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Overview and systematic review of studies of microbiome in schizophrenia and bipolar disorder

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ABSTRACT

Schizophrenia and bipolar disorder are among the leading causes of disability, morbidity, and mortality worldwide. In addition to being serious mental illnesses, these disorders are associated with considerable systemic physiological dysfunction, including chronic inflammation and elevated oxidative stress. The advent of sophisticated sequencing techniques has led to a growing interest in the potential role of gut microbiota in human health and disease. Advances in this area have transformed our understanding of a number of medical conditions and have generated a new perspective suggesting that gut microbiota might be involved in the development and maintenance of brain/mental health. Animal models have demonstrated strong though indirect evidence for a contributory role of intestinal microbiota in psychiatric symptomatology and have linked the microbiome with neuropsychiatric conditions. We present a systematic review of clinical studies of microbiome in schizophrenia and bipolar disorder. The published literature has a number of limitations; however, the investigations suggest that these disorders are associated with reduced microbial diversity and show global community differences compared to non-psychiatric comparison samples. In some reports, specific microbial taxa were associated with clinical disease characteristics, including physical health, depressive and psychotic symptoms, and sleep, but little information on the functional potential of those community changes. Studies also suggest increased intestinal inflammation and permeability, which may be among the principal mechanisms by which microbial dysbiosis impacts systemic physiological functioning. We highlight gaps in the current literature and implications for diagnosis and therapeutic interventions, and outline future directions for microbiome research in psychiatry.

Severe mental illnesses (SMI), mainly schizophrenia and bipolar disorder (BD), are a leading global cause of disability (Whiteford et al., 2013) and rank among the most substantial causes of death worldwide (Walker et al., 2015). Compared with the general population, people with these psychiatric disorders have higher rates of chronic medical conditions and die younger (Brown, 1997; Cuijpers and Smit, 2002; Harris and Barraclough, 1998; Roshanaei-Moghaddam and Katon, 2009; Saha et al., 2007). Excess deaths in these groups are not primarily from mental disorders themselves or suicide, but due to metabolic and cardiovascular diseases, cancers, and other chronic diseases (Casey et al., 2009; De Hert et al., 2009; Hennekens et al., 2005; Katon, 2003; Kupfer, 2005; Tsuang and Woolson, 1978). Even more concerning is the fact that the gap in longevity between people with schizophrenia and general population has increased 37% since the 1970s (Lee et al., in press). Despite the enormous burden of SMI, the underlying mechanisms associated with disease pathogenesis and progression are still not fully understood. The potential role of intestinal microbiota in the etiology of various human diseases has attracted considerable attention during the last decade. However, no article to our knowledge has systematically reviewed all the available studies of the microbiome in human, clinical populations of schizophrenia and BD. We highlight gaps in our knowledge, potential implications for diagnosis and therapeutic interventions, and outline future directions for microbiome research in psychiatry.

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1. Why microbiome?

The microbiome is a dynamic ecological community of microorganisms and their genes, including mainly bacteria, but also archaea, microbial eukaryotes, fungi, and viruses that inhabit the human body. For decades, the importance of the human microbiome remained elusive, due to technical challenges in studying unculturable microorganisms (Pace, 1997; Qin et al., 2010; Sogin et al., 1972; Woese and Fox, 1977). Only with the advent of high-throughput sequencing techniques has it become apparent that the microbiome is a rich and diverse ecosystem with implications for human health and disease (Human Microbiome Project Consortium, 2012; Knight et al., 2017). Humans, on average, harbor at least as many bacteria as the "human" cells in our bodies (Sender et al., 2016). Of the many distinct environments inhabited by microbes (e.g., skin, mouth, upper gastrointestinal tract), the distal large intestine has the greatest microbial biomass, with 1000 + unique bacterial species and between 2 million and 20 million unique genes, which dwarf the human genome (20,000 genes) by more than 100:1 (Costello et al., 2009; Human Microbiome Project Consortium, 2012; Qin et al., 2010). Unlike the human genome, which is fixed from birth, the microbiome is a dynamic environment that is highly variable over time (Caporaso et al., 2011) and can be shaped by development (from birth through old age) (Dominguez-Bello et al., 2010; Koenig et al., 2011; Yatsunenko et al., 2012) and in response to intrinsic (e.g., immune system) and extrinsic (e.g., diet, exposure to drugs/medications, or physical geography) environmental factors. Thus, the microbiome is potentially more easily modifiable than human genome.

The microbiome has emerged as the "new" biomarker of human health. It is critical in maintaining host physiology, particularly in developing and shaping the immune system (Duerkop et al., 2009; Forsythe and Bienenstock, 2010). The human microbiome has been shown to have a pivotal role across a range of medical conditions including gastrointestinal (GI) disorders, such as inflammatory bowel disease (Kostic et al., 2014), obesity and metabolic diseases (Bouter et al., 2017; Hartstra et al., 2015), cancer (Schwabe and Jobin, 2013), and chronic pulmonary diseases (Budden et al., 2017; O'Dwyer et al., 2016), to name a few. Parallels can be drawn between these medical disorders and SMI. Gut (Severance et al., 2015) and metabolic (De Hert et al., 2009; Hennekens et al., 2005) dysfunction is highly prevalent in SMI, and cardiovascular, cerebrovascular, and digestive diseases rank as the top three leading causes of natural death in schizophrenia (Saha et al., 2007). Thus, schizophrenia and BD are not just severe *mental* illnesses but also severe *physical* illnesses (Jeste et al., 2011). As microbial colonization of the gut is critical for the development of the immune system (Round and Mazmanian, 2009), imbalance and/or depletion of the intestinal ecosystem may alter immune responses (Kamada et al., 2013) and contribute to systemic physiological dysfunctions, including elevated inflammation and oxidative stress, seen in these disorders (Berk et al., 2011; Flatow et al., 2013; Kirkpatrick and Miller, 2013). Therefore, microbiome research may contribute to a greater understanding of the pathogenesis and treatment of chronic mental illnesses.

2. Preclinical studies of the microbiome in neuropsychiatric disorders

In this ever-expanding field, researchers are now investigating how the intestinal microbiota influence distal sites, particularly the brain. In psychiatric disorders, the gut microbiome has been of particular interest because it plays a significant role in brain function and behavior (Diaz Heijtz et al., 2011), which has led to coining of the term "gut-brain axis." The mechanisms by which peripheral intestinal microorganisms are linked to emotional and cognitive functions of the brain are not fully understood, but they are thought to include the vagus nerve, gut hormone signaling, the immune system, tryptophan metabolism, and microbial metabolites such as short-chain fatty acids (Cryan and Dinan, 2012). Investigations using germ-free animals have been critical in allowing direct assessment of the microbiome's impact on different aspects of behavior relevant to psychiatric disorders, including depression and anxiety.

It is beyond the scope of this article to review all the preclinical articles relevant to brain and behavior; these have been more comprehensively reviewed elsewhere (Cryan and Dinan, 2012). However, we highlight some of the landmark studies that have shaped our understanding of the gut-brain axis.

Sudo et al. (2004) first demonstrated that the intestinal microbiota could modulate the hypothalamus-pituitary-adrenal (HPA) axis. In their study, germ-free mice exposed to mild stress displayed elevated adrenocorticotrophic hormone and corticosterone release compared to control mice with normal gut microflora. This stress response could be fully reversed by reconstitution with *Bifidobacterium infantis* and partially reversed by colonization with fecal matter from control mice. Subsequent studies have also shown that germ-free mice have reduced anxiety-like behavior and altered levels of neurotransmitters and neurotrophic factors in the brain (Clarke et al., 2013; Crumeyrolle-Arias et al., 2014; Heijtza et al., 2011; Neufeld et al., 2011). In an innovative translational study, Zheng et al. (2016) incorporated both preclinical and clinical samples to assess how gut microbiota physiologically influence psychobehavioral characteristics and determine whether alterations of gut microbiota may have a causal role in depression-like behavior. The investigators demonstrated that germ-free mice display decreased depression-like behavior, and that patients diagnosed with major depressive disorder (MDD) have microbiota compositions that were significantly different from non-psychiatric comparison subjects, characterized by changes in the relative abundance of *Firmicutes*, *Actinobacteria*, and *Bacteroidetes*. Furthermore, fecal microbiota transplantation (FMT) of germ-free animals with the microflora derived from MDD patients resulted in increased depression-like behaviors compared to mice that had received FMT from healthy control individuals. Similar results were replicated in an independent study in which FMT from MDD patients to germ-free rats induced behavioral and physiological features characteristic of depression in the recipient animals, including anhedonia, anxiety-like behaviors, and alterations in tryptophan metabolism (Kelly et al., 2016). These experiments provide compelling evidence that the gut microbiota can physiologically induce depression- and anxiety-like behavior in animals.

An emerging body of research is also beginning to link the intestinal microbiota with neurodevelopmental and neurodegenerative disorders. Studies have demonstrated differences in the gut microbial composition of children with autism spectrum disorders compared to typically developing children (Ding et al., 2017). In a notable study using a maternal immune activation (MIA) mouse model that is known to display features of autism, Hsiao et al. (2013) demonstrated that certain microbial shifts in the gut led to subsequent onset of behavioral changes consistent with the clinical picture of autism. Alongside microbial dysbiosis, defects in intestinal permeability and elevated inflammatory cytokines were also observed. Treatment with the commensal bacterium *Bacteroides fragilis*, which had been previously demonstrated to restore GI pathology through immunomodulatory effects in mouse models of colitis (Mazmanian et al., 2008), reversed the physiological, neurological, metabolic, and immunological abnormalities. Importantly, findings from this study suggest leaky gut and related elevations in pro-inflammatory cytokines as potential mechanisms for intestinal dysbiosis and by which commensal bacteria may improve GI and behavioral abnormalities in autism. On the other end of the developmental spectrum, patients with Parkinson's disease (PD) display altered microbiomes (Hasegawa et al., 2015; Keshavarzian et al., 2015; Scheperjans et al., 2015), and the microbiome has been shown to promote progression to PD in genetically susceptible individuals. Using mice that overexpress α-synuclein, a neuropathological protein relevant to Parkinsonian movement disorders, Sampson et al. (2016)