Chapter 22

Inflammation, stress, and gut-brain axis as therapeutic targets in bipolar disorder

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22.1 Introduction

Bipolar disorder (BD) is a highly heterogeneous affective disorder that impacts approximately 1%−2% of the population worldwide (Alonso et al., 2011). While BD is most commonly known for its mood polarities, the astonishingly high rates of medical comorbidity have prompted investigation into a more comprehensive account of BD's pathogenesis. Over half of diagnosed individuals are considered overweight or obese, increasing the likelihood of comorbid disorders such as diabetes, high blood pressure, hyperlipidemia, and digestive ailments (Goldstein et al., 2009; Leboyer et al., 2012). The interaction of medical burden and psychiatric symptoms has been found to be associated, worse treatment outcomes, lower quality of life, and higher mortality rates in BD (Fenn et al., 2005). A considerable portion of patients with BD exhibits a low-grade, persistent activation of the immune system compared to healthy individuals (Berk et al., 2011; Goldstein et al., 2009). Abnormalities in T-cell activation, inflammatory cytokines, and microglial activation suggest wide-spread inflammation at both the periphery and in the brain (Haarman et al., 2014; Rosenblat & McIntyre, 2016). Long-term dysregulation of the immune system may contribute to neuroprogression often observed in late-stage BD. Neuroprogression is characterized by shorter remission intervals between manic and depressive episodes, and has been associated with greater impairments in cognitive and daily functioning and atrophy in brain areas associated with emotion (Bora, Fornito, Yücel, & Pantelis, 2010). As such, BD

Biomarkers in Bipolar Disorders. DOI: https://doi.org/10.1016/B978-0-12-821398-8.00008-4

should be conceptualized as a "multisystem inflammatory disease," rather than solely an affective disorder (Leboyer et al., 2012). However, the exact underlying causes of chronic inflammation in BD are unclear. Recent evidence suggests that chronic inflammation may result from an imbalance or "dysbiosis" of the organisms that make up the gastrointestinal (GI) system or "gut microbiota" (Arrieta, Bistritz, & Meddings, 2006). How this process occurs can be understood as an interaction of multiple, complex mechanisms between the gut and immune system.

22.2 Gastrointestinal dysfunction and inflammation

The GI system plays a vital role in digestion, liquid retention, and waste excretion (Collatz, 1987; Morton, 1967; Svihus, 2014). The intestinal epithelium is a defensive barrier, essential for a properly functioning digestive tract, which restricts the passage of microorganisms and pathogens from the lumen, the most internal region of the intestine, into the lamina propria (Hollander, 1999) (Fig. 22.1A). In addition to providing physical structure to the intestines, the lamina propria contains various immune cells and lymphocytes and serves a vital role in immune system functioning (Hollander, 1999). When the delicate balance of the GI system becomes compromised due to disease, inflammation, or dysbiosis, the lipid membrane and tight junctions of the epithelium can become disrupted, thereby increasing GI barrier permeability (Arrieta et al., 2006). The increased permeability causes the barrier to become less selective than it would typically be in a healthy state, allowing an influx of gut microbes out through the mucosal immune system of the lamina propria and into systemic circulation. This process is known as "translocation" and can trigger an inflammatory reaction in response to the introduced pathogens (Nagpal & Yadav, 2017) (Fig. 22.1B). Gastroenterologists commonly use translocation markers as a diagnostic tool in GI disorders, such as irritable bowel syndrome (IBS) and irritable bowel disease (IBD) (Vrakas et al., 2017). Crohn's disease, for example, is detected through antibody secretion to *Saccharomyces cerevisiae*, a yeast usually found in the gut. The presence of anti-*S. cerevisiae* antibodies would confirm that this yeast is circulating in the blood (Desplat-Jégo et al., 2007).

22.3 Gastrointestinal dysfunction in psychiatric disorders

In 1931 G.W. Henry was one of the first to speculate an association between GI functioning and mental illness. In his case report summaries, he identified disturbances in gut motility in patients who were depressed or manic (Henry, 1931). Two decades later in 1954, Buscaino highlighted an increased prevalence of GI disorders, ranging from 50% to as high as 90%, in patients with schizophrenia (Buscaino, 1953). Today, epidemiological evidence indicates multiple GI disorders, including Crohn's disease (Loftus et al., 2011), colon

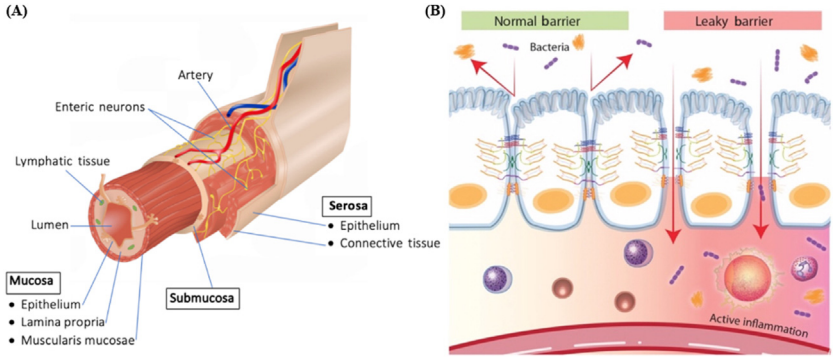

FIGURE 22.1 (A) Diagram of the gastrointestinal tract layers. Starting at the innermost layer, the mucosa lines the lumen of the digestive system. The epithelium, lamina propria, and a layer of smooth muscle called the muscularis mucosae comprise this layer. The epithelium serves as a barrier between the luminal contents and the lamina propria, containing most of this system's lymphatic tissue. The submucosa surrounds the mucosa and consists of a thick layer of loose connective tissue. This layer also contains glands, blood vessels, and nerves. Between the submucosa and the outmost layer (serosa) are additional smooth muscle layers, which via innervation of the enteric neurons, are responsible for sensory and motor functions of the digestive tract. (B) Normal versus impaired barrier function. In a healthy state, tight junctions and other important components maintain the integrity of the epithelial cells, creating a highly selective barrier. In states of gut dysbiosis, the intestinal epithelium may become compromised. Translocation of toxins, viruses, and bacteria can occur, resulting in an immune response and consequent inflammation. Disruption of the intestinal barrier or "leaky gut" may result in the development of chronic inflammation and disease. *Data from (A) "Layers of the GI Tract Unlabeled.jpg" by Goran tek-en is licensed under CC BY-SA 3.0 and (B) Stewart, A. S., Pratt-Phillips, S., & Gonzalez, L. M. (2017). Alterations in intestinal permeability: The role of the "leaky gut" in health and disease. Journal of Equine Veterinary Science, 52, 10–22.*

cancer (Hippisley-Cox et al., 2007), and celiac disease (Kalaydjian et al., 2006), to be highly comorbid with psychiatric diseases. IBS commonly cooccurs with mood and anxiety disorders (Lee et al., 2009; Mykletun et al., 2010), obsessive-compulsive disorder (Masand et al., 2006), and BD (Tseng et al., 2016). Several brain imaging studies suggest dysfunctional attention, emotion, and pain networks in patients with IBS (Blankstein, Chen, Diamant, & Davis, 2010; Labus et al. 2009, 2013). A large national cohort study revealed that the prevalence of BD was higher among individuals diagnosed with IBS than in matched controls (incidence rate ratio 2.44), over an 11-year follow-up period (Lee et al., 2015). Strikingly, the presence of chronic GI disorders is among the strongest predictors of mortality in patients with schizophrenia and BD (Dickerson et al., 2016).

Microbial translocation resulting from a compromised intestinal barrier or "leaky gut," may partially explain why a subset of patients with psychiatric illness exhibit GI symptoms. Studies by Severance and colleagues have shown increased levels of circulating gut yeasts antibodies, *Saccharomyces*

cerevisiae and *Candida albicans*, in BD and schizophrenia (Severance et al., 2012, 2016). Specifically, *S. cerevisiae* antibodies were associated with recent onset of schizophrenia (Severance et al., 2012), whereas *C. albicans* antibodies were associated with GI disorder comorbidity, homelessness, and worse cognitive performance in BD (Severance et al., 2016). Translocation is believed to drive a peripheral proinflammatory state and can have deleterious consequences for the brain (Brenchley et al., 2006; Klatt et al., 2010). The microvasculature structure of the central nervous system (CNS), referred to as the blood–brain barrier (BBB), tightly regulates CNS homeostasis. Disruption of the BBB allows pathogens to enter the CNS, causing neurotoxic effects and further inflammation (Abbott, 2000). Systemic circulation of gut-derived lipopolysaccharide (LPS), is a potent activator of the immune system and is linked to BBB disruption. For example, chronically elevated LPS is associated with alteration in BBB endothelial cell metabolism and elevations of reactive oxygen and nitrogen species (Morris et al., 2018). Although most transient inflammatory states do not cause disruptive BBB changes, chronic inflammation can lead to neurotoxicity, thereby speeding up neuronal loss and gray matter atrophy (Zipp & Aktas, 2006).

Despite the evident overlap between GI dysfunction and mental illness, it is challenging to determine the directionality of this relationship or conclude any causality. A plausible explanation may be that lifestyle factors, inflammation, and psychiatric disease synergistically interact to increase the risk for cognitive impairment, illness, and mortality (Depp, Dev, & Eyler, 2016). Burgeoning research has demonstrated that the microorganisms that reside within the human gut play a crucial role in maintaining intestinal barrier function (Di Mauro et al., 2013; Kelly et al., 2015; Natividad & Verdu, 2013). In spite of early scientific interest in how the GI tract might influence mood and behavioral disorders, the role of the gut microbiome, has been elusive, due to technical challenges in studying unculturable microorganisms (Pace, 1997; Qin et al., 2010; Sogin, Sogin, & Woese, 1972; Woese & Fox, 1977). However, recent technological advances and the advent of high-throughput, next-generation sequencing techniques have allowed for a more detailed understanding of the intestinal microbiota in human physical and mental health and behavior.

22.4 What is the human gut microbiota?

The human microbiome consists of diverse microorganisms such as bacteria, fungi, archaea, microbial eukaryotes, viruses, and their corresponding genes (Marchesi & Ravel, 2015). These organisms can be found in abundance throughout the human body, including skin, mouth, nose, lung, stomach, intestine, and vagina (Wilson, 2005). With the largest concentration residing in the large intestine (Saxena & Sharma, 2016). Current estimates suggest there are over 10^3 microorganisms with at least 1000 unique bacterial species

in the gut (Zhu, Wang, & Li, 2010). In fact, the number of bacterial cells that inhabit the human body is 10 times more abundant than the number of human somatic and germ cells, and the complex genetic structure of the microbiota has approximately 100 times more genes than the human genome (Turnbaugh et al., 2010) (Box 22.1).

Until the moment of birth, mammals are born virtually free of microorganisms. Immediately, environmental factors begin to dictate the colonization of specific microbes that will occur. Method of delivery, geographic location, hospitalization, antibiotics, breastfeeding, and feeding rates have all been shown to play a role in determining which bacteria will flourish (Adlerberth, 2008; Dominguez-Bello et al., 2010). Certain bacterial species such as *Escherichia coli, Lactobacillus*, and *Bifidobacterium* with high multiplication rates dominate the gut during early life. As development progresses, the microbiota becomes increasingly diverse and complex, though a few of these taxa remain dominant, such as *Bacteroidetes* and *Firmicutes* (Ley et al., 2008). Each person is believed to have a highly individualized gut microbiota composition (Gilbert et al., 2018; Turnbaugh et al., 2010) that is composed of a relatively stable core microbial community, largely determined by unique genetic profiles (Benson, 2015). However, each person also has a number of bacteria that are flexible and respond to unique environmental perturbations (Clemente et al., 2012) such as diet (Flint et al., 2012), stress (Qin et al., 2010), air quality, and other environmental factors, that continue to shape gut microbiota throughout the lifespan (Salim, Kaplan, & Madsen, 2014).

Humans and their gut microbiota have coevolved and participate in an intimate symbiotic relationship. Commensal microbes and the human host coexist in a shared environment with intricate bidirectional influences. The microorganisms within the gut provide a wide range of benefits to host, including digestion, absorption of nutrients (Turnbaugh & Gordon, 2009), detoxification (Relman, 2012), and maturation of the immune system (Hooper, Littman, & Macpherson, 2012). A mutualistic symbiosis occurs when a mutual benefit between host and microorganisms exists. However, the relationship between humans and their gut microbiome is best described as conditionally mutualistic. There are certain states in which the microbiota may contribute to disease susceptibility, malnutrition, and inflammatory conditions (e.g., IBS) (Chong et al., 2019).

The present understanding of how microbial molecular functions alter host physiology is still under exploration. Nonetheless, the consensus is that classifying gut microorganisms as either "good" or "bad" is overly simplistic. The gut microbiome is a complex ecosystem, and optimal functioning of this ecosystem requires equilibrium (Lozupone et al., 2012). Drawing parallels between the microbiome and other macro ecological systems, pollution, global warming, and resource exploitation can alter the composition of a rainforest or coral reef. Drastic changes in temperature and elimination of

BOX 22.1 Definition of key terms

Terms	Definitions
Microbiota	An assemblage of microorganisms present in a defined environment.
Microbiome	The entire habitat, including the microorganisms (bacteria, archaea, eukaryotes, and viruses, their genomes and the surrounding environmental conditions).
Metagenome	The collection of genomes and genes from the members of a microbiota. Obtained through shotgun sequencing (i.e., metagenomics) of DNA extracted from a sample.
Microbiome-gut-brain axis	Bidirectional communication system between the gastrointestinal tract and the brain. Includes the central nervous system, autonomic nervous system, enteric nervous system, and hypothalamic–pituitary–adrenal axis. Maintains gastrointestinal homeostasis and connects emotional and cognitive centers of the brain with peripheral intestinal functions.
Enteric nervous system	A collection of neurons in the gastrointestinal tract. Represents a division of the autonomic nervous system that governs the functions of the gastrointestinal system. Communicates with the central nervous system via the "microbiome-gut-brain-axis."
Taxonomy	The classification of biological organisms on the basis of shared characteristics. Taxonomic rank is the relative level of a group of organisms (e.g., taxon) in a taxonomic hierarchy. The principal ranks, in order, are kingdom, phylum, class, order, family, genus, species.
Phylogeny	The history or evolution of a group of organisms (e.g., taxa), especially in reference to lines of descent and relationships among broad groups of organisms.
16S ribosomal RNA gene	The marker gene commonly sequenced (e.g., 16s rRNA sequencing) used for taxonomic classification and phylogenetic analysis of microbes. It contains highly conserved regions that are ubiquitous to all bacteria.
Whole genome metagenomic sequencing	A method that involves untargeted sequencing of all microbial genomes present in a sample. Also known as shotgun sequencing.
Operational taxonomic unit	Clusters of organisms that are grouped by similarities in DNA sequence based on 16s rRNA sequencing. Often take the place of "species" in many microbiome analyses because named species genomes are often unavailable for particular marker sequences.
Metabolomics	The large-scale study of the small molecules or metabolites or small molecules produced by microorganisms in the gut.

Alpha-diversity	A measure of within-sample variation and distribution. Captures the organismal richness and evenness of organisms' abundance.
Betadiversity	A measure of between-samples variation. Represents the similarity (or difference) in organismal composition between samples.
Differentially abundant taxa	The difference in the mean relative abundances of taxa between population groups of interest. These taxa are of scientific interest as they may serve as disease biomarkers.
Metabolites	Molecules produced by gut bacteria as a result of anaerobic fermentation of exogenous undigested dietary components that reach the colon as well as endogenous compounds that are generated by microorganisms and the host. Relevant examples include bile acids, short-chain fatty acids, and neurotransmitters.
Bacterial translocation	Process by which bacteria or bacterial products (e.g., lipopolysaccharides) pass through the intestinal epithelium to normally sterile tissues (e.g., lymph nodes and the internal organs). Generally considered as an indicator and outcome of impaired intestinal integrity.
Dysbiosis	A general term describing a condition that occurs when the normal balance of the gut microbiota is disrupted. May be characterized by a diminishing presence of normally dominating species and/or overgrowth of a normally contained species. Chronic imbalances are commonly associated with GI ailments and diseases.
Germ-free and (gnotobiotic) animals	An animal reared in a sterile environment to prevent colonization of bacteria fungi, viruses, and other microorganisms. Allow researchers to introduce known microbial species to study their effects in isolation.
Fecal microbiota transplant	A process of transferring a complete fecal microbiota from a donor to a host. Method used in gnotobiotic animal research studies and as a clinical treatment for some gastrointestinal disorders (e.g., *C. difficile* infection).
Probiotics	Foods or supplements that contain live microorganisms that exert a health benefit.
Prebiotics	Compounds that when fermented in the gut produce specific changes in bacterial composition or activity.
Psychobiotics	A term that refers to a class of probiotics, prebiotics, or any substance that exerts an effect on the brain or behavior that is mediated by the microbiome.

particular plant or animal species can radically alter the overall state or ecology of the rainforest and marine habitat (James, Washington, & Rowell, 2013; Kaiser et al., 2011; Laurance, Goosem, & Laurance, 2009). An adaptive trait of any ecosystem is its stability or resilience to external

perturbations, such as resistance to foreign invasion by pathogenic bacteria (Fukuda et al., 2011) or the ability to return to homeostasis after a stressful event. Ecosystems benefit from the ability to flexibly adapt to change. However, in this case, a state of disease or dysbiosis that is highly resilient and stable is less desirable, posing unique challenges in treating chronic GI ailments (Lozupone et al., 2012).

Modern technological advances have allowed for characterization of the human gut microbiome. Whereas early research relied on culture-dependent techniques, current methods utilize DNA and RNA sequencing to quantify the diversity, identity, and functions of specific microbes. 16s amplicon sequencing methods involve amplification and sequencing of the 16s ribosomal subunit gene. The 16s rRNA gene contains highly conserved regions that are ubiquitous to all bacteria. Due to the slow rate of evolution of this gene, it is a reliable marker for the taxonomic classification and phylogenetic analysis of microbes. Sequences found to be highly similar are grouped together into operational taxonomic unit (OTU) (Tringe & Hugenholtz, 2008), and OTUs are then compared to large 16S databases to allow for phylotype identification. However, 16s sequencing typically only allows for resolution to the genus level, which limits the accuracy and precision of ecological inferences and metabolic reconstruction. Whole genome metagenomic sequencing can profile taxonomic composition and functional pathways with greater depth. Metagenomics can be combined with other *-omics* methods, such as *metabolomics* (characterization of small molecules or metabolites generated by organisms) (Turnbaugh & Gordon, 2008), *metatranscriptomics* (profiling of gene expression of microbes) (Gilbert et al., 2008), and *metaproteomics* (quantification of protein and peptide levels) (Verberkmoes et al., 2009), to shed greater light on how microbial communities function in the human body and contribute to health and disease.

22.5 The microbiome-gut-brain axis

The term "microbiome-gut-brain axis" (MGB axis) denotes the complex bidirectional signaling system between the CNS and GI system (Fig. 22.2). The intricate communication highways between the gut and brain involve neuro-immuno-endocrine mediators, including the CNS, the autonomic nervous system (ANS), the enteric nervous system (ENS), the hypothalamic−pituitary−adrenal axis (HPA), and the metabolites produced by the gut microbiota (Cryan & Dinan, 2012).

The ENS embedded within the walls of the GI system, contains more neurons (200−600 million) than any peripheral organ and can operate independently of the CNS, to some degree. Afferent and efferent nerve fibers provide extensive interaction between the gut and CNS and other organs (Furness et al., 2014). Afferent signals originate in the lumen, pass through the ENS, and travel up the spinal and vagal pathways to the CNS. Efferent

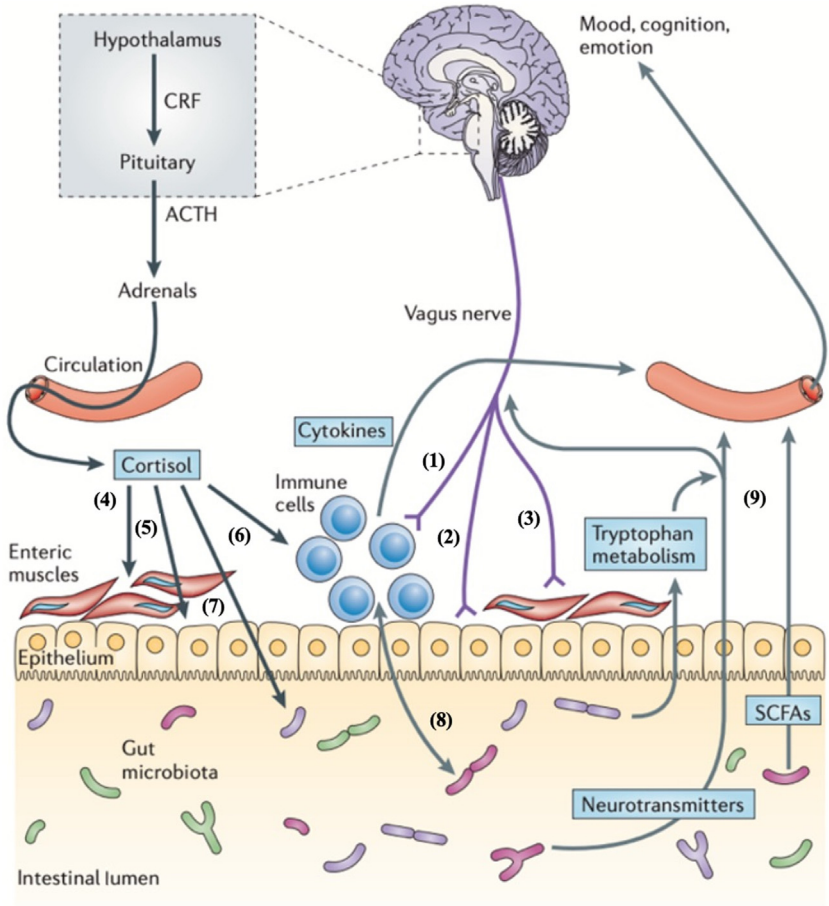

FIGURE 22.2 The microbiota-gut-brain axis. A simplified representation of the crosstalk between the central nervous system and gastrointestinal system. The vagus nerve highlighted as the main cranial nerve, which communicates with the gastrointestinal system via modulation of the (1) immune cells, (2) epithelial barrier, and (3) enteric muscles. Of critical importance is the hypothalamic–pituitary–adrenal axis, which via cortisol secretion, can also modulate (4) enteric muscle function, (5) the epithelial barrier, (6) immune cells, in addition to (7) the direct influence of the microbiota. In turn, the gut and microbiota can alter mood, cognition, and emotion by (8) initiating an immune response and subsequent cytokine production and by (9) neurotransmitter and metabolite secretion and metabolism. *Altered image from Cryan, J. F. & Dinan, T. G. (2012). Mind-altering microorganisms: The impact of the gut microbiota on brain and behaviour. Nature Reviews Neuroscience, 13(10), 701–712.*

signals travel directly from the CNS to the intestinal walls (Carabotti, Scirocco, Masello, & Severi, 2015). The CNS is the primary driver of intestinal motoric functions, such as motility, acid secretion, mucus production,

fluid regulation, and intestinal immune response (Macfarlane & Dillon, 2007). The vagus nerve is the single longest cranial nerve in the ANS and carries both afferent and efferent signals between the ENS and CNS. The majority of its nerve fibers are responsible for sending sensory information to the brain stem, where signals are then integrated (Tome et al., 2009). Evidence suggests that activation of the vagus nerve may promote antiinflammatory activity. Both animal (Meregnani et al., 2011) and human studies (Corcoran et al., 2005) have demonstrated reductions in peripheral inflammatory markers as a result of vagus nerve stimulation, rendering it a putative noninvasive option for treatment-resistant depression (Daban et al., 2008).

The HPA axis is the chief neuroendocrine system of stress responsivity and regulation. The HPA axis can be conceptualized as a hormonal cascade, bringing about a series of biological events that are triggered by stress or infection. Stress response dysfunction has been identified in several psychiatric disorders, such as anxiety (Mantella et al., 2008) and mood disorders (Watson et al., 2006), and GI disorders, such as IBS (Chang et al., 2009). Patients with BD exhibit HPA abnormalities during mood polarities and euthymia, suggesting that HPA axis dysfunction may be an enduring trait in this population (Daban et al., 2005). The interplay between stress reactivity and the MGB axis has been observed at various sites. Some studies have found that peripheral injection of corticotropin-releasing hormone increases visceral hypersensitivity, exaggerated colonic motility, and inhibition of upper gut motility (Fukudo, Nomura, & Hongo, 1998; Taché et al., 2001) Acute stress has been shown to alter both BBB (Esposito et al., 2002) and intestinal permeability (Overman, Rivier, & Moeser, 2012), chronic stress can alter gut microbiota composition and increase cytokine production (Bailey et al., 2011), further disrupting intestinal permeability and permitting luminal antigens and toxins into the bloodstream and CNS (Santos et al., 2001). Finally, bacterial translocation can trigger the HPA stress response, potentially resulting in a dangerous positive-feedback loop.

Another route of gut-brain communication occurs indirectly via microbiota-derived metabolites. Gut bacteria have enzymes that break down exogenous or endogenous carbohydrates, proteins, and peptides, synthesizing them into a wide range of metabolites. For example, bile acids, choline, and short-chain fatty acids (SCFAs) are important for several aspects of host health, such as energy homeostasis (Nicholson et al., 2012) and immune response via regulation of the T-cell network (Furusawa et al., 2013). SCFAs are the most abundant products derived from microbial fermentation of indigestible carbohydrate fibers, and are an important energy source for the epithelial cells of the colon and the gut microbiota (Slavin, 2013). In some cases, SCFAs were found to have immunomodulatory effects via downregulation of proinflammatory cytokine tumor necrosis factor alpha (TNF-α) (Usami et al., 2008; Vinolo et al., 2011). Furthermore, SCFAs play a prominent role in CNS immunity and development of neural circuitry by

modulating microglia maturation and function (Bilimoria & Stevens, 2015; Erny et al., 2015) However, metabolites are not always beneficial to the host and, in some instances, can exert neurotoxic effects (MacFabe, 2013; Sheedy et al., 2009; Skowrońska & Albrecht, 2012).

In addition, the gut microbiota is capable of synthesizing a wide range of neurometabolites, including producing neurotransmitters. *Lactobacillus* and *Bifidobacterium spp*. (species) have been shown to produce GABA, the main inhibitory transmitter in the brain, which regulates mood and anxiety (Barrett, Ross, O'Tooele, Fitzgerald, & Stanton, 2012). Other bacteria, such as *Escherichia spp., Bacillus spp*., and *Saccharomyces spp*. produce noradrenalin; *Bacillus* spp. produce dopamine; *Candida spp*., *Streptococcus* spp., *Escherichia spp*., and *Enterococcus spp*. produce serotonin; and *Lactobacillus* spp. produce acetylcholine (Brzozowski, 2012; Lyte, 2011). The role of serotonin in mood disorders, has been well documented (Collier et al., 1996; Ichimiya et al., 2002; Lee, 2001; Miozzo, 2018). What is less known, is the role of peripheral serotonin on the brain. Up to 90%−95% of serotonin is produced in the gut and plays an important role in GI motility, secretion, and perception. Probiotic supplementation of *Bifidobacterium infantis* can impact the production of amino acid tryptophan, a precursor to several biological agents, including serotonin and melatonin, the main neurotransmitter in sleep regulation (Clarke et al., 2009). Tryptophan levels are significantly lower in patients with BD during a manic state, compared to controls (Myint et al., 2007) suggesting that tryptophan and its metabolites play a role in BD. However, the neurobiology of BD is complex, and dysfunction of multiple neurotransmitter systems has been proposed (Newberg et al., 2008). Whereas serotonin may be more relevant during depressed states, ample evidence indicates that the dopamine system may be primarily involved during manic episodes and psychosis (Goodwin & Jamison, 2007). Therefore further research is needed to understand the role of the gut microbiota in its regulation and contribution to the relevant neurotransmitter systems and BD-related clinical states.

22.6 Microbiome-gut-brain-axis findings in neuropsychiatric disorders

22.6.1 Animal models

Germ-free (GF) animal studies have played a monumental role in demonstrating causal links between the gut microbiome and brain/behavior and have shaped our general understanding of the gut-brain axis. GF designs allow for strict experimental manipulation, optimized to study the interaction between host and bacteria. GF animals (typically mice) are born and raised in a completely sterile environment, thereby preventing colonization of bacteria, fungi, viruses, and other microorganisms (Al-Asmakh & Zadjali,

2015). GF or gnotobiotic studies allow researchers to compare GF to normally reared animals, investigating the effects of unique microbial species on various systems, including the immune system and brain and behavioral development (Gordon & Pesti, 1971; Heijtz et al., 2011). These studies also allow the ability to introduce one or a few known microorganisms at a time, or a complete microbiota from a donor host [through fecal microbiota transplantation (FMT)], and examine their interactions in a simpler, controlled environment (Tlaskalová-Hogenová et al., 2011).

Studies utilizing GF mice have demonstrated that commensal bacteria effect complex behaviors, such as sociability and anxiety-like behaviors, and contribute to brain development and function in mice (Collins, Surette, & Bercik, 2012; Cryan & Dinan, 2012; Neufeld et al., 2011). Sudo and colleagues were the first to demonstrate that the microbiota modulates the development of the HPA axis. In this landmark study, GF mice exhibited an elevated adrenocorticotropic hormone (ACTH) and corticosterone release, compared to control mice, when exposed to a mild stressor. Interestingly, the altered stress response was reversible by reconstitution with *Bifidobacterium infantis*, and partially reversible by colonization with fecal matter from control mice (Sudo et al., 2004). Other studies have suggested that GF mice have reduced anxiety-like and depressive-like behavior and significantly altered levels of brain-derived neurotransmitters and neurotrophic factors (Bercik et al., 2011; Neufeld et al., 2011). Zheng and colleagues transferred the gut microbiota from either healthy individuals or patients with major depressive disorder (MDD) to GF mice. Mice that were colonized with the microbiota of patients with MDD exhibited increases in depression-like behaviors along with disturbances in metabolites implicated in carbohydrate and amino acid metabolism (Zheng et al., 2016). These studies among other translational research [see (Luczynski et al., 2016) for a comprehensive review] have been monumental in highlighting that microbiota can physiologically induce alterations in depressive symptomology.

Other preclinical evidence has suggested a role for the microbiota in aging (Fransen et al., 2017; Nagpal et al., 2018) and neurodegeneration (Chen et al., 2016; Jiang et al., 2017; Sampson et al., 2016; Zhang et al., 2017). A dysfunctional MGB axis may contribute to mechanisms related to oxidative stress, cellular damage, and increased medical burden, which are associated with accelerated aging (Kim et al., 2016). In animal models of Alzheimer's disease (AD), LPS induces the formation of amyloid-beta fibrils, proteins involved in the neuropathology of AD (Zhang et al., 2017). Similarly, intestinal microbiota alterations have been linked to α-synuclein formation, a protein implicated in Parkinson's disease (PD). Sampson and colleagues demonstrated that GF mice overexpressing α-synuclein do not exhibit the hallmark motor deficits or neuropathological changes, such as microglial activation and α-synuclein buildup, characteristic of PD. Furthermore, FMT from patients with PD to the GF α-synuclein

overexpressing mice resulted in increased manifestation of PD physical impairments, compared to mice who received transplants from healthy donors (Sampson et al., 2016).

22.7 Human studies

Knowledge of the gut microbiome in clinical populations with psychiatric illnesses has been much more limited, although rapidly growing. Quantifying and describing the gut microorganisms in psychiatric populations may eventually lead to a better understanding of early risk factors, disease progression, and illness prognosis (Kasper et al., 2004). For instance, prenatal or early life infections, such as *Toxoplasma gondii*, have been detected as a risk factor for both BD and schizophrenia (Hamdani et al., 2017; Tedla et al., 2011; Torrey & Yolken, 2003). Notably, *T. gondii* is a parasite that infects humans through the oral route, and whose symptomatic profile very closely resembles IBD (Kasper et al., 2004). Chronic stress exposure at a young age can disrupt normal HPA axis functioning (Gunnar et al., 2009) and contribute to alterations in the gut microbiota (O'Mahony et al., 2017). A growing number of studies are comparing how microbial characteristics, such as species richness, community structure, and taxonomic abundance, differ across disorders.

Across various psychiatric disorders, findings regarding microbial diversity (i.e., within-sample alpha-diversity; richness or evenness) have been mixed in samples of individuals with MDD, schizophrenia, generalized anxiety disorder (GAD), and posttraumatic stress disorder (PTSD) (Bajaj et al., 2019; Borgo et al., 2017; Chen et al., 2019; Turna et al., 2020). Some studies report no differences between patients and controls (Naseribafrouei et al., 2014; Nguyen et al., 2019; Shen et al., 2018; Zheng et al., 2016) whereas others have reported decreased (Bajaj et al., 2019; Chen et al., 2019; He et al., 2018; Simpson et al., 2020; Zheng et al., 2019) or increased (Jiang et al., 2015; Loohuis et al., 2018) alpha-diversity. Although lower microbial diversity is commonly associated with negative health outcomes (Nowak et al., 2015; Wu et al., 2017; Xie et al., 2016) its role in brain function is not clearly established. For example, higher alpha-diversity in infancy has been shown to be predictive of worse overall cognition, visual reception, and expressive language in children at 2 years of age (Carlson et al., 2018). Thus the notion that higher alpha-diversity is always better in neuropsychiatric or neurocognitive outcomes has been challenged. More research is needed to better understand the relationship between alpha-diversity and brain/behavioral health.

Despite discordant findings among alpha-diversity, results from betadiversity analyses consistently indicate differences in global community structure and composition in MDD (Lin et al., 2017; Peter et al., 2018; Zheng et al., 2016) and schizophrenia (He et al., 2018; Loohuis et al., 2018; Nguyen et al., 2019; Schwarz et al., 2018; Shen et al., 2018) compared to healthy comparison subjects. Moreover, patients with first-episode psychosis that demonstrated the

most significant abnormalities in community structure, showed lower rates of illness remission at 1-year follow-up (Schwarz et al., 2018).

Taxonomic analyses have revealed that psychiatric illness is associated with differential abundances of various bacteria. In MDD, genera *Coprococcus, Faecalibacterium, Ruminococcus, Bifidobacterium*, and *Escherichia* and families *Veillonellaceae, Prevotellaceae*, and *Sutterellaceae* have been found to be relatively reduced, compared to healthy individuals (Aizawa et al., 2016; Chen et al., 2018; Huang et al., 2018; Jiang et al., 2015; Kelly et al., 2016; Liang et al., 2018; Lin et al., 2016, 2017; Naseribafrouei et al., 2014; Zheng et al., 2016). In schizophrenia, findings across studies have been inconsistent with regard to taxonomic results (He et al., 2018; Nguyen et al., 2019). However, an increased abundance of Lactobacillales is the single reliable difference between patients with schizophrenia and healthy individuals (He et al., 2018; Schwarz et al., 2018; Shen et al., 2018) Notably, Lactobacillales was positively correlated with severity of positive symptoms and global functioning scores (Schwarz et al., 2018). To date, the literature on anxiety disorders, PTSD, and obsessive-compulsive disorder is scarce, though some findings suggest a correlation between taxonomic abundance and clinical phenotypes (Bajaj et al., 2019; Chen et al., 2019).

A growing body of research has established a predominant role of the MGB axis in both healthy and pathological aging. Franceschi and colleagues have reported on the chronic low-grade inflammation associated with old age "inflammaging" (Franceschi & Campisi, 2014), which contributes to multicomorbidity and may be partially maintained by a dysbiosis of the gut (Gonzalez Alonso, Gomez, & O'Dowd, 2020). Accelerated aging may be a clinical feature of BD (Berk et al., 2011; Fries et al., 2017; Kessing et al., 2015; Rizzo et al., 2014). The hypothesis of accelerated aging in BD is supported by evidence of lower life expectancy (Fenn et al., 2005), accelerated cognitive aging (Torrent et al., 2012), higher levels of inflammatory cytokines (Berk et al., 2011), shorter telomere length (Powell et al., 2018), and increased mitochondrial DNA copy number (Fries et al., 2017). Therefore understanding the role of the gut microbiota BD, may provide insight into healthy versus pathological aging in this population.

22.8 Bipolar disorder

To date, there have been 12 studies investigating the gut microbiota in BD. Two of these studies examined the effect of psychotropic medications (Flowers et al., 2017, 2019) and one study included longitudinal assessment of microbial changes before and after treatment with antipsychotic medication (Hu et al., 2019). Two studies compared patients with BD, healthy controls, and either twins or first-degree relatives (Coello et al., 2019; Vinberg et al., 2019). Similar to studies of other psychiatric disorders, findings of alpha-diversity between BD and healthy controls were mixed, with some

reporting no differences (Painold et al., 2019; Rong et al., 2019) and others reporting increased (Guo et al., 2018) or decreased (Flowers et al., 2017; Hu et al., 2019; McIntyre et al., 2019; Vinberg et al., 2019) alpha-diversity. In a monozygotic twin study, alpha-diversity was lower in twins affected with BD but not in twins at high risk for the disorder (Vinberg et al., 2019). Perhaps more informative than larger scale health versus diseased group differences, alpha-diversity has been found to be associated with subgroup differences and clinical variables. Compared to euthymia, patients in an acute manic episode have higher alpha-diversity (Guo et al., 2018) whereas those in a depressive episode have lower alpha-diversity (Bengesser et al., 2019). In addition, lower alpha-diversity is associated with longer illness duration (Painold et al., 2019) and antipsychotic treatment, when compared to untreated patients (Flowers et al., 2017). Lower alpha-diversity in BD was also associated with decreased expression of a gene relevant to circadian functioning and mood regulation (Bengesser et al., 2019). This clock-gene under healthy conditions activates the breakdown of a neurotransmitter degrading enzyme. Lower expression of the clock-gene may lead to increased levels of circulating neurotransmitters such as serotonin, dopamine, and noradrenaline. Heightened activity of these neurotransmitter systems has been implicated in triggering or sustaining manic episodes (Bengesser et al., 2019).

Results of betadiversity across studies have not shown a distinct pattern. Three studies found differences in community membership and structure between healthy individuals and patients with BD (Coello et al., 2019; Evans et al., 2017; Hu et al., 2019) whereas others using the same measures did not (Coello et al., 2019; Painold et al., 2019). In familial comparisons, betadiversity was different between high- and low-risk twins (Vinberg et al., 2019) and between patients with BD and their first-degree relatives (Coello et al., 2019). One study comparing betadiversity between active bipolar depression and MDD did not observe any significant group differences (Rong et al., 2019). Frankly, only a portion of the studies reported betadiversity measures, rendering it challenging to interpret conclusions about BD microbiota characteristics compared to healthy individuals or patients with other psychiatric illnesses.

All 12 studies reported taxonomic level analyses. Among the reported studies, there was a wide-spread distribution of significant taxonomic differences. At the phylum level, Bacteroidetes (Hu et al., 2019), Actinobacteria (Painold et al., 2019; Rong et al., 2019), and Firmicutes (Rong et al., 2019) were more abundant in BD patients, compared to healthy controls. At the class level, Coriobacteria was more abundant (Painold et al., 2019) and at family level, *Clostridiaceae*, *Ruminococcaceae*, and *Coriobacteriaceae* were relatively more abundant in BD, compared to controls (McIntyre et al., 2019; Painold et al., 2019; Vinberg et al., 2019) on the other hand, *Christensenellaceae* was relatively less abundant in BD (Vinberg et al., 2019). Bacteroidetes and Firmicutes are typically dominant in a healthy gut microbiome (Ley et al., 2008), but the

reason for their increased abundance in BD is not completely understood. Increases in Bacteroidetes have been previously noted in Crohn's disease (Dicksved et al., 2008) whereas increases in Firmicutes have been observed following fat diet administration in mice (Hildebrandt et al., 2009). Actinobacteria are also part of the four major phyla of the human gut. Although Actinobacteria make up only a small percentage of the total gut microbiome, they play a crucial role in lipid metabolism and gut barrier integrity (Binda et al., 2018). It is possible that their higher abundance in the BD group may be associated with alterations in metabolism and gut homeostasis, although these specific relationships have not yet been investigated in BD.

At the genus level, there was less consensus among findings. *Prevotella, Faecalibacterium, Roseburia* (Hu et al., 2019), *Flavonifractor* (Coello et al., 2019), *Bifidobacterium* (Guo et al., 2018; Rong et al., 2019), and *Oscillibacter* (Rong et al., 2019) have been found to be relatively increased in BD, compared to controls. In contrast, one study did not find differences in *Bifidobacterium* (Aizawa et al., 2019) and others reported *Faecalibacterium* (Evans et al., 2017) and *Prevotella* (Rong et al., 2019) to be relatively decreased in BD. Reports of increased *Bifidobacterium* may seem counterintuitive, considering these bacteria are commonly used as in probiotics. In light of these findings, it has been speculated that a very high level of probiotics may not always signal health but, instead, a marker for acute intestinal environmental changes (Rong et al., 2019).

Phylogenetic investigations have shown that there are taxonomic differences between BD subtypes and mood states. Patients with type I and type II BD differ in the relative abundances of taxa at several levels. Class Erysipelotrichia, order Lactobacillales and Erysipelotrichales, family *Streptococcaceae* and *Erysipelotrichaceae*, and genera *Streptococcus*, *Bacilli*, and *Veillonella* were relatively increased in BD I patients, whereas genus *Ruminococcus* was relatively increased in BD II patients (Guo et al., 2018). *Enterobacteriaceae*, *Ruminococcus*, *Megamonas*, and *Bifidobacterium adolescentis* were higher in BD patients during manic states, compared to healthy individuals. Conversely, Selenomonadales, Lachnospira, Eubacrerium, and Plebeius were higher during depressed states, compared to healthy individuals. When manic and depressed states were compared, *E. coli* and *Bifidobacterium adolescentis* were higher during mania and *Stercoris* was higher during depression (Guo et al., 2018).

Studies have also addressed whether microbial taxonomic characteristics may be associated with BD clinical phenotypes. Abundance of *Lactobacillus* and *Bifidobacterium* was associated with worse sleep quality and increased cortisol levels, respectively (Aizawa et al., 2019). *Faecalibacterium* was associated with improved physical health, depression, and sleep quality (Evans et al., 2017). Longer illness duration was positively correlated with *Allisonella*, but negatively correlated with *Escherichia/Shigella*, *Flavonifractor*, and *Staphylococcus* (Hu et al., 2019).

Antipsychotic treatment may contribute to medical burden in BD (Soreca, Frank, & Kupfer, 2009), and the gut microbiota may underlie

metabolic changes associated with long-term use (Chen, Park, Li, & DeLisi, 2020). Indeed, long-term antipsychotic use is associated with increased risk of weight gain, diabetes, and GI disturbances, such as nausea and constipation (Nasrallah, 2008). In BD, antipsychotic treatment has shown to alter gut microbiota. The antipsychotic quetiapine was associated with a relative increase in the abundance of phylum Proteobacteria. At genus level, *Klebsiella*, *Lactobacillus*, *Anareroglobus*, *Colinsella*, *Paraprevotella*, *Solobacterium*, and *Veillonella* were also increased (Hu et al., 2019). Increased levels of *Colinsella* have also been detected in patients with type II diabetes (Lambeth et al., 2015). One study comparing obese and nonobese BD patients treated with antipsychotics found that *Akkermansia* was more prevalent in the intestinal tract of nonobese patients (Flowers et al., 2017). This genus has been previously shown to present an inverse relationship with inflammation, insulin resistance, and lipid metabolism (Schneeberger et al., 2015). Hence, lower levels of *Akkermansia* may be related to increased inflammation and metabolic perturbations that have been associated with antipsychotic treatment of BD. However, the current research has not been able to disentangle differences in the microbiota due to medication effects versus inherent effects of BD. With further research, some of these taxa may become useful predictors of outcomes.

22.9 Treatment

The modifiable nature of the human gut microbiome makes it a compelling therapeutic option for psychiatric disorders. The concept of "psychobiotics" has emerged in recent years, referring to any intervention that exerts an effect on the brain that is mediated by the gut microbiome (Dinan, Stanton, & Cryan, 2013; Sarkar et al., 2016). Psychobiotics are commonly used in reference to probiotics or prebiotics, but have been recently expanded to include dietary intervention, FMT, antibiotics, and antipsychotics, all of which may be capable of altering gut microbial composition, effect mood, cognition, and vagal activity (Haan et al., 2013; Morshedi, Saghafi-Asl, & Hosseinifard, 2020; Reininghaus et al., 2020).

Observational studies have reported that individuals with BD often exhibit poor dietary habits (Jacka et al., 2011; Tsuruga et al., 2015) profoundly affecting overall physical health and microbiota composition (Cryan & Dinan, 2012). Currently, whether chronically poor nutrition is a symptom of the illness or plays a causative role is unknown. Nonetheless, dietary choices can exacerbate both clinical and medical symptomology common to BD (Depp et al., 2016). The Western diet is characterized by high amounts of processed food, red meat, dairy, sodium, and artificially sweetened food (Carrera-Bastos, Fontes-Villalba, O'Keefe, Lindeberg, & Cordain, 2011). Numerous studies have found that the Western diet is more likely to lead to metabolic disorders and gut dysbiosis, compared to diets rich in vegetables,

fruit, seafood, whole grains, and lean meat (Ferreira et al., 2002; Fung et al., 2004; Hardin-Fanning, 2008; Martinez, Leone, & Chang, 2017). In mice models, the Western diet mimics the intestinal inflammation observed in IBD and alters gut microbial composition, including increased levels of *E. coli* (Agus et al., 2016). Brain-derived neurotrophic factor (BDNF) is decreased with long-term adherence to the Western diet (Hansen et al., 2018). Low BDNF levels are associated with both affective (Post, 2007) and psychotic disorders (Palomino et al., 2006), which are believed to be mediated by increased stressed and peripheral inflammation (Mondelli et al., 2011). To date, no studies have investigated the effects of dietary intervention on the gut microbiota in BD. One study examined differences in gut microbiota composition among patients with BD based on self-reported dietary choices and did not find any betadiversity differences among Mediterranean, Western, and Vegetarian diet groups (McIntyre et al., 2019). Further investigation into the longitudinal effects of diet is needed. For example, foods rich in nutrients such as omega-3 fatty acids and antioxidants have been shown to reduce gut-related inflammation (Yan et al., 2013). In mice, curcumin (a polyphenol that is the main antioxidant and antiinflammatory agent in turmeric) was found to increase growth of *Lactobacilli* and *Bifidobacteria* proliferation and prevent LPS-induced intestinal permeability (Bereswill et al., 2010).

Probiotics are supplements or foods that contain viable microorganisms that alter the microflora of the host (Patel & Denning, 2013). A variety of live *Lactobacilli* and *Bifidobacteria* cultures are typically found in fermented foods such as pickled vegetables, kimchi, tempeh, and yogurt. The history of probiotic usage dates back to the early 20th century (Metchnikoff, 2004) and many are used today to alleviate a range of GI symptoms (Nikfar et al., 2008). The beneficial effects of probiotics are thought to include multiple mechanisms of action, such as inhibiting the growth of pathogenic/invasive bacteria (Gopal et al., 2001), improving the colon's cellular integrity (Madsen et al., 2001; Mangell et al., 2002), stabilizing immune dysregulation (McCarthy et al., 2003; Rachmilewitz et al., 2004), decreasing visceral sensitivity (Verdu et al., 2006), reducing stress-induced bacterial translocation (Zareie et al., 2006), and promoting SCFA production (Johansson et al., 1998). One study investigated the effects of probiotic supplementation in recently hospitalized patients with mania and found that probiotic use was associated with a lower rate of rehospitalization (Dickerson, Severance, & Yolken, 2017). Another study found that following probiotic administration, patients with BD demonstrate a significant improvement in cognition, including processing speed and attention (Reininghaus et al., 2020).

Prebiotics are nondigestible foods or supplements that selectively stimulate the growth and activity of indigenous bacteria (Patel & Denning, 2013). The main dietary source of prebiotics is oligosaccharides, which are found at high levels in human breast milk and stimulate *Bifidobacteria* growth in

infants (Lawson et al., 2020). Prebiotics are also present in dietary fiber such as chicory root, garlic, onion, asparagus, wheat bran, and banana. Prebiotics ferment in the gut and lead to increased production of SCFAs, thereby reducing inflammation (Fernández et al., 2016). Some evidence has shown that prebiotic treatment decreases salivary cortisol and negative emotional bias in healthy individuals (Schmidt et al., 2015). To our knowledge, only one study has investigated prebiotics in BD and found that resistant starch administration led to increased Actinobacteria and starch-degrading *Bifidobacterium faecale* and *Bifidobacterium adolescentis* (Flowers et al., 2019).Other studies suggest that combining probiotics and prebiotics (synbiotics) may result in a synergistic action, providing the most benefit to the host. Preclinical data demonstrate that a combination of *Lactobacillus plantarum* and inulin had a more substantial effect than either supplement alone in improving gut dysbiosis, oxidative stress, serotonin, and BDNF/tyrosine receptor kinase B signaling pathways as well as enhancing learning and memory performance (Morshedi et al., 2020). Overall, research on pro-, pre-, and synbiotics is currently limited, and not all studies have reported positive effects on mood and blood-markers inflammation (Romijn et al., 2017). Adverse side effects of pro- and prebiotic supplementation are rare, but can include bloating, diarrhea, and mental fogginess (Ouwehand et al., 2005). Methodological factors such as length of treatment, the strain used, adjuvant therapy, and illness severity should be carefully considered in designing treatment studies.

FMT involves the transfer of a complete microbiota from donor to host. In clinical applications, FMT seeks to replenish the gut bacteria of a diseased host with the gut bacteria from a healthy donor. Today, FMT is most commonly used in the treatment of *Clostridium difficile* bacterial infection. *C. difficile* infection symptoms can range from mild GI disturbances to severe life-threatening inflammation of the colon (Cammarota, Ianiro, & Gasbarrini, 2014). Treating *C. difficile* with conventional methods is problematic. Since its spores are resistant to antibiotics, the traditional treatment may contribute to disease progression (Freeman & Wilcox, 1999). FMT is believed to treat *C. difficile* infection via recovery of community diversity (Song et al., 2013) and restoration of SCFAs and bile acid production (Seekatz et al., 2018). Preclinical studies demonstrating robust behavioral modification following FMT (Kelly et al., 2016; Zheng et al., 2016) suggest that this may have possible benefits in treating mood and psychotic disorders. Novel clinical applications of FMT have shown an amelioration in depression and anxiety symptoms, and sleep quality in patients with functional GI disease (Kurokawa et al., 2018). In children with autism spectrum disorders, an 80% decrease in GI symptoms was observed following FMT, as well as notable improvements in hallmark autistic behaviors such as repetitive motor behaviors, communication, daily living skills, and socialization (Kang et al., 2017). However, FMT is regarded as a more extreme and moderately invasive intervention. To date, FMT is not widely used due to

the inherent risks and possible difficulties with stigma and treatment adherence (Kahn et al., 2013).

22.10 Conclusion and future directions

BD is a complex illness. A variety of factors likely contribute to its etiology and disease progression. Current evidence suggests that immune system dysregulation (Goldstein et al., 2009; Leboyer et al., 2012) as well as GI permeability and inflammation (Dickerson et al., 2017; Severance et al., 2012, 2016) may be involved in the pathophysiology of BD. The gut microbiota is important in maintaining host health and can be altered in states of disease, inflammation, and stress (Kohane et al., 2012; Sudo et al., 2004; Williams et al., 2011). The MGB axis is a complex bidirectional communication system between the gut and brain. Preclinical studies using GF animals have demonstrated that altering microbiota profoundly affects behavior (Collins et al., 2012; Cryan & Dinan, 2012; Sudo et al., 2004). A recent influx of clinical studies has further highlighted the microbiome as a relevant biomarker for psychiatry. In BD, the composition of the gut microbiota is distinct from healthy individuals (Coello et al., 2019; Evans et al., 2017; Guo et al., 2018; Hu et al., 2019) and from other affective disorders, such as MDD (Rong et al., 2019). Nevertheless, this field of research is still nascent, and there is considerable variability in findings across studies, particularly in reports of differential taxonomic abundance.

Limitations in the extant literature present challenges in comparing results across studies and drawing definitive conclusions. Variability in study design and technical sequencing methodology, confounding factors, and sample heterogeneity may contribute to mixed results. Moreover, the gut microbiota is highly diverse, not only across individuals but also within the same individual at different time points (Gilbert et al., 2018; Turnbaugh et al., 2010) possibly obscuring differences due to normal fluctuations versus intraindividual, interindividual, or intergroup differences. Metaanalyses and studies with larger sample sizes are needed to replicate and substantiate existing findings. In addition, prospective longitudinal studies may better capture individual versus group trajectories. Studies should carefully measure and consider the effects of confounding factors that may influence microbiota composition, such as demographics, clinical variables, medication use, health behaviors (e.g., diet, tobacco use). BD disease characteristics, including disorder subtype and mood state, are particularly important to consider. Only a minority of studies examined differences between BD I and II subtypes (Coello et al., 2019; Hu et al., 2019; McIntyre et al., 2019). The majority of studies investigated BD patients with active depression (Aizawa et al., 2019; Bengesser et al., 2019; Hu et al., 2019; McIntyre et al., 2019; Painold et al., 2019; Rong et al., 2019), a much smaller proportion focused on euthymia (Bengesser et al., 2019; Coello et al., 2019; Vinberg et al., 2019) and

only one study included a comparison between mania and depression (Guo et al., 2018) others did not report mood states (Flowers et al., 2017, 2019). Future studies should focus on evaluations between patients during periods of euthymia and healthy controls. Other meaningful comparisons might include more robust within-group comparisons to ascertain mood state differences. Additional clinical variables, such as illness severity and medical comorbidity, should be taken into account. Finally, methodological approaches in sequencing the microbiota need to be considered. Each processing step from storage to DNA extraction and sequencing can introduce technical biases (Lozupone et al., 2013; Walters et al., 2011). There is a need for unification and standardization of protocols in the field as well as transparency in methods reporting and data sharing for reproducibility and integration efforts (Knight et al., 2018).

The future of psychiatric medicine may greatly benefit from an increasingly precise and individualized approach to diagnostics and therapeutics. BD is among the most commonly misdiagnosed psychiatric illnesses, increasing patients' risk of negative functional outcomes by delaying proper treatment (Singh & Rajput, 2006). The microbiome has high potential to be a diagnostic biomarker to predict at-risk individuals, characterize clinical endophenotypes of BD, and aid in differential diagnoses. As a therapeutic tool, targeting the microbiome may help to identify and alleviate the chronic inflammation and medical comorbidity often cooccurring with BD. Current treatment methods, which primarily consist of antipsychotics and mood stabilizers, are often riddled with adverse side effects (Gitlin, 2016; Nasrallah, 2008) and may contribute to multiple aspects of disease pathology (Chen, Park, Li, & DeLisi, 2020). On the other hand, treatments that optimize the microbiome, such as diet and probiotic or prebiotic supplementation, typically have minimal risk associated with them (Ouwehand et al., 2005). Advances in our understanding of the microbiome and its relationship to psychiatric functioning provide an exciting opportunity for individualized medicine through a data-driven and cost-effective approach.

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