



Named Series: Brain, Behavior, Immunity and the Microbiome

The microbiome, immunity, and schizophrenia and bipolar disorder

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ABSTRACT

Schizophrenia and bipolar disorder are serious neuropsychiatric disorders of uncertain etiology. Recent studies indicate that immune activation may contribute to the etiopathogenesis of these disorders. Numerous studies in animal models indicate that the mucosal microbiome may influence cognition and behavior by altering the functioning of the immune system. It is thus likely that the microbiome plays a role in human psychiatric disorders. The study of immune alterations and the microbiome in schizophrenia and bipolar disorder is in its infancy. Two recent investigations of the oro-pharyngeal microbiota in schizophrenia found differences between cases and controls. Other studies have found increased gastrointestinal inflammation in schizophrenia and bipolar disorder based on measures of microbial translocation. Several studies have also found an association between the receipt of antibiotics and an increased incidence of psychiatric disorders, perhaps due to alterations in the microbiome. Studies to characterize the intestinal microbiome of individuals with these disorders are in progress. The ultimate test of the role of the microbiome and immune-mediated pathology in schizophrenia and bipolar disorder will come from clinical trials of therapeutic agents which alter gut microbiota or gastrointestinal inflammation. The successful development of such modalities would represent a novel strategy to prevent and treat serious psychiatric disorders.

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1. Introduction

Schizophrenia is a neuropsychiatric disorder with an onset typically in adolescence or young adulthood and a course which usually persists throughout the lifespan. Characteristic symptoms include hallucinations and delusions as well as apathy and social withdrawal; many affected individuals also have reduced cognitive abilities and impaired social functioning. Because the disorder disrupts multiple life domains and typically persists for decades, the global burden of disease is high (Whiteford et al., 2015). Bipolar disorder is another serious mental illness and shares many features with schizophrenia including some of the characteristic symptoms and the lifelong course (Dacquino et al., 2015; Jobe and Harrow, 2005). Both disorders are categorized by their phenotypic features rather than any biological markers and their etiology is not fully understood. Genome-wide association studies show a great deal of genetic overlap between schizophrenia and bipolar disorder (Lichtenstein et al., 2009; Van Snellenberg and de Candia, 2009). However, while genetic factors are involved in both disorders, risk genes which have been identified account for a small portion of

disease risk. For example, a recent genome wide study in schizophrenia found 108 independent loci that account for approximately 7% of the risk of developing schizophrenia from polygenic scores, (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Of note, many of the genetic loci that were identified are known to modulate inflammation and the immune response.

Previous studies have demonstrated that both schizophrenia and bipolar disorder are associated with alterations of the systemic immune system including low-grade chronic inflammation (increased plasma cytokines, soluble cytokine receptors, chemokines, acute phase reactants) and T-cell activation features; these findings are delineated in previously-published review articles (Anderson and Maes, 2015; Rosenblat et al., 2014; Leboyer et al., 2016). The immune system provides a two way communication pathway between the gut and the brain via the vagus nerve, short chain fatty acids, and a number of soluble mediators (Erny et al., 2016; Hyland and Cryan, 2016; Levite, 2016; Sherwin et al., 2016). It has been established that the gut microbiota can influence brain function and thus may play a role in diseases such as schizophrenia and bipolar disorder which are traditionally seen as brain-based (Fond et al., 2015).

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The study of the microbiome is relatively new and most of the investigations to date have taken place in animal models. Multiple studies have documented an interaction between the gut microbiome, immunity, cognitive functioning and behavior in a number of models, most of which involve rodents (Desbonnet et al., 2015). Studies linking these findings to human psychiatric disorders are more limited.

2. Scope of review

The purpose of this article is to summarize what is known about immune alterations and the microbiome based on human studies in schizophrenia and bipolar disorder. This field of inquiry is still in its infancy and the number of studies to date is small. However, the groundwork is being laid to better understand immune abnormalities which contribute to the etiology of these major psychiatric disorders and to identify how knowledge of the microbiome might result in novel methods for the treatment of these disorders.

3. Results

Research about immune alterations and the microbiome in schizophrenia and bipolar disorder falls into several categories as described below.

3.1. Studies of the oropharyngeal microbiota in schizophrenia

There have been numerous studies of the fecal microbiome in otherwise healthy children and adults (Collado et al., 2015; Lozupone et al., 2012). However the collection and prompt processing of fecal samples from individuals with severe psychiatric disorders is problematic. Published studies analyzing the fecal microbiome of individuals with schizophrenia are currently lacking. The oropharyngeal microbiome can be assessed from throat swab samples which are more easily accessed than samples from the gastrointestinal tract and thus allow potentially for larger sample sizes. Furthermore, while there are many differences in the microbial composition of the fecal and oral microbiome, some studies have documented overlapping metabolic pathways in the different sites (Segata et al., 2012). For this reason many of the studies in our population have focused on the oral microbiome. Furthermore, we have relied on metagenomic sequencing rather than the commonly used 16S sequencing since studies have documented a role for viruses (Houenou et al., 2014), fungi (Severance et al., 2016) and protozoa (Torrey et al., 2012) in the pathogenesis of the psychiatric disorders.

A meta-genomic analysis of the oropharyngeal microbiome in 16 adults with schizophrenia and 16 non-psychiatric controls found differences at both the phylum and the genus levels (Castro-Nallar et al., 2015). At the phylum level, schizophrenia samples exhibited higher proportions of Firmicutes across samples in comparison to controls; in the controls a higher relative proportion of Bacteroidetes and Actinobacteria was observed. Regarding species diversity, controls were richer in the number of species compared to schizophrenia samples but less even in their distribution (Fig. 1).

Out of a total of 25 differentially abundant species (bacteria and fungi), 6 microbial species were more abundant in cases than controls after adjusting for relevant covariates. Lactic acid bacteria were relatively more abundant in schizophrenia including *Lactobacillus* and *Bifidobacterium* with the largest effect found in *Lactobacillus gasseri* which appeared to be at least 400 times more abundant in schizophrenia patients than in controls. The study also found that 18 metabolic pathways that were enriched and 14 decreased in schizophrenia relative to controls. Pathways that

were significantly altered in schizophrenia were related to environmental information processes such as saccharide, polio, and lipid transport systems (Fig. 2).

Another study of the oropharyngeal microbiome focused on bacteriophages, viruses that infect bacteria and alter their metabolism and replication, in samples from 41 adults with schizophrenia and 33 non-psychiatric controls (Yolken et al., 2015). Of the 79 distinct bacteriophage samples that were identified, one, *Lactobacillus phage phiadh*, was significantly more abundant in schizophrenia cases than in controls after adjustment for multiple comparisons and demographic covariates (Fig. 3). Interestingly the group differences were larger for the phage than for its host bacteria underscoring the importance of examining viral sequences in studies of the microbiome relating to psychiatric disorders.

Within the schizophrenia group, the level of this phage was significantly associated with the presence of immunological disorders such as diabetes, which are common co-morbid conditions in individuals with schizophrenia (Schoepf et al., 2014). The level of *Lactobacillus phage phiadh* was also relatively increased in individuals who were being treated with therapeutic valproate, a medication commonly used for the adjunctive treatment of schizophrenia (Tseng et al., 2016). This finding is of interest since valproate has been shown to modify the microbiome in mouse models of autism in the context of in utero exposure, probably related to us homology with short chain fatty acids (de Theije et al., 2014). This finding is of note since the mechanisms by which valproate improves the symptoms in some individuals with schizophrenia was not previously known. This finding suggests that other molecules which alter the microbiome may be found that are effective as adjunct therapies for schizophrenia, including ones with less toxicity than valproate (Haddad et al., 2009).

3.2. Studies of intestinal inflammation in schizophrenia and bipolar disorder

Gastrointestinal (GI) pathologies are long-standing comorbidities of psychiatric disorders, supporting the centuries old hypotheses that gut and brain physiologies are inter-dependent (Severance et al., 2015). In schizophrenia and bipolar disorder, a low-grade inflammatory state is prevalent in a subset of individuals (Bechter, 2013; Fillman et al., 2014; Miller et al., 2011). The origin of this inflammation is not currently well understood, but recent as well as older studies suggest that it stems from processes related to dysbiosis of the gut microbiome. This dysbiosis provides a mechanism to generate a GI-based inflammatory state through the process of microbial translocation of gut microbes into systemic circulation.

One of the earliest specific documentations of GI inflammation associated with schizophrenia was a post-mortem study of 82 individuals with schizophrenia, where researchers found that 50% had gastritis, 88% enteritis and 92% colitis (Buscaino, 1953). Interestingly, a converse phenomenon also holds true with reports of psychiatric comorbidities in people with intestinal disorders which have an inflammatory component. Prevalence estimates for any psychiatric comorbidity in patients diagnosed with irritable bowel syndrome (IBS), for example, range from 54 to 94% (Whitehead et al., 2002), and specifically estimates for a schizophrenia comorbidity approach 20% (Gupta et al., 1997). In a large-scale case-control cohort of 4689 IBS patients and 18,756 matched controls without IBS, a diagnosis of IBS increased the risk for anxiety and mood disorders as well (Lee et al., 2015). Collectively, these epidemiological studies illustrate that GI inflammation and psychiatric disorders are connected. However the delineation of the magnitude of the correlation is limited by the difficulty in making an accurate diagnosis of intestinal diseases in individuals with psy-

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