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The microbiome, immunity, and schizophrenia and bipolar disorder

Faith Dickerson[1,*], **Emily Severance**[2], and **Robert Yolken**[3]

[1]Sheppard Pratt Health System, Baltimore, MD USA

[2,3]Johns Hopkins School of Medicine, Baltimore, MD USA

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.

Keywords

immunity; microbiome; schizophrenia; bipolar disorder; gastrointestinal; antibiotics; probiotics

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

[*]Corresponding Author: Stanley Research Program, Sheppard Pratt Health System, 6501 North Charles St, Baltimore, MD USA 21204; fdickerson@sheppardpratt.org; Phone 410-938-4359, Fax 410-938-4364.

[2]Johns Hopkins School of Medicine, Stanley Laboratory of Neurovirology, Department of Pediatrics, 600 N. Wolfe St., Baltimore, MD USA 21287; Esevera1@jhmi.edu

[3]Johns Hopkins School of Medicine, Stanley Laboratory of Neurovirology, Department of Pediatrics, 600 N. Wolfe St., Baltimore, MD USA 21287; rhyolken@gmail.com

functioning. Because the disorder disrupts multiple life domains and typically persists for decades, the global burden of disease is high (Whiteford, Ferrari, Degenhardt, Feigin, & Vos, 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, De Rossi, & Spalletta, 2015; Jobe & 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 & 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 & Maes, 2015).(Rosenblat, Cha, Mansur, & McIntyre, 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, de Angelis, & Prinz, 2016; Hyland & Cryan, 2016; Levite, 2016; Sherwin, Sandhu, Dinan, & Cryan, 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).

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, Rautava, Isolauri, & Salminen, 2015; Lozupone, Stombaugh, Gordon, Jansson, & Knight, 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, Bartko, & Yolken, 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 Badteroidetes 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 (Figure 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 (Figure 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.(R. H. 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 (Figure 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, Uppal, Potluri, & Heun, 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, Das, Ashfaq, & Wieck, 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, Prandovszky, Castiglione, & Yolken, 2015). In schizophrenia and bipolar disorder, a low-grade inflammatory state is prevalent in a subset of individuals (Bechter, 2013; Fillman, Sinclair, Fung, Webster, & Shannon Weickert, 2014; Miller, Buckley, Seabolt, Mellor, & Kirkpatrick, 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 54–94% (Whitehead, Palsson, & Jones, 2002), and specifically estimates for a schizophrenia comorbidity approach 20%(Gupta, Masand, Kaplan, Bhandary, & Hendricks, 1997). In a large-scale case-control cohort of 4689 IBS patients and 18756 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 psychiatric symptoms and the possible confounding effects of medications.

Numerous biological indices corroborate a role for GI inflammation in schizophrenia and bipolar disorder pathophysiology. GI-derived inflammation is often measured based on biomarkers of the microbial translocation process. The panel of markers used to diagnose Crohn's Disease for example includes detection of antibodies to the yeast *Saccharomyces cerevisiae*, an organism that is part of the normal human gut microbiome (Desplat-Jego et al., 2007) The presence of antibodies to this yeast indicates that an immune response has been generated against the organism presumably due to its presence at a potentially compromised gut mucosa-blood vasculature interface. Elevated antibodies to *S. cerevisiae* were found in individuals with schizophrenia and bipolar disorder and these levels were particularly increased in individuals experiencing a recent onset of their disorder (Severance et al., 2012; Severance, Gressitt, et al., 2014). Furthermore, antibody levels were significantly higher in those with schizophrenia who were antipsychotic-naïve than in those who were medicated suggesting that the relationship between these disorders and gastrointestinal inflammation cannot be attributed solely to the effect of antipsychotic medications. In a follow-up study of a different commensal yeast species, *Candida albicans*, antibody levels were not only significantly increased in subsets of individuals with schizophrenia, but were particularly elevated in those who had GI symptoms(Severance, Gressitt, et al., 2016). In a similar investigation, markers of bacterial translocation were altered in individuals with schizophrenia and to a certain degree bipolar disorder (Severance et al., 2013).

The theme for translocation of microbial components into circulation via a breached gut barrier can be expanded to include other GI-derived substances such as digested foods. There is a long literature on the anti-milk casein and anti-wheat gluten immune response associated with schizophrenia and a sensitivity to these foods is known to also generate an inflammatory response in the intestinal tract (Severance, Yolken, & Eaton, 2014). Finally, exposure to the neurotropic protozoan pathogen, *Toxoplasma gondii*, is a well-studied risk factor for the development of schizophrenia(Torrey et al., 2012). Interestingly, *T. gondii* enters and establishes itself in its host via the intestinal tract and is used in experimental animal models to generate intestinal disorders associated with inflammatory processes (Bereswill et al., 2010). In human studies, antibodies to this parasite were significantly associated with markers of food sensitivity in those with schizophrenia (Severance et al., 2012). Thus, it cannot be ruled out that the association of exposure to this parasite with psychiatric disorders may be a function of its pathological effects in the gut.

3.3. Study of bacterial infections and antimicrobial agents in acute mania

Bacterial infections are a source of immune activation and have been shown to be a risk factor for the subsequent development of schizophrenia and mood disorders(Benros, Mortensen, & Eaton, 2012; Benros et al., 2013; Nielsen, Benros, & Mortensen, 2013) Consistent with some previous population-based studies (Kohler et al., 2014), a recent study employed the prescription of antibiotic agents as a measure of bacterial infections. The study population consisted of 234 individuals hospitalized for acute mania, most diagnosed with bipolar disorder, in either an inpatient unit or a day hospital and also individuals hospitalized for schizophrenia, bipolar depression, major depression, as well as non-psychiatric controls(R. Yolken et al., 2016). The study found that in patients with acute mania, but not

those hospitalized for the other conditions, had a substantially increased rate of recent antimicrobial prescription when adjusting for demographic variables. Within the mania group, the prescription of antibiotics was associated with having increased mania symptom severity but not with other clinical ratings. The urinary tract was the most common site of infection in women while the respiratory tract and mucosal surfaces were the most common sites in men. An association between antibiotic exposure and mood disorder has also been found in population based studies performed in the United Kingdom (Lurie, Yang, Haynes, Mamtani, & Boursi, 2015) and Denmark (Kohler et al., 2016).

There are several mechanisms by which antibiotic usage might be associated with episodes of acute mania. One possibility is that the underlying bacterial infections responsible for the antibiotic prescriptions result in immune activation which then leads to the onset of mania. A second possibility is that the higher rate of presumed bacterial infections in individuals with mania is reflective of decreased levels of ability of the immune system to prevent infections in this population. A third possibility is that the administration of antibiotics can result in changes in the microbiome which themselves increased the risk of altered mood states. This finding is consistent with a number of studies in animal models linking the microbiome to altered behavior and cognition. However, the possible role of alterations in the microbiome in the onset of mania in this study population was rendered less likely by the fact that, in many cases, antibiotics were not administered to patients until after they had been admitted to the hospital. However, the possibility that the microbiome may have been altered in these individuals by past administration of antibiotics cannot be excluded. It is of note that these proposed mechanisms of action are not mutually exclusive but might be interacting in different degrees to result in mania or other psychiatric symptoms in different individuals.

3.4. Trials of probiotic compounds in schizophrenia and bipolar disorder

Another research strategy to probe the role of the microbiome in schizophrenia and bipolar disorder involves clinical trials with compounds that may alter the gut microbiome and modulate the immune response and thus potentially have an effect on psychiatric illness symptoms. Probiotic compounds provide a safe and well tolerated means for the modulation of the immune response to harmful antigens such as food-derived proteins. Probiotics have been studied in animal models and have shown benefits in trials of individuals with some gastrointestinal disorders and allergic conditions (De Angelis et al., 2006; Guerra et al., 2011; Saulnier, Kolida, & Gibson, 2009).

One of the first trials of probiotic compounds in schizophrenia involved an add-on probiotic compound (combined *Lactobacillus rhammosus* strain GG and *Bifidobacterium animals* subsp. Lactis strain Bb12 (F. B. Dickerson et al., 2014). Results showed no significant difference in psychiatric symptom severity between probiotic and placebo supplementation at the end of the trial thought those patients who received the probiotic compound vs. the placebo were less likely to develop severe bowel difficulty over the course of the trial, consistent with an effect of probiotics on the gastrointestinal tract. In addition, the probiotic supplementation did significantly alter the levels of several serum proteins assessed before and after the trial including von Willebrand factor and brain-derived neurotrophic factor (Tomasik, Yolken, Bahn, & Dickerson, 2015). Probiotic treatment also lowered the level of

antibodies to the fungus Candida albicans and associated gastrointestinal symptoms in male individuals in the trial (Severance, Gressit, et al., 2016).

Another trial of probiotic supplementation is underway in psychiatric patients, this one in mania. This trial is based on a longitudinal observational study of individuals with acute mania, which found that levels of immune makers, IgG antibodies to gliadin, a measure of gluten sensitivity and levels of antibodies to the NR2 peptide of the NMDA receptor, were significantly increased during the acute manic episode but did not differ from the levels of controls at a 6 month follow up(F. Dickerson, Stallings, Origoni, et al., 2012; F. Dickerson, Stallings, Vaughan, et al., 2012) (F. Dickerson et al., 2013) In addition, a combined inflammation score, calculated by factor analysis of the levels of class specific antibodies to the NR peptide of the NMDA receptor, gliadin, Mason-Pfizer monkey virus protein 24, and *Toxoplasma gondii*, differed from the controls during the acute episode but not at the 6 month follow up(F. Dickerson et al., 2013). In addition, within the mania group, an elevated inflammation score during the acute episode predicted rehospitalization for a new mood episode during the follow-up period. Clinical trials of therapeutic agents which alter gut microbiota or gastrointestinal inflammation will be the ultimate test of the role of the microbiome and immune-mediated pathology in schizophrenia and bipolar disorder

4. Limitations in Current Knowledge

There are a number of limitations in the current state of knowledge regarding the role of the microbiome in etiopathogenesis of schizophrenia and bipolar disorder. These include the following

1. There are as yet no published descriptions of the fecal or intestinal microbiome of individuals with schizophrenia or bipolar disorder. This limitation is undoubtedly related to the difficulty of obtaining relevant sample in this study population. Of particular importance in this regard would be longitudinal studies in which changes in the fecal or intestine microbiome could be studies over time. Such studies could also address the effects of environmental factors such as medications (Bahra et al., 2015), hospitalization, cigarette smoking and living conditions on the composition of the microbiome. Since there are also differences in the microbiome at different levels of the human gastrointestinal tract, studies of the microbial composition of the small bowel and colon in individuals with psychiatric disorders might provide information supplementary to that obtained from analyses of fecal samples in this population.
2. It is not known whether changes in the microbiota associated with schizophrenia and bipolar disorder are state or trait related and how the microbiome may be involved in mood switching in bipolar disorder and in psychotic exacerbations in schizophrenia.
3. Animal studies directed specifically at models of serious psychiatric disorders are limited. Of particular importance would be the interaction of immune related risk genes such as those involved in the complement system (Xiao et al., 2016) with the composition of the microbiome. Animal models would also be useful to

better define the effects of psychiatric medications on the composition of the microbiome in terms of both psychiatric activity and side effects such as weigh gain (Bahr et al., 2015).

Conclusions and Perspectives

Studies to date indicate a role for the microbiome in the etiopathogenesis of serious human psychiatric disorders such as schizophrenia and bipolar disorder. While animal models focus on the bacterial composition of the intestinal tract, studies to date in individuals with psychiatric disorders also point to the possible role of viruses and fungi as well as the involvement of other mucosal body sites such as the nasopharynx. Critical research needs include prospective studies to define risk prior to the onset of therapeutic interventions as well as methods for the accurate assessment of the microbiome at different mucosal sites in a practical manner. There is also a need for effective modalities for the modulation of the microbiome and the control of inflammation in a population of individuals who are taking a range of psychiatric medications. Despite these limitations the analysis of the microbiome in individuals with psychiatric disorders and the development of methods for its modulation offer great promise in terms of developing new methods for the prevention and treatment of these devastating disorders.

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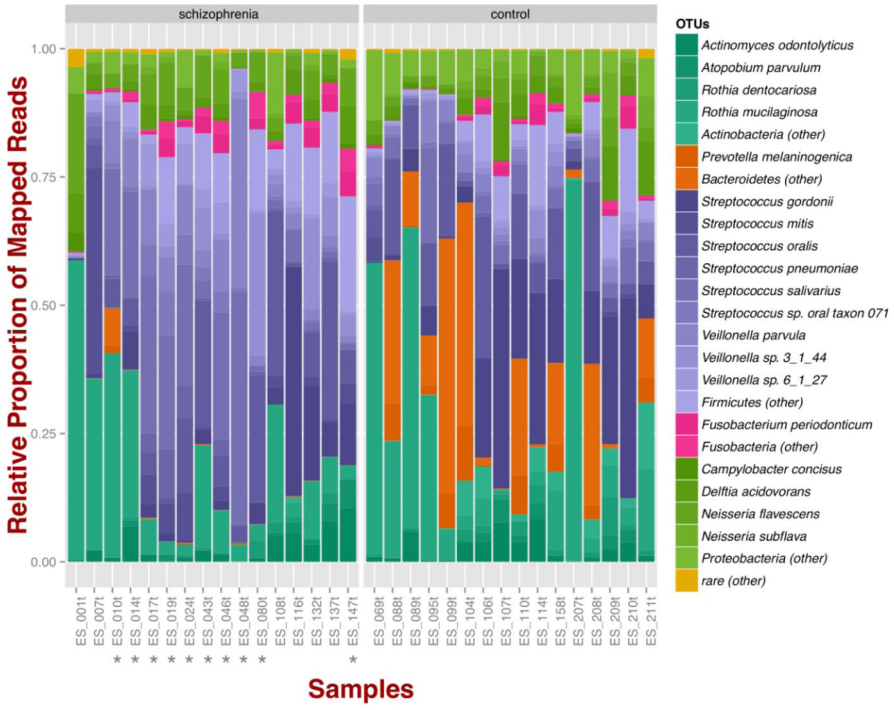

Figure 1. Oropharyngeal microbial composition at phylum and species levels exhibits different patterns for schizophrenia and control samples

The stacked bar chart shows the most prevalent species present in schizophrenia and controls color-coded by phylum. Green, Actinobacteria; Orange, Bacteroidetes; Blue, Firmicutes; Green, Proteobacteria. The symbol (*) indicates samples from smoker individuals. (Reprinted from Castro-Naller et al PubMed 26336637)

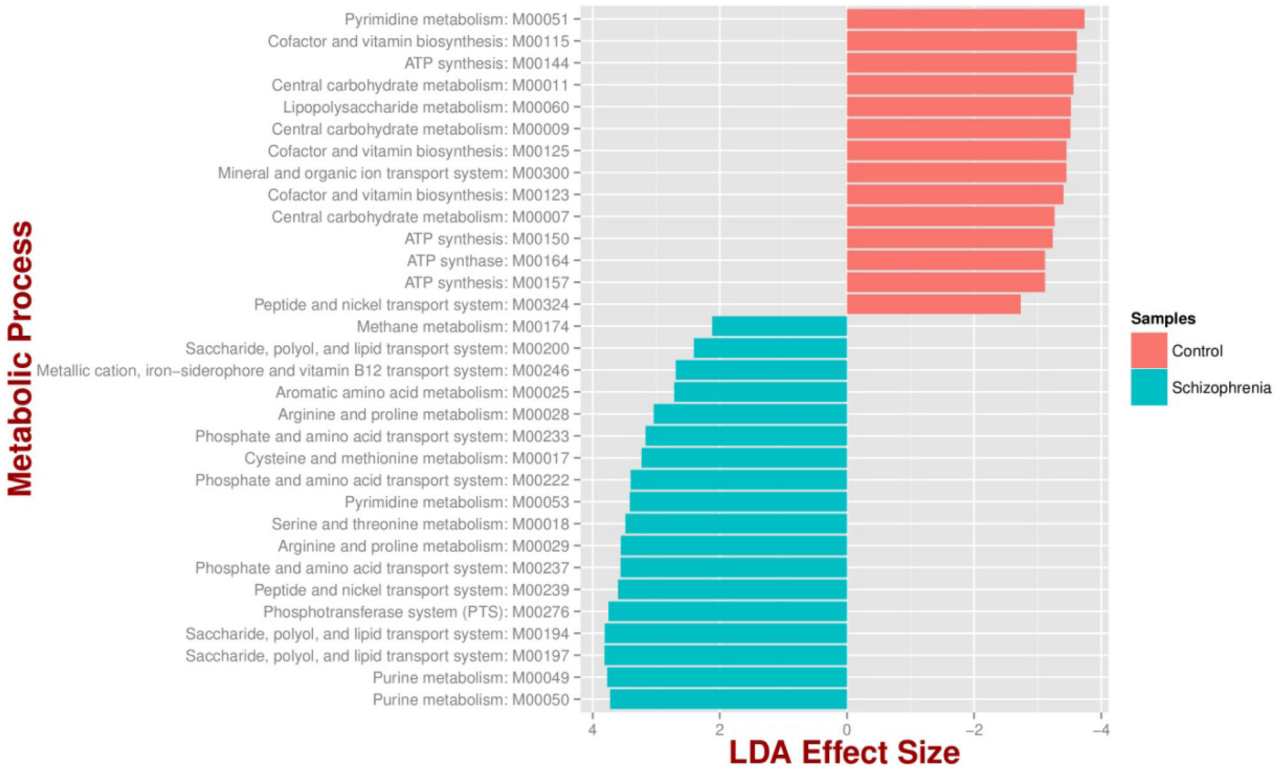

Figure 2. Microbial metabolic pathways with significantly altered abundances in the schizophrenia oropharyngeal microbiome

MXXXXX codes correspond to KEGG modules, i.e., a collection of manually defined functional units (genes). LDA, linear discriminant analysis. (Reprinted from Castro-Naller et al. PubMed 26336637)

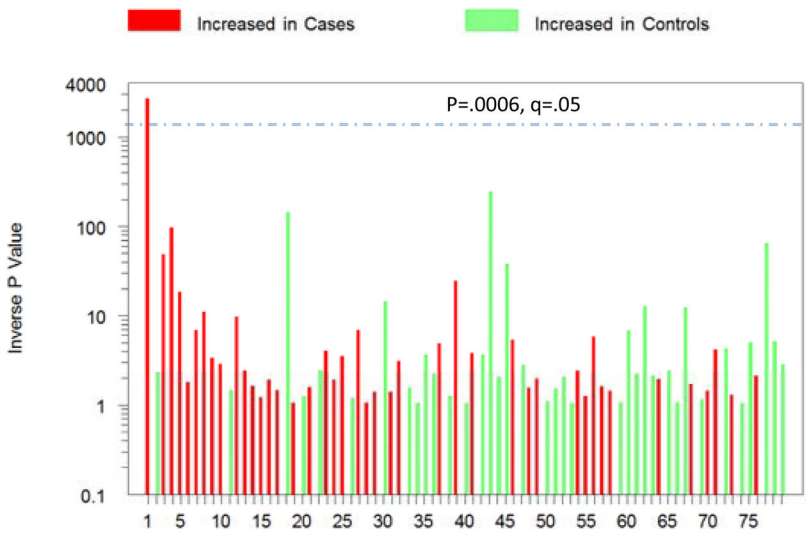

Figure 3. P values representing different levels of phages in 41 individuals with schizophrenia and 33 controls without a psychiatric disorder

The red and green colors indicate levels of the individual phages which are increased or decreased in cases, respectively. The dashed line indicates p<.05 corrected for multiple comparisons. (Reprinted from Yolken et al. Pub Med27425597)