. (2011). Naturally transmitted segmented filamentous bacteria segregate with diabetes protection in nonobese diabetic mice. Proc. Natl. Acad. Sci. USA *108*, 11548–11553.

Leclerc, E., Mansur, R.B., and Brietzke, E. (2013). Determinants of adherence to treatment in bipolar disorder: a comprehensive review. J. Affect. Disord. *149*, 247–252.

Lee, Y.T., Hu, L.Y., Shen, C.C., Huang, M.W., Tsai, S.J., Yang, A.C., Hu, C.K., Perng, C.L., Huang, Y.S., and Hung, J.H. (2015). Risk of psychiatric disorders following irritable bowel syndrome: a nationwide population-based cohort study. PLoS One *10*, e0133283.

Ley, R.E., Hamady, M., Lozupone, C., Turnbaugh, P.J., Ramey, R.R., Bircher, J.S., Schlegel, M.L., Tucker, T.A., Schrenzel, M.D., Knight, R., et al. (2008). Evolution of mammals and their gut microbes. Science *320*, 1647–1651.

Liang, S., Wang, T., Hu, X., Luo, J., Li, W., Wu, X., Duan, Y., and Jin, F. (2015). Administration of *Lactobacillus helveticus* NS8 improves behavioral, cognitive, and biochemical aberrations caused by chronic restraint stress. Neuroscience *310*, 561–577.

Littman, D.R. and Pamer, E.G. (2011). Role of the commensal microbiota in normal and pathogenic host immune responses. Cell Host Microbe *10*, 311–323.

Lukens, J.R., Gurung, P., Vogel, P., Johnson, G.R., Carter, R.A., McGoldrick, D. J., Bandi, S.R., Calabrese, C.R., Vande Walle, L., Lamkanfi, M., et al. (2014). Dietary modulation of the microbiome affects autoinflammatory disease. Nature *516*, 246–249.

Maes, M., Kubera, M., Leunis, J.C., and Berk, M. (2012a). Increased IgA and IgM responses against gut commensals in chronic depression: further evidence for increased bacterial translocation or leaky gut. J. Affect. Disord. *141*, 55–62.

Maes, M., Twisk, F.N.M., Kubera, M., Ringel, K., Leunis, J.C., and Geffard, M. (2012b). Increased IgA responses to the LPS of commensal bacteria is associated with inflammation and activation of cell-mediated immunity in chronic fatigue syndrome. J. Affect. Disord. *136*, 909–917.

Majarmaa, H. and Isolauri, E. (1997). Probiotics: a novel approach in the management of food allergy. J. Allergy Clin. Immunol. *99*, 179–186.

Mansur, R.B., Cha, D.S., Asevedo, E., McIntyre, R.S., and Brietzke, E. (2013). Selfish brain and neuroprogression in bipolar disorder. Prog. Neuropsychopharmacol. Biol. Psychiatry *43*, 66–71.

Mansur, R.B., Brietzke, E., and McIntyre, R.S. (2015). Is there a 'metabolic-mood syndrome'? a review of the relationship between obesity and mood disorders. Neurosci. Biobehav. Rev. *52*, 89–104.

Maurya, P.K., Noto, C., Rizzo, L.B., Rios, A.C., Nunes, S.O., Barbosa, D.S., Sethi, S., Zeni, M., Mansur, R.B., Maes, M., et al. (2016). The role of oxidative and nitrosative stress in accelerated aging and major depressive disorder. Prog. Neuropsychopharmacol. Biol. Psychiatry *65*, 134–144.

Modabbernia, A., Taslimi, S., Brietzke, E., and Ashrafi, M. (2013). Cytokine alterations in bipolar disorder: a meta-analysis of 30 studies. Biol. Psychiatry *74*, 15–25.

Morgan, X.C., Tickle, T.L., Sokol, H., Gevers, D., Devaney, K.L., Ward, D.V., Reyes, J.A., Shah, S.A., LeLeiko, N., Snapper, S.B., et al. (2012). Dysfunction of the intestinal microbiome in inflammatory bowel disease and treatment. Genome Biol. *13*, R79.

Nakayama, J., Kobayashi, T., Tanaka, S., Korenori, Y., Tateyama, A., Sakamoto, N., Kiyohara, C., Shirakawa, T., and Sonomoto, K. (2011). Aberrant structures of fecal bacterial community in allergic infants profiled by 16S rRNA gene pyrosequencing. FEMS Immunol. Med. Microbiol. *63*, 397–406.

Naseribafrouei, A., Hestad, K., Avershina, E., Sekelja, M., Linløkken, A., Wilson, R., and Rudi, K. (2014). Correlation between the human fecal microbiota and depression. Neurogastroenterol. Motil. *26*, 1155–1162.

Neufeld, K.A. and Foster, J.A. (2009). Effects of gut microbiota on the brain: implications for psychiatry. J. Psychiatry Neurosci. *34*,230–231.

Neufeld, K.M., Kang, N., Bienenstock, J., and Foster, J.A. (2011). Reduced anxiety-like behavior and central neurochemical change in germ-free mice. Neurogastroenterol. Motil. *23*, 255–264, e119.

Noto, C., Rizzo, L.B., Mansur, R.B., McIntyre, R.S., Maes, M., and Brietzke, E. (2014). Targeting the inflammatory pathway as a therapeutic tool for major depression. Neuroimmunomodulation *21*, 131–139.

O'Mahony, S.M., Clarke, G., Borre, Y.E., Dinan, T.G., and Cryan, J.F. (2014). Serotonin, Tryptophan metabolism and the brain-gut-microbiome axis. Behav. Brain Res. *277*, 32–48.

O'Sullivan, E., Barrett, E., Grenham, S., Fitzgerald, P., Stanton, C., Ross, R.P., Quigley, E.M., Cryan, J.F., and Dinan, T.G. (2011). BDNF expression in the hippocampus of maternally separated rats: does *Bifidobacterium breve* 6330 alter BDNF levels? Benef. Microbes. *2*, 199–207.

Park, A.J., Collins, J., Blennerhassett, P.A., Ghia, J.E., Verdu, E.F., Bercik, P., and Collins, S. M. (2013). Altered colonic function and microbiota profile in a mouse model of chronic depression. Neurogastroenterol. Motil. *25*, 733–e575.

Parma, M., Stella Vanni, V., Bertini, M., and Candiani, M. (2014). Probiotics in the prevention of recurrences of bacterial vaginosis. Altern. Ther. Health Med. *20*, 52–57.

Patel, J.P. and Frey, B.N. (2015). Disruption in the blood-brain barrier: the missing link between brain and body inflammation in bipolar disorder? Neural Plast. *2015*, 708306.

Pérez-Losada, M., Castro-Nallar, E., Bendall, M.L., Freishtat, R.J., and Crandall, K.A. (2015). Dual transcriptomic profiling of host and microbiota during health and disease in pediatric asthma. PLoS One *10*, e0131819.

Perron, B.E., Howard, M.O., Nienhuis, J.K., Bauer, M.S., Woodward, A.T., and Kilbourne, A.M. (2009). Prevalence and burden of general medical conditions among adults with bipolar I disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions. J. Clin. Psychiatry *70*, 1407–1415.

Polyakova, M., Schroeter, M.L., Elzinga, B.M., Holiga, S., Schoenknecht, P., de Kloet, E.R., and Molendijk, M.L. (2015). Brain-derived neurotrophic factor and antidepressive effect of electroconvulsive therapy: systematic review and meta-analyses of the preclinical and clinical literature. PLoS One *10*, e0141564.

Pyndt J. B., Hansen, J.T., Krych, L., Larsen, C., Klein, A.B., Nielsen, D.S., Josefsen, K., Hansen, A.K., and Sørensen, D.B. (2014). A possible link between food and mood: dietary impact on

gut microbiota and behavior in BALB/c mice. PLoS One *9*, e103398.

Rafiei, A., Hosseini, S.H., Taheri, M., Hosseni-khah, Z., Hajilooi, M., and Mazaheri, Z. (2013). Influence of IL-1RN intron 2 variable number of tandem repeats (VNTR) polymorphism on bipolar disorder. Neuropsychobiology *67*, 116–121.

Renz, H., Brandtzaeg, P., and Hornef, M. (2012). The impact of perinatal immune development on mucosal homeostasis and chronic inflammation. Nat. Rev. Immunol. *12*, 9–23.

Rizzo, L.B., Costa, L.G., Mansur, R.B., Swardfager, W., Belangero, S.I., Grassi-Oliveira, R., McIntyre, R.S., Bauer, M.E., and Brietzke, E. (2014). The theory of bipolar disorder as an illness of accelerated aging: implications for clinical care and research. Neurosci. Biobehav. Rev. *42*, 157–169.

Rook, G.A.W., Raison, C.L., and Lowry, C.A. (2014). Microbiota, immunoregulatory old friends and psychiatric disorders. Adv. Exp. Med. Biol. *817*, 319–356.

Savignac, H.M., Corona, G., Mills, H., Chen, L., Spencer, J.P.E., Tzortzis, G., and Burnet, P.W. (2013). Prebiotic feeding elevates central brain derived neurotrophic factor, *N*-methyl-D-aspartate receptor subunits and D-serine. Neurochem. Int. *63*, 756–764.

Scher, J.U. and Abramson, S.B. (2011). The microbiome and rheumatoid arthritis. Nat. Rev. Rheumatol. *7*, 569–578.

Schloss, P.D., Iverson, K.D., Petrosino, J.F., and Schloss, S.J. (2014). The dynamics of a family's gut microbiota reveal variations on a theme. Microbiome *2*, 25.

Severance, E.G., Dupont, D., Dickerson, F.B., Stallings, C.R., Origoni, A.E., Krivogorsky, B., Yang, S., Haasnoot, W., and Yolken, R.H. (2010). Immune activation by casein dietary antigens in bipolar disorder. Bipolar Disord. *12*, 834–842.

Severance, E.G., Gressitt, K.L., Yang, S., Stallings, C.R., Origoni, A.E., Vaughan, C., Khushalani, S., Alaedini, A., Dickerson, F.B., and Yolken, R.H. (2014). Seroreactive marker for inflammatory bowel disease and associations with antibodies to dietary proteins in bipolar disorder. Bipolar Disord. *16*, 230–240.

Severance, E.G., Prandovszky, E., Castiglione, J., and Yolken, R.H. (2015). Gastroenterology issues in schizophrenia: why the gut matters. Curr. Psychiatry Rep. *17*, 27.

Sharma, R., Kapila, R., Dass, G., and Kapila, S. (2014). Improvement in Th1/Th2 immune homeostasis, antioxidative status and resistance to pathogenic *E. coli* on consumption of probiotic *Lactobacillus rhamnosus* fermented milk in aging mice. Age (Dordr) *36*, 9686.

Smith, K., McCoy, K.D., and Macpherson, A.J. (2007). Use of axenic animals in studying the adaptation of mammals to their commensal intestinal microbiota. Semin. Immunol. *19*, 59–69.

Soczynska, J.K., Kennedy, S.H., Goldstein, B.I., Lachowski, A., Woldeyohannes, H.O., and McIntyre, R.S. (2009). The effect of tumor necrosis factor antagonists on mood and mental health-associated quality of life: novel hypothesis-driven treatments for bipolar depression? Neurotoxicology *30*, 497–521.

Stecher, B. and Hardt, W.D. (2011). Mechanisms controlling pathogen colonization of the gut. Curr. Opin. Microbiol. *14*, 82–91.

Steiner, J. and Bogerts, B. (2015). N-Methyl-d-aspartate receptor autoantibodies in schizophrenia and affective disorders. Schizophr. Res. *162*, 291.

Sudo, N., Chida, Y., Aiba, Y., Sonoda, J., Oyama, N., Yu, X.N., Kubo, C., and Koga, Y. (2004). Postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response in mice. J. Physiol. *558*, 263–275.

Suez, J., Korem, T., Zeevi, D., Zilberman-Schapira, G., Thaiss, C.A., Maza, O., Israeli, D., Zmora, N., Gilad, S., Weinberger, A., et al. (2014). Artificial sweeteners induce glucose intolerance by altering the gut microbiota. Nature *514*, 181–186.

Sun, J. and Chang, E.B. (2014). Exploring gut microbes in human health and disease: pushing the envelope. Genes Dis. *1*, 132–139.

Sütas, Y., Soppi, E., Korhonen, H., Syväoja, E. L., Saxelin, M., Rokka, T., and Isolauri, E. (1996). Suppression of lymphocyte proliferation *in vitro* by bovine caseins hydrolyzed with *Lactobacillus casei* GG-derived enzymes. J. Allergy Clin. Immunol. *98*, 216–224.

Teitelbaum, J.E. and Walker, W.A. (2002). Nutritional impact of pre- and probiotics as protective gastrointestinal organisms. Annu. Rev. Nutr. *22*, 107–138.

Toh, Z.Q., Anzela, A., Tang, M.L.K., and Licciardi, P.V. (2012). Probiotic therapy as a novel approach for allergic disease. Front. Pharmacol. *3*, 171.

Tondo, L., Vázquez, G.H., and Baldessarini, R.J. (2014). Options for pharmacological treatment of refractory bipolar depression. Curr. Psychiatry. Rep. *16*, 431.

Tralau, T., Sowada, J., and Luch, A. (2015). Insights on the human microbiome and its xenobiotic metabolism: what is known about its effects on human physiology? Expert Opin. Drug Metab. Toxicol. *11*, 411–425.

van Hemert, S., Meijerink, M., Molenaar, D., Bron, P.A., de Vos, P., Kleerebezem, M., Wells, J.M., and Marco, M.L. (2010). Identification of *Lactobacillus plantarum* genes modulating the cytokine response of human peripheral blood mononuclear cells. BMC Microbiol. *10*, 293.

Wang, Y. and Kasper, L.H. (2014). The role of microbiome in central nervous system disorders. Brain. Behav. Immun. *38*, 1–12.

Wieck, A., Grassi-Oliveira, R., do Prado, C.H., Rizzo, L.B., de Oliveira, A.S., Kommers-Molina, J., Viola, T.W., Marciano Vieira, E.L., Teixeira, A.L., and Bauer, M.E. (2014). Pro-inflammatory cytokines and soluble receptors in response to acute psychosocial stress: differential reactivity in bipolar disorder. Neurosci. Lett. *580*, 17–21.

Wu, H.J., Ivanov, I.I., Darce, J., Hattori, K., Shima, T., Umesaki, Y., Littman, D. R., Benoist, C., and Mathis, D. (2010). Gut-residing segmented filamentous bacteria drive autoimmune arthritis via T helper 17 cells. Immunity *32*, 815–827.