From Infection to the Microbiome: An Evolving Role of Microbes in Schizophrenia

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Contents

Abstract The study of microorganisms such as bacteria, viruses, archaea, fungi, and protozoa in the context of psychiatric disorders may be surprising to some. This intersection of disciplines, however, has a rich history and is currently revitalized by newfound functions of the microbiome and the gut-brain axis in human diseases. Schizophrenia, in particular, fits this model as a disorder with gene and environmental roots that may be anchored in the immune system. In this context, the combination of a precisely timed pathogen exposure in a person with genetically encoded altered immunity may have especially destructive consequences for the central nervous system (CNS). Furthermore, significant components of immunity, such as the development of the immune response and the concept of immune tolerance, are largely dictated by the commensal residents of the microbiome. When this community of microbes is imbalanced, perhaps as the result of a pathogen invasion, stress, or immune gene deficiency, a pathological cycle of localized inflammation, endothelial barrier compromise, translocation of gut-derived products, and systemic inflammation may ensue. If these pathologies enable access of gut and microbial metabolites and immune molecules to the CNS across the blood-brain

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barrier (BBB), and studies of the gut-brain axis support this hypothesis, a worsening of cognitive deficits and psychiatric symptoms is predicted to occur in susceptible individuals with schizophrenia. In this chapter, we review the role of microbes in various stages of this model and how these organisms may contribute to documented phenotypes of schizophrenia. An increased understanding of the role of pathogens and the microbiome in psychiatric disorders will better guide the development of microbial and immune-based therapeutics for disease prevention and treatment.

Keywords Gastrointestinal · Host-pathogen interactions · Microbiota · Neuroimmune · Psychiatry

1 Introduction

Schizophrenia is a chronic, debilitating, and etiologically complex psychiatric disorder that is likely the product of various combinations of interacting genetic and environmental influences (Demjaha et al. 2012; European Network of National Networks studying Gene-Environment Interactions in Schizophrenia (EU-GEI) et al. 2014; Kavanagh et al. 2015; Modinos et al. 2013; Nimgaonkar et al. 2017; Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014; Tsuang 2000). Currently favored hypotheses regarding its causes converge on a key role of the immune system, the dysfunction of which is reflected in the body's peripheral organs and in the central nervous system (CNS). While schizophrenia is not a classic example of a disorder associated with immunity, evidence points toward an immune gene susceptibility that may be further compounded by environmental factors challenging the immune system. For example, genetic studies have implicated a series of immune genes in the chromosome 6 region that contains the MHC/HLA and complement C4 genes as important susceptibility loci associated with schizophrenia (Mayilyan et al. 2008; Sekar et al. 2016; Shi et al. 2009; Stefansson et al. 2009). A role for a microbial component in the etiology, pathogenesis, and pathophysiology of schizophrenia has been examined in various forms and would also be consistent with immune-related hypotheses for this disorder (Crow 1983; Dickerson et al. 2017a; Torrey and Peterson 1973, 1976; Yolken and Torrey 2008). Defining the nature of this microbial contribution to a host phenotype as heterogeneous as schizophrenia has been challenging and has changed in focus over the years without a successful consensus regarding cause and effect. In this review, we cover the evolving microbial landscape pertinent to this disorder and in particular highlight the shift from a search for an incontrovertible pathogen to understanding microbiome-mediated modulations of the gut-brain axis. An overview of some putative mechanisms by which pathogens and commensal microbes might contribute to schizophrenia pathophysiology is diagrammed in Fig. 1.

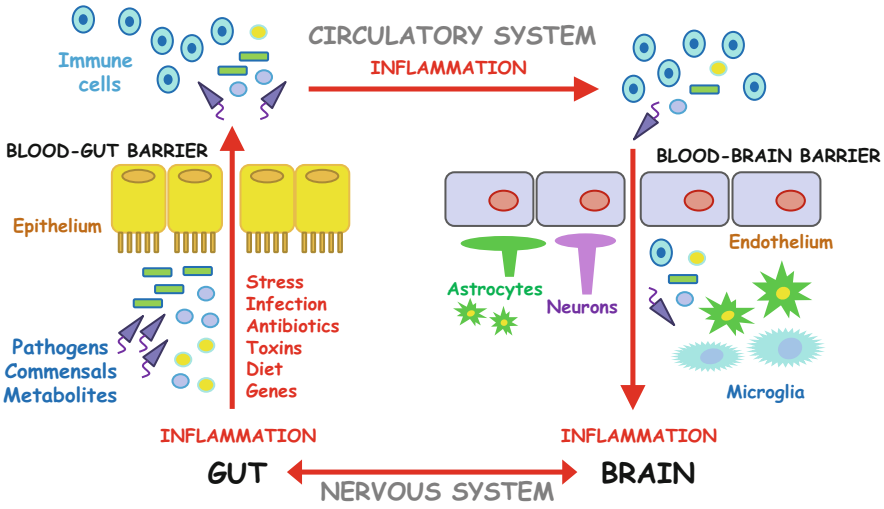

Fig. 1 Pathogens, commensal microbes, and the gut-brain axis in schizophrenia. The proposed model illustrates an overview of how neurotropic pathogens and microbial dysbioses can create an inflammatory environment in the GI tract, a process which leads to systemic inflammation and loss of integrity of the blood-gut and blood-brain barriers. Permeabilized barriers lead to the translocation of resident microbes, metabolites, and toxic products, activation of the immune response, and access to the brain for these gut-derived and immune molecules. The brain's own immune machinery becomes activated as glial cells respond to the intruders. This immune activation both peripherally and centrally includes the complement pathway, components of which can function to modify synaptic connections. The gut-brain axis is bi-directional, and through the vagus nerve, a direct neural conduit joins the enteric and central nervous systems

2 Search for a Pathogen

Jean-Étienne Esquirol (1845) was among the first who suggested that an infectious component might be relevant to psychoses, as based on his observations, psychotic episodes seemed to progress over time in a manner similar to an epidemic-like process (Esquirol 1845). Toward the end of the nineteenth century, Emile Kraepelin hypothesized that dementia praecox, the term for schizophrenia before it was so named by Eugen Bleuler in 1911, was the product of autointoxication. This autotoxication was characterized by the presence of an infectious reservoir that caused accumulation of toxins systemically, which could ultimately detrimentally affect the brain (Noll 2004; Yolken and Torrey 2008). In later years, epidemics of psychosis were reported following the 1918 influenza outbreak with additional observations that psychoses often were comorbid to typhoid, tuberculosis, diphtheria, syphilis, and other encephalitis-type states, thus supporting the earlier observations (Kirch 1993; Menninger 1919, 1926; Torrey and Peterson 1973, 1976; Yolken and Torrey 2008). The possible role of a specific pathogenic organism that might cause a brain disorder such as schizophrenia is exemplified by investigations of neurotropic viruses, such as the herpes simplex viruses (HSV), cytomegalovirus

(CMV), Epstein-Barr virus, measles, and rubella (Alam et al. 2017; Crow 1978; Meyer 2014; Torrey and Peterson 1973; Yolken and Torrey 2008). These studies formed the basis for the viral hypothesis of schizophrenia, which is still prevalent and supported today. Exposure to these neurotropic viruses, furthermore, was also found in multiple studies to be associated with deficits in cognition and gray matter loss in people with schizophrenia (Nimgaonkar and Yolken 2012; Prasad et al. 2011, 2012; Schretlen et al. 2010; Shirts et al. 2008; Watson et al. 2013; Yolken et al. 2011). Interestingly, incorporation of the human leukocyte antigen (HLA) typing has recently identified, through imputations of genome-wide association study (GWAS) data, those HLA types that were most significantly associated with neurotropic infections including the viruses, CMV and HSV1 (Parks et al. 2018). These HLA associations were significant predominantly in healthy controls and were not present in the schizophrenia group, indicating a possible disease-specific alteration of these HLA pathways. Also intriguing is the concept of retrovirus and retrotransposon integration into places within the genome that are involved with regulating cerebral growth and other functions (Crow 1984). Indeed, other viruses demonstrating significant associations with schizophrenia and psychoses over the years have included human endogenous retrovirus, as well as polio, influenza, coronaviruses, and Borna disease virus (Arias et al. 2012; Azami et al. 2018; Dickerson et al. 2010a; Karlsson et al. 2001, 2004; Khandaker et al. 2014; Leweke et al. 2004; Mednick et al. 1988; Perron et al. 2012; Prasad et al. 2007; Severance et al. 2011; Suvisaari et al. 1999). Direct sequencing of brain tissue with the aim to detect viral sequences in post-mortem brains has generally been less successful than antibody-based efforts to document seroprevalence rates in people with schizophrenia. For example, in a recent metagenomics screening of post-mortem prefrontal cortex, 156 unique viral RNA fragments were detected, but there were no differences in viral sequences between cases and controls (Tomasik et al. 2018). Difficulties finding viral nucleic acids in the brain and thus establishing potentially significant differences between diagnostic groups could be due to any number of variables including the time since infection, sensitivity of the assays, and a highly localized, and therefore well-hidden, infectious agent.

This search for a pathogen which would demonstrate a concrete connection between infectious disease agents and schizophrenia etiology or pathophysiology has not been limited to viruses. A possible bacterial basis for schizophrenia was put forth mid-twentieth century based on observed cutaneous reactions to the Rosenow antibody-antigen skin reaction. These findings suggested that schizophrenia may result following exposure to alpha-hemolytic streptococci, although not all individuals with the disorder were affected (Gurassa and Fleischhacker 1958; Rosenow 1948). In hindsight, these mixed results at the time and those garnered well into the future in similar studies, likely merely reflected the heterogeneity of the disorder and collectively suggested that there were subsets of individuals with schizophrenia who were affected in this manner. Later in this chapter, we will focus further on the bacterial contribution to schizophrenia, in particular with respect to the body's microbiome and gut-brain axis. Another microbe, the neurotropic parasite, *Toxoplasma gondii*, has been repeatedly implicated in schizophrenia

etiopathogenesis, and this relationship is reviewed in numerous analyses and meta-analyses (Arias et al. 2012; Monroe et al. 2015; Severance et al. 2016b; Torrey et al. 2007, 2012). Exposure to this parasite has been associated with important clinical effects such as decreased cognition, suicidal behavior, and severity of the psychotic symptoms (Dickerson et al. 2017b; Esshili et al. 2016; Hamdani et al. 2017; Kannan et al. 2017; Lindgren et al. 2018). Studies have also uncovered evidence for heightened exposures to fungal species such as the yeasts, *Candida albicans* and *Saccharomyces cerevisiae*, in individuals with schizophrenia (Severance et al. 2012, 2016a). For *C. albicans*, cognitive deficits and worse psychiatric symptoms have been reported in those who were seropositive (Severance et al. 2016a).

3 Is It the Infectious Disease Process?

To date, an undisputed, causative pathogen has not been singularly identified, in spite of intensive effort and technical advances in deep sequencing of the genome and transcriptome. The rationale for studying pathogenic microorganisms in schizophrenia has been based on the hypothesis that a given microbe or its products are neurotropic and thus potentially directly pathogenic to brain neurons and tissue. In the absence of a conclusive etiological pathogenic species, immune activation as a process is a logical next appropriate focus of these investigations. Epidemiological studies have surveyed for the presence of infections, irrespective of a specific infectious agent, as a risk factor for the development of schizophrenia. For example, in a large cohort study of the Swedish National Register, viral but not bacterial CNS infections during childhood were found to result in the later development of schizophrenia and nonaffective psychoses (Dalman et al. 2008). A similar study of the Danish National Hospital Register indicated an increased risk of schizophrenia in individuals who had hospital contact due to an infection, with specifically bacterial infection showing the highest risk (Nielsen et al. 2014). In other study populations, urinary tract infections, likely of bacterial origin, were found at higher rates in people with schizophrenia or acute psychosis, and these infections were associated with acute relapse of psychosis (Carson et al. 2017; Graham et al. 2014; Miller et al. 2013). A variation of this type of investigation comes from epidemiological studies examining the use of anti-infective agents in schizophrenia. In one such study, the use of antibiotics, but not antivirals, antimycotics, or anti-parasitic agents, was associated with an increased risk for schizophrenia. Furthermore, in this study, if the infection required hospitalization, the risk for developing the disorder was even greater (Kohler et al. 2017). Although the results of these studies are varied in terms of the relative contribution of the type of pathogen (bacterial, viral, fungal), collectively, all point toward microbial infection as an informative comorbidity for at least a portion of those with schizophrenia.

It has long been hypothesized that schizophrenia is a neurodevelopmental disorder (Murray and Lewis 1987; Weinberger 1987); therefore, it seems likely that it is

the process of immune system activation or its dysregulation at sensitive pre-, peri-, and postnatal time-points which may dictate the degree of pathogenicity that will result in the subsequent development of schizophrenia. Numerous mouse models have been developed to illustrate altered behavior or brain biochemistry in offspring of mothers whose immune system has been challenged experimentally during pregnancy (Brown and Derkits 2010; Estes and McAllister 2016; Labouesse et al. 2015; Meyer 2014). In humans, studies of specific pathogens in this context are made possible by the availability of maternal sera drawn during pregnancy or neonatal blood spots obtained at birth. Findings from these studies do, in fact, reveal that a variety of pathogen exposures are associated with the future development of schizophrenia or psychosis in offspring (Blomstrom et al. 2016; Brown et al. 2004; Brown and Derkits 2010; Buka et al. 2008; Ellman et al. 2009; Estes and McAllister 2016; Khandaker et al. 2013; Mortensen et al. 2010; Xiao et al. 2009). Furthermore, prenatal exposure to maternal sinusitis, tonsillitis, pneumonia, as well as genital and other reproductive infections was also associated with the subsequent development of schizophrenia (Babulas et al. 2006; Sorensen et al. 2009). In another study of the Danish National Register, it was found that prenatal infection and peri-pubertal psychological trauma not only each increased the risk of schizophrenia with some sex-specific differences, but the combination of these two factors acted in synergy to compound that risk for disease (Debost et al. 2017). It has also been shown that activation of innate immunity including cytokines and components of the complement pathway were elevated in mothers whose adult offspring developed schizophrenia or psychoses as adults (Allswede et al. 2016; Severance et al. 2014).

4 Gut Inflammation

Immune activation due to infection or another source, or immune dysregulation in general, appears to be as relevant to schizophrenia as exposure to a specific pathogen. Studies of innate immunity in schizophrenia support a low-grade inflammatory component peripherally and in the CNS, which is prevalent in the disorder (Bechter 2013; Catts et al. 2014; Dickerson et al. 2016; Fillman et al. 2013, 2014, 2016; Kirkpatrick and Miller 2013; Miller et al. 2011; Muller 2016; Severance et al. 2012, 2013). The source of this inflammation, however, remains unknown, as does whether this inflammation reflects a pathophysiology of the disease state or a comorbidity resulting from lifestyle choices or medication.

Interestingly, even older than the hypothesis that infection is at the crux of schizophrenia is the hypothesis that all diseases begin in the gut (Hippocrates). The tenets of Hippocratic medicine premised that health was based on four balanced humors, black bile, yellow bile, phlegm, and blood. One of these humors, black bile, referred to the temperament of melancholy, or what we now know as depression (Jackson 2001). In the mid-nineteenth century, purgatives and emetics were suggested treatments for psychiatric symptoms (Prichard 1837). Other historical accounts support a pervasive gastrointestinal (GI) inflammatory state present in

individuals with psychoses and schizophrenia, even well before these psychiatric disorders were described by the earliest versions of our current psychiatric classification systems, the *Diagnostic and Statistical Manual of Mental Disorders* (DSM; 1952) and the International Classification of Diseases (ICD; 1949) (APA 1952; WHO 1949; Alander et al. 2005; Buscaino 1953; Hemmings 2004; Reiter 1926; Schneck 1946). Reports of this GI inflammation likewise preceded the 1950's discovery of modern antipsychotics that are often indicated as the cause of GI comorbidities due to strong anticholinergic effects contributing to decreased bowel motility and constipation (Dean 2010; Dome et al. 2007; McNamara et al. 2011; Watanabe et al. 2010). Indeed, over the years, a number of enteropathic disorders have been studied for association with schizophrenia including celiac disease, gluten intolerance, ulcerative colitis, Crohn's disease, and irritable bowel syndrome (Dohan 1970; Eaton et al. 2004; Gupta et al. 1997; Makikyro et al. 1998; Severance et al. 2015b, 2016c). Serological measures of antibodies directed against *Saccharomyces cerevisiae* (ASCA), which are used clinically to diagnose inflammatory bowel diseases, are also elevated in schizophrenia and especially so in those early-stage patients who were medication-naïve (Ashorn et al. 2009; Desplat-Jego et al. 2007; Kotze et al. 2010; Mallant-Hent et al. 2006; Oshitani et al. 2000; Severance et al. 2012). Likewise, antibodies directed against other antigens that contribute to GI inflammation, such as antigenic foods and gut pathogens, are elevated, in schizophrenia (Dickerson et al. 2010b; Kelly et al. 2018; Severance et al. 2010, 2012, 2016c). The well-studied parasite, *T. gondii*, to which seroprevalence is increased in schizophrenia, is, in fact, a routinely used laboratory tool to model inflammatory bowel diseases in experimental rodents (Craven et al. 2012; Grainger et al. 2013; Hand et al. 2012; Heimesaat et al. 2006).

GI inflammation leads to permeability of the endothelial blood-gut barrier and the potential crossing of microbes, microbial-generated toxins or metabolites, and food-related peptides and antigens into the circulation (Brenchley et al. 2006; Lambert 2009; Sandler and Douek 2012). The translocation of GI-related products has been the focus of studies of depression (Maes et al. 2008, 2012a, b) and to a more limited extent in schizophrenia (Caso et al. 2016; Karakula-Juchnowicz et al. 2016; Severance et al. 2013; Weber et al. 2018). Two surrogate biomarkers of the bacterial translocation process, soluble CD14 (sCD14) and lipopolysaccharide (LPS) binding protein (LBP), were found to be intercorrelated with each other, with a general marker of inflammation, C-reactive protein, and with antibodies to food antigens in individuals with schizophrenia (Severance et al. 2013). In this study and in a follow-up investigation, levels of sCD14 were significantly upregulated not only in individuals with established schizophrenia but also in individuals with pre-onset schizophrenia, as identified based on blood samples and medical records from a US military cohort. In both studies, LBP levels did not match the elevated sCD14 suggesting that additional pathogenic mechanisms related to bacterial translocation and dysregulated monocyte activation may be operative in schizophrenia (Severance et al. 2013; Weber et al. 2018).

5 Microbial Dysbiosis and the Brain

Microbial translocation reflects a gut commensal community that is imbalanced or dysbiotic and that fosters a cycle of inflammation, barrier compromise, and bowel dysfunction. A healthy gut is required for digestion, nutrient absorption, metabolism, maintenance of gut-blood barrier integrity, and development of host immunity (Ismail and Hooper 2005; Round et al. 2010; Smith and Garrett 2011; Sommer and Backhed 2013). Gut function is coordinated by a diverse community of bacteria, viruses, fungi, and archaea, which are at equilibrium with host cell activities (Dinan and Cryan 2015; Sandhya et al. 2016). This equilibrium can be disrupted by stress, diet, antibiotics, toxins, infectious agents, and products generated by host genetics (Sandhya et al. 2016). Thus, for schizophrenia, dysbiosis of the gut microbiome is important to document because it provides a mechanism of GI-localized inflammation that has systemic consequences that are relevant to neuroinflammation and the brain. Importantly, translocated GI products act as triggers of the body's systemic immune machinery, such as the complement pathway, put in motion to clear antigens perceived as foreign from the bloodstream (Brenchley et al. 2006; Lambert 2009; Sandler and Douek 2012). Complement also has important functions in the brain which include the removal of inappropriate synapses, and the genetic and functional associations of this pathway with schizophrenia have been reported and reviewed elsewhere (Nimgaonkar et al. 2017; Presumey et al. 2017; Sekar et al. 2016). Physical access to the brain is a converging and critical consideration in this context, both with respect to translocated gut products and immune molecules. Endothelial barrier defects at both the blood-gut and blood-brain barriers present pathologies that are consistent with a compromised gut-brain pathway operative in schizophrenia (Kannan et al. 2017). Findings from studies employing various approaches suggest an altered function of endothelial cells and BBB permeability associated with schizophrenia (Greene et al. 2017; Khandaker and Dantzer 2016; Severance et al. 2015a). For example, markers of endothelial cell activation including the selectin family of adhesion molecules have been found to be elevated in schizophrenia (Iwata et al. 2007; Khandaker and Dantzer 2016). This endothelial cell activation in the BBB has been shown to follow systemic inflammation and is associated with the translocation of inflammatory cells into the brain (D'Mello and Swain 2014; Khandaker and Dantzer 2016). Accompanying this activation are increased monocyte levels and monocyte infiltration of the BBB which are consistent with the elevations of sCD14 reported in the previous section.

The ability to interrogate rodent models in a germ-free setting has provided much insight regarding the possible mechanisms by which gut microbes are actively engaged in biological pathways that regulate the gut-brain axis. Importantly, these studies allow associations to be made and solidified without a plethora of confounding variables that often accompany and cloud results from clinical studies. Summarily, in the absence of a gut microbiome, the brain fails to develop normally (Sampson and Mazmanian 2015). Altered brain biochemistry, cognition, and behaviors are repeatedly demonstrated following manipulations of gut microbiota in

germ-free and/or pathogen-specific animals (Collins et al. 2012; Diaz Heijtz et al. 2011; Erny et al. 2015; Foster and McVey Neufeld 2013; Hsiao et al. 2013; Luczynski et al. 2016; Stilling et al. 2014). In the germ-free setting, such abnormalities included alterations of myelination, microglial regulation, neurogenesis, and neurotransmitter abundances such as serotonin and precursor tryptophan and trophic factors. These deficits were recovered with further manipulations or corrections of bacterial compositions, vagotomy, and administration of probiotics and/or antibiotics. As relevant to schizophrenia, a revealing set of experiments were those that showed how directly the gut microbiota can impact BBB permeability (Braniste et al. 2014). The absence of a microbiome increased BBB permeability, and this defect was restored following transplantation of germ-free animals with a normal microbiota. Thus, garnered from these studies is evidence of some of the most promising pathways in support of a gut-brain axis including the following: (1) the parasympathetic nervous system and related enteric innervation including the vagus nerve, (2) the neuroendocrine system including stress hormones and the HPA axis, (3) metabolic pathways including microbially generated short-chain fatty acids that bind to G protein-coupled receptors and that are epigenetic modulators, (4) the circulatory system which enables the delivery of gut-generated neuroactive metabolites and neurotransmitters to the vicinity of the brain, and (5) the immune system which is extensively referenced throughout this chapter (Alam et al. 2017; Berger et al. 2009; Dinan et al. 2018; El Aidy et al. 2014).

Of interest are metagenomic and 16S rRNA gene sequencing studies of the oropharyngeal and fecal microbiomes in people with schizophrenia and psychoses compared to controls (Castro-Nallar et al. 2015; Schwarz et al. 2018; Shen et al. 2018; Yolken et al. 2015). In the oropharyngeal microbiome, the genera lactobacilli and bifidobacteria were more abundant in schizophrenia compared to controls, and intriguingly, these are the genera that help to modulate inflammation (Castro-Nallar et al. 2015). Similarly, the oropharyngeal microbiome in schizophrenia contained altered levels of the phage, *Lactobacillus* phiadh, which infects *Lactobacillus gasseri*, a bacteria that functions in part to maintain epithelial cell integrity and to modulate the immune system (Yolken et al. 2015). Differences in fecal lactobacilli were also observed in patients with first-episode psychosis compared to controls, and numbers of these taxa were particularly elevated in those who were most treatment resistant (Schwarz et al. 2018). In another study of the fecal microbiome, case-control differences in numerous taxa were observed including an elevation of the phylum, *Proteobacteria*, and those taxa that functioned in metabolic pathways (Shen et al. 2018).

Clinical trials of probiotics in schizophrenia can be similarly informative regarding potentially correcting a microbe- or gut-based pathology. In a randomized, placebo-controlled trial of adjunctive probiotics in schizophrenia, improved GI function was reported, but there was no change in the severity of psychiatric symptoms associated with probiotic treatment (Dickerson et al. 2014). Serologically, there were significant alterations in an array of immune proteins that pathway analyses indicated were suggestive of improved GI epithelial and immune pathologies associated with probiotic treatment (Tomasik et al. 2015). Of interest also is

how other non-bacterial components of the microbiome might influence these clinical trial findings. For example, in healthy people, commensal yeast species cohabitate with resident bacteria in a homeostatic balance. If this balance is shifted perhaps by diet or antibiotics, bacterial dysbioses, species depletion, and yeast overgrowth can result (Kim and Sudbery 2011). In the probiotic trial cited above, we found evidence for improvement in psychiatric symptoms associated with probiotics, but only in those who were not positive for these invasive yeast infections (Severance et al. 2017). *C. albicans* was, in fact, particularly overrepresented in individuals with schizophrenia compared to controls, and these yeast-positive individuals had correspondingly more cognitive impairments and severe psychiatric symptoms (Severance et al. 2016a, 2017).

6 Conclusions

As such, we are only just beginning to unravel the extent to which microbes regulate human health and disease. Disciplines as dissimilar as gastroenterology, oncology, dermatology, endocrinology, hepatology, neuroscience, and psychiatry are all actively engaged in researching the microbiome. As summarized in this chapter, microbes are associated with schizophrenia etiology, pathogenesis, and pathophysiology in a diversity of ways, ranging from infection-based pathologies to alterations of the gut-brain axis. Infection, inflammation, and gut dysbioses are all treatable conditions, but to develop an effective therapeutic applicable to schizophrenia, it is critical to identify the source of the pathology and to identify those individuals who are impacted. The surge of interest and effort directed toward understanding the microbiome will hopefully accelerate the improvement of methods for manipulating microbiota and lead to novel agents to prevent and treat a wide range of human disorders.

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