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

Emily G. Severance and Robert H. Yolken

Contents
1 Introduction 68
2 Search for a Pathogen 69
3 Is It the Infectious Disease Process? 71
4 Gut Inflammation 72
5 Microbial Dysbiosis and the Brain 74
6 Conclusions 76
References 76

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...
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.
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

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.

Acknowledgments This work was supported by a NIMH P50 Silvio O. Conte Center at Johns Hopkins (grant# MH-94268) and by the Stanley Medical Research Institute.

References

Alam R, Abdolmaleky HM, Zhou JR (2017) Microbiome, inflammation, epigenetic alterations, and mental diseases. Am J Med Genet B Neuropsychiatr Genet 174:651–660
Alander T, Svardsudd K, Johansson SE, Agreus L (2005) Psychological illness is commonly associated with functional gastrointestinal disorders and is important to consider during patient consultation: a population-based study. BMC Med 3:8
Allswede DM, Buka SL, Yolken RH, Torrey EF, Cannon TD (2016) Elevated maternal cytokine levels at birth and risk for psychosis in adult offspring. Schizophr Res 172:41–45
APA (1952) Diagnostic and statistical manual of mental disorders (DSM-I), 1st edn. American Psychiatric Association, Washington
Arias I, Sorlozano A, Villegas E, de Dios Luna J, McKenney K, Cervilla J et al (2012) Infectious agents associated with schizophrenia: a meta-analysis. Schizophr Res 136:128–136
Ashorn S, Valinova T, Kaukinen K, Ashorn M, Braun J, Raukola H et al (2009) Serological responses to microbial antigens in celiac disease patients during a gluten-free diet. J Clin Immunol 29:190–195
Azami M, Jalilian FA, Khorshidi A, Mohammadi Y, Tardeh Z (2018) The association between Borna disease virus and schizophrenia: a systematic review and meta-analysis. Asian J Psychiatr 34:67–73
Babulas V, Factor-Litvak P, Goertz R, Schaefer CA, Brown AS (2006) Prenatal exposure to maternal genital and reproductive infections and adult schizophrenia. Am J Psychiatry 163:927–929
Bechter K (2013) Updating the mild encephalitis hypothesis of schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 42:71–91
Berger M, Gray JA, Roth BL (2009) The expanded biology of serotonin. Annu Rev Med 60:355–366
Blomstrom A, Karlsson H, Gardner R, Jorgensen L, Magnusson C, Dalman C (2016) Associations between maternal infection during pregnancy, childhood infections, and the risk of subsequent psychotic disorder – a Swedish cohort study of nearly two million individuals. Schizophr Bull 42:125–133
Braniste V, Al-Asmakh M, Kowal C, Anuar F, Abbaspour A, Toth M et al (2014) The gut microbiota influences blood-brain barrier permeability in mice. Sci Transl Med 6:263ra158
Brenchley JM, Price DA, Schacker TW, Asher TE, Silvestri G, Rao S et al (2006) Microbial translocation is a cause of systemic immune activation in chronic HIV infection. Nat Med 12:1365–1371
Brown AS, Derkits EJ (2010) Prenatal infection and schizophrenia: a review of epidemiologic and translational studies. Am J Psychiatry 167:261–280
Brown AS, Begg MD, Gravenstein S, Schaefer CA, Wyatt RJ, Bresnahan M et al (2004) Serologic evidence of prenatal influenza in the etiology of schizophrenia. Arch Gen Psychiatry 61:774–780
Buka SL, Cannon TD, Torrey EF, Yolken RH, Collaborative Study Group on the Perinatal Origins of Severe Psychiatric Disorders (2008) Maternal exposure to herpes simplex virus and risk of psychosis among adult offspring. Biol Psychiatry 63:809–815
Buscaino V (1953) Patologia extraneurale della schizofrenia. Fegato, tubo digerente, sistema reticolo-endoteliale. Acta Neurol 8:1–60
Carson CM, Phillip N, Miller BJ (2017) Urinary tract infections in children and adolescents with acute psychosis. Schizophr Res 183:36–40
Caso JR, Balanza-Martinez V, Palomo T, Garcia-Bueno B (2016) The microbiota and gut-brain axis: contributions to the immunopathogenesis of schizophrenia. Curr Pharm Des 22:6122–6133
Castro-Nallar E, Bendall ML, Perez-Losada M, Sabuncyan S, Severance EG, Dickerson FB et al (2015) Composition, taxonomy and functional diversity of the oropharynx microbiome in individuals with schizophrenia and controls. PeerJ 3:e1140
Catts VS, Wong J, Fillman SG, Fung SJ, Shannon Weickert C (2014) Increased expression of astrocyte markers in schizophrenia: association with neuroinflammation. Aust N Z J Psychiatry 48:722–734
Collins SM, Surette M, Bercik P (2012) The interplay between the intestinal microbiota and the brain. Nat Rev Microbiol 10:735–742
Craven M, Egan CE, Dowd SE, McDonough SP, Dogan B, Denkers EY et al (2012) Inflammation drives dysbiosis and bacterial invasion in murine models of ileal Crohn’s disease. PLoS One 7: e41594
Crow TJ (1978) Viral causes of psychiatric disease. Postgrad Med J 54:763–767
Crow TJ (1983) Is schizophrenia an infectious disease? Lancet 1:173–175
Crow TJ (1984) A re-evaluation of the viral hypothesis: is psychosis the result of retroviral integration at a site close to the cerebral dominance gene? Br J Psychiatry 145:243–253

Dalman C, Allebeck P, Gunnell D, Harrison G, Kristensson K, Lewis G et al (2008) Infections in the CNS during childhood and the risk of subsequent psychotic illness: a cohort study of more than one million Swede subjects. Am J Psychiatry 165:59–65

Dean B (2010) Understanding the role of inflammatory-related pathways in the pathophysiology and treatment of psychiatric disorders: evidence from human peripheral studies and CNS studies. Int J Neuropsychopharmacol 14:997–1012

Debost JP, Larsen JT, Munk-Olsen T, Mortensen PB, Meyer U, Petersen L (2017) Joint effects of exposure to prenatal infection and peripubertal psychological trauma in schizophrenia. Schizophr Bull 43:171–179

Demjaha A, MacCabe JH, Murray RM (2012) How genes and environmental factors determine the different neurodevelopmental trajectories of schizophrenia and bipolar disorder. Schizophr Bull 38:209–214

Desplat-Jego S, Johanet C, Escande A, Goetz J, Fabien N, Olsson N et al (2007) Update on anti-Saccharomyces cerevisiae antibodies, anti-nuclear associated anti-neutrophil antibodies and antibodies to exocrine pancreas detected by indirect immunofluorescence as biomarkers in chronic inflammatory bowel diseases: results of a multicenter study. World J Gastroenterol: WJG 13:2312–2318

Diaz Heijtz R, Wang S, Anuar F, Qian Y, Bjorkholm B, Samuelsson A et al (2011) Normal gut microbiota modulates brain development and behavior. Proc Natl Acad Sci U S A 108:3047–3052

Dickerson F, Stallings C, Origoni A, Copp C, Khushalani S, Yolken R (2010a) Antibodies to measles in individuals with recent onset psychosis. Schizophr Res 119:89–94

Dickerson F, Stallings C, Origoni A, Vaughan C, Khushalani S, Leister F et al (2010b) Markers of gluten sensitivity and celiac disease in recent-onset psychosis and multi-episode schizophrenia. Biol Psychiatry 68:100–104

Dickerson FB, Stallings C, Origoni A, Katsafanas E, Savage CL, Schweinfurth LA et al (2014) Effect of probiotic supplementation on schizophrenia symptoms and association with gastrointestinal functioning: a randomized, placebo-controlled trial. Prim Care Companion CNS Disord 16. https://doi.org/10.4088/PCC.13m01579

Dickerson F, Stallings C, Origoni A, Schroeder J, Katsafanas E, Schweinfurth L et al (2016) Inflammatory markers in recent onset psychosis and chronic schizophrenia. Schizophr Bull 42:134–141

Dickerson F, Severance E, Yolken R (2017a) The microbiome, immunity, and schizophrenia and bipolar disorder. Brain Behav Immun 62:46–52

Dickerson F, Wilcox HC, Adams M, Katsafanas E, Khushalani S, Origoni A et al (2017b) Suicide attempts and markers of immune response in individuals with serious mental illness. J Psychiatr Res 87:37–43

Dinan TG, Cryan JF (2015) The impact of gut microbiota on brain and behaviour: implications for psychiatry. Curr Opin Clin Nutr Metab Care 18:552–558

Dinan TG, Cryan JF, Stanton C (2018) Gut microbes and brain development have black box connectivity. Biol Psychiatry 83:97–99

D’Mello C, Swain MG (2014) Liver-brain interactions in inflammatory liver diseases: implications for fatigue and mood disorders. Brain Behav Immun 35:9–20

Dohan FC (1970) Coeliac disease and schizophrenia. Lancet 1:897–898

Dome P, Teleki Z, Kotanyi R (2007) Paralytic ileus associated with combined atypical antipsychotic therapy. Prog Neuro-Psychopharmacol Biol Psychiatry 31:557–560

Eaton W, Mortensen PB, Agerbo E, Byrne M, Mors O, Ewald H (2004) Coeliac disease and schizophrenia: population based case control study with linkage of Danish national registers. BMJ 328:438–439

El Aidy S, Dinan TG, Cryan JF (2014) Immune modulation of the brain-gut-microbe axis. Front Microbiol 5:146
From Infection to the Microbiome: An Evolving Role of Microbes in Schizophrenia

Ellman LM, Yolken RH, Buka SL, Torrey EF, Cannon TD (2009) Cognitive functioning prior to the onset of psychosis: the role of fetal exposure to serologically determined influenza infection. Biol Psychiatry 65:1040–1047

Erny D, Hrabe de Angelis AL, Jaitin D, Wieghofer P, Staszewski O, David E et al (2015) Host microbiota constantly control maturation and function of microglia in the CNS. Nat Neurosci 18:965–977

Esquirol JE (1845) Mental maladies, a treatise on insanity. Lea and Blanchard, Philadelphia

Esshili A, Thabet S, Jemli A, Trifa F, Mechri A, Zaafra F et al (2016) Toxoplasma gondii infection in schizophrenia and associated clinical features. Psychiatry Res 245:327–332

Estes ML, McAllister AK (2016) Maternal immune activation: implications for neuropsychiatric disorders. Science 353:772–777

European Network of National Networks studying Gene-Environment Interactions in Schizophrenia (EU-GEI), van Os J, Rutten BP, Myin-Germeys I, Delespaul P, Viechtbauer W et al (2014) Identifying gene-environment interactions in schizophrenia: contemporary challenges for integrated, large-scale investigations. Schizophr Bull 40:729–736

Fillman SG, Cloonan N, Catts VS, Miller LC, Wong J, McCrossin T et al (2013) Increased inflammatory markers identified in the dorsolateral prefrontal cortex of individuals with schizophrenia. Mol Psychiatry 18:206–214

Fillman SG, Sinclair D, Fung SJ, Webster MJ, Shannon Weickert C (2014) Markers of inflammation and stress distinguish subsets of individuals with schizophrenia and bipolar disorder. Transl Psychiatry 4:e365

Fillman SG, Weickert TW, Lenroot RK, Catts SV, Bruggemann JM, Catts VS et al (2016) Elevated peripheral cytokines characterize a subgroup of people with schizophrenia displaying poor verbal fluency and reduced Broca’s area volume. Mol Psychiatry 21:1090–1098

Foster IA, McVey Neufeld KA (2013) Gut-brain axis: how the microbiome influences anxiety and depression. Trends Neurosci 36:305–312

Graham KL, Carson CM, Ezeoke A, Buckley PF, Miller BJ (2014) Urinary tract infections in acute psychosis. J Clin Psychiatry 75:379–385

Grainger JR, Wohlfert EA, Fuss II, Bouladoux N, Askenase MH, Legrand F et al (2013) Inflammatory monocytes regulate pathologic responses to commensals during acute gastrointestinal infection. Nat Med 19:713–721

Greene C, Kealy J, Humphries MM, Gong Y, Hou J, Hudson N et al (2017) Dose-dependent expression of claudin-5 is a modifying factor in schizophrenia. Mol Psychiatry 23:2156–2166

Gupta S, Masand PS, Kaplan D, Bhandary A, Hendricks S (1997) The relationship between schizophrenia and irritable bowel syndrome (IBS). Schizophr Res 23:265–268

Gurassa WP, Fleischhacker HH (1958) An investigation of the Rosenow antibody antigen skin reaction in schizophrenia. J Neurol Neurosurg Psychiatry 21:141–145

Hamdani N, Daban-Huard C, Godin O, Laouamri H, Jamain S, Attiba D et al (2017) Effects of cumulative herpesviridae and Toxoplasma gondii infections on cognitive function in healthy, bipolar, and schizophrenia subjects. J Clin Psychiatry 78:e18–e27

Hand TW, Dos Santos LM, Bouladoux N, Molloy MJ, Pagan AJ, Pepper M et al (2012) Acute gastrointestinal infection induces long-lived microbiota-specific T cell responses. Science 337:1553–1556

Heimesaat MM, Bereswill S, Fischer A, Fuchs D, Struck D, Niebergall J et al (2006) Gram-negative bacteria aggravate murine small intestinal th1-type immunopathology following oral infection with Toxoplasma gondii. J Immunol 177:8785–8795

Hemnings G (2004) Schizophrenia. Lancet 364:1312–1313

Hsiao EY, McBride SW, Hsien S, Sharon G, Hyde ER, McCue T et al (2013) Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. Cell 155:1451–1463

Ismail AS, Hooper LV (2005) Epithelial cells and their neighbors. IV. Bacterial contributions to intestinal epithelial barrier integrity. Am J Physiol Gastrointest Liver Physiol 289:G779–G784
Iwata Y, Suzuki K, Nakamura K, Matsuzaki H, Sekine Y, Tsuchiya KJ et al (2007) Increased levels of serum soluble l-selectin in unmedicated patients with schizophrenia. Schizophr Res 89:154–160
Jackson WA (2001) A short guide to humoral medicine. Trends Pharmacol Sci 22:487–489
Kannan G, Gressitt KL, Yang S, Stallings CR, Katsafanas E, Schweinfurth LA et al (2017) Pathogen-mediated NMDA receptor autoimmunity and cellular barrier dysfunction in schizophrenia. Transl Psychiatry 7:e1186
Karakula-Juchnowicz H, Dzikowski M, Peleczarska A, Dzikowska I, Juchnowicz D (2016) The brain-gut axis dysfunctions and hypersensitivity to food antigens in the etiopathogenesis of schizophrenia. Psychiatr Pol 50:747–760
Karlsson H, Bachmann S, Schroder J, McArthur J, Torrey EF, Yolken RH (2001) Retroviral RNA identified in the cerebrospinal fluids and brains of individuals with schizophrenia. Proc Natl Acad Sci U S A 98:4634–4639
Karlsson H, Schroder J, Bachmann S, Bottner C, Yolken RH (2004) HERV-W-related RNA detected in plasma from individuals with recent-onset schizophrenia or schizoaffective disorder. Mol Psychiatry 9:12–13
Kavanagh DH, Tansey KE, O’Donovan MC, Owen MJ (2015) Schizophrenia genetics: emerging themes for a complex disorder. Mol Psychiatry 20:72–76
Kelly DL, Demyanovich HK, Eaton WW, Cascella N, Jackson J, Fasano A et al (2018) Anti gliadin antibodies (AGA IgG) related to peripheral inflammation in schizophrenia. Brain Behav Immun 69:57–59
Khandaker GM, Dantzer R (2016) Is there a role for immune-to-brain communication in schizophrenia? Psychopharmacology 233:1559–1573
Khandaker GM, Zimbron J, Lewis G, Jones PB (2013) Prenatal maternal infection, neurodevelopment and adult schizophrenia: a systematic review of population-based studies. Psychiat Med 43:239–257
Khandaker GM, Stochl J, Zammit S, Lewis G, Jones PB (2014) Childhood Epstein-Barr virus infection and subsequent risk of psychotic experiences in adolescence: a population-based prospective serological study. Schizophr Res 158:19–24
Kim J, Sudbery P (2011) Candida albicans, a major human fungal pathogen. J Microbiol 49:171–177
Kirch DG (1993) Infection and autoimmunity as etiologic factors in schizophrenia: a review and reappraisal. Schizophr Bull 19:355–370
Kirkpatrick B, Miller BJ (2013) Inflammation and schizophrenia. Schizophr Bull 39:1174–1179
Kohler O, Petersen L, Mors O, Mortensen PB, Yolken RH, Gasse C et al (2017) Infections and exposure to anti-infective agents and the risk of severe mental disorders: a nationwide study. Acta Psychiatr Scand 135:97–105
Kotze LM, Nisihara RM, Utiyama SR, Kotze PG, Theiss PM, Olanderski M (2010) Antibodies anti-Saccharomyces cerevisiae (ASCA) do not differentiate Crohn’s disease from celiac disease. Arq Gastroenterol 47:242–245
Labouesse MA, Langhans W, Meyer U (2015) Long-term pathological consequences of prenatal infection: beyond brain disorders. Am J Physiol Regul Integr Comp Physiol 309:R1–R12
Lambert GP (2009) Stress-induced gastrointestinal barrier dysfunction and its inflammatory effects. J Anim Sci 87:E101–E108
Leweke FM, Gerth CW, Koethe D, Klosterkotter J, Ruslanova I, Krivogorsky B et al (2004) Antibodies to infectious agents in individuals with recent onset schizophrenia. Eur Arch Psychiatry Clin Neurosci 254:4–8
Lindgren M, Tormiainen-Holm M, Harkanen T, Dickerson F, Yolken RH, Suvisaari J (2018) The association between Toxoplasma and the psychosis continuum in a general population setting. Schizophr Res 193:329–335
Luczynski P, Whelan SO, O’Sullivan C, Clarke G, Shanahan F, Dinan TG et al (2016) Adult microbiota-deficient mice have distinct dendritic morphological changes: differential effects in the amygdala and hippocampus. Eur J Neurosci 44:2654–2666
Maes M, Kubera M, Leunis JC (2008) The gut-brain barrier in major depression: intestinal mucosal dysfunction with an increased translocation of LPS from gram negative enterobacteria (leaky gut) plays a role in the inflammatory pathophysiology of depression. Neuro Endocrinol Lett 29:117–124

Maes M, Kubera M, Leunis JC, Berk M (2012a) Increased IgA and IgM responses against gut commensals in chronic depression: further evidence for increased bacterial translocation or leaky gut. J Affect Disord 141:55–62

Maes M, Kubera M, Leunis JC, Berk M, Geffard M, Bosmans E (2012b) In depression, bacterial translocation may drive inflammatory responses, oxidative and nitrosative stress (O&NS), and autoimmune responses directed against O&NS-damaged neoepitopes. Acta Psychiatr Scand 127:344–354

Makikyro T, Karvonen JT, Hakko H, Nieminen P, Joukamaa M, Isohanni M et al (1998) Comorbidity of hospital-treated psychiatric and physical disorders with special reference to schizophrenia: a 28 year follow-up of the 1966 northern Finland general population birth cohort. Public Health 112:221–228

Mallant-Hent R, Mary B, von Blomberg E, Yuksel Z, Wahab PJ, Gundy C et al (2006) Disappearance of anti-Saccharomyces cerevisiae antibodies in coeliac disease during a gluten-free diet. Eur J Gastroenterol Hepatol 18:75–78

Mayilyan KR, Dodds AW, Boyajyan AS, Soghoyan AF, Sim RB (2008) Complement c4b protein in schizophrenia. World J Biol Psychiatry 9:225–230

McNamara RK, Jandacek R, Rider T, Tso P (2011) Chronic risperidone normalizes elevated pro-inflammatory cytokine and C-reactive protein production in omega-3 fatty acid deficient rats. Eur J Pharmacol 652:152–156

Mednick SA, Machon RA, Hutunnen MO, Bonett D (1988) Adult schizophrenia following prenatal exposure to an influenza epidemic. Arch Gen Psychiatry 45:189–192

Menninger KA (1919) Psychoses associated with influenza. J Am Med Assoc 72:235–241

Menninger KA (1926) Influenza and schizophrenia: an analysis of post-influenza “dementia praecox” as of 1918 and five years later. Am J Psychiatr 5:469–529

Meyer U (2014) Prenatal poly(i:C) exposure and other developmental immune activation models in rodent systems. Biol Psychiatry 75:307–315

Miller BJ, Buckley P, Seabolt W, Mellor A, Kirkpatrick B (2011) Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. Biol Psychiatry 70:663–671

Miller BJ, Graham KL, Bodenheimer CM, Culpepper NH, Waller JL, Buckley PF (2013) A prevalence study of urinary tract infections in acute relapse of schizophrenia. J Clin Psychiatry 74:271–277

Modinos G, Iyegbe C, Prata D, Rivera M, Kempton MJ, Valmaggia LR et al (2013) Molecular genetic gene-environment studies using candidate genes in schizophrenia: a systematic review. Schizophr Res 150:356–365

Monroe JM, Buckley PF, Miller BJ (2015) Meta-analysis of anti-Toxoplasma gondii IgM antibodies in acute psychosis. Schizophr Bull 41:989–998

Mortensen PB, Pedersen CB, Hougaard DM, Norgaard-Petersen B, Mors O, Borglum AD et al (2010) A Danish national birth cohort study of maternal HSV-2 antibodies as a risk factor for schizophrenia in their offspring. Schizophr Res 122:257–263

Muller N (2016) What role does inflammation play in schizophrenia? Expert Rev Neurother 16:1337–1340

Murray RM, Lewis SW (1987) Is schizophrenia a neurodevelopmental disorder? Br Med J (Clin Res Ed) 295:681–682

Nielsen PR, Benros ME, Mortensen PB (2014) Hospital contacts with infection and risk of schizophrenia: a population-based cohort study with linkage of Danish national registers. Schizophr Bull 40:1526–1532

Nimgaonkar VL, Yolken RH (2012) Neurotropic infectious agents and cognitive impairment in schizophrenia. Schizophr Bull 38:1135–1136
Nimgaonkar VL, Prasad KM, Chowdari KV, Severance EG, Yolken RH (2017) The complement system: a gateway to gene-environment interactions in schizophrenia pathogenesis. Mol Psychiatry 22:1554–1561

Noll R (2004) Historical review: autointoxication and focal infection theories of dementia praecox. World J Biol Psychiatry 5:66–72

Oshitani N, Hato F, Matsumoto T, Jinno Y, Sawa Y, Hara J et al (2000) Decreased anti-Saccharomyces cerevisiae antibody titer by mesalazine in patients with Crohn’s disease. J Gastroenterol Hepatol 15:1400–1403

Parks S, Avramidopoulos D, Mulle J, McGrath J, Wang R, Goes FS et al (2018) HLA typing using genome wide data reveals susceptibility types for infections in a psychiatric disease enriched sample. Brain Behav Immun 70:203–213

Perron H, Hamdani N, Faucard R, Lajnef M, Jamain S, Daban-Huard C et al (2012) Molecular characteristics of human endogenous retrovirus type-w in schizophrenia and bipolar disorder. Transl Psychiatry 2:e201

Prasad KM, Shirts BH, Yolken RH, Keshavan MS, Nimgaonkar VL (2007) Brain morphological changes associated with exposure to HSV1 in first-episode schizophrenia. Mol Psychiatry 12:105–113, 101

Prasad KM, Eack SM, Goradia D, Pancholi KM, Keshavan MS, Yolken RH et al (2011) Progressive gray matter loss and changes in cognitive functioning associated with exposure to herpes simplex virus 1 in schizophrenia: a longitudinal study. Am J Psychiatry 168:822–830

Prasad KM, Watson AM, Dickerson FB, Yolken RH, Nimgaonkar VL (2012) Exposure to herpes simplex virus type 1 and cognitive impairments in individuals with schizophrenia. Schizophr Bull 38:1137–1148

Presumey J, Bialas AR, Carroll MC (2017) Complement system in neural synapse elimination in development and disease. Adv Immunol 135:53–79

Prichard JC (1837) A treatise on insanity and other disorders affecting the mind. E.L. Carey & A. Hart, Philadelphia

Reiter P (1926) Extrapyramidal motor disturbances in dementia praecox. Acta Psychiatr Neurol 1:287–304

Rosenow EC (1948) Bacteriologic, etiologic, and serologic studies in epilepsy and schizophrenia; cutaneous reactions to intradermal injection of streptococcal antibody and antigen. Postgrad Med 3:367–376

Round JL, O’Connell RM, Mazmanian SK (2010) Coordination of tolerogenic immune responses by the commensal microbiota. J Autoimmun 34:J220–J225

Sampson TR, Mazmanian SK (2015) Control of brain development, function, and behavior by the microbiome. Cell Host Microbe 17:565–576

Sandhya P, Danda D, Sharma D, Scaria V (2016) Does the buck stop with the bugs?: an overview of microbial dysbiosis in rheumatoid arthritis. Int J Rheum Dis 19:8–20

Sandler NG, Douek DC (2012) Microbial translocation in HIV infection: causes, consequences, and treatment opportunities. Nat Rev Microbiol 10:655–666

Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014) Biological insights from 108 schizophrenia-associated genetic loci. Nature 511:421–427

Schneck JM (1946) Gastro-intestinal symptomatology in schizophrenia. Am J Dig Dis 13:257–260

Schreiten DI, Vannorsdall TD, Winicki JM, Mushtaq Y, Hikida T, Sawa A et al (2010) Neuroanatomic and cognitive abnormalities related to herpes simplex virus type 1 in schizophrenia. Schizophr Res 118:224–231

Schwarz E, Maukonen J, Hyttiainen T, Kieseppa T, Oresic M, Sabunciyan S et al (2018) Analysis of microbiota in first episode psychosis identifies preliminary associations with symptom severity and treatment response. Schizophr Res 192:398–403

Sekar A, Bialas AR, de Rivera H, Davis A, Hammond TR, Kamitaki N et al (2016) Schizophrenia risk from complex variation of complement component 4. Nature 530:177–183
Severance EG, Dickerson FB, Halling M, Krivogorsky B, Haile L, Yang S et al (2010) Subunit and whole molecule specificity of the anti-bovine casein immune response in recent onset psychosis and schizophrenia. Schizophr Res 118:240–247

Severance EG, Dickerson FB, Viscidi RP, Bossis I, Stallings CR, Origoni AE et al (2011) Coronavirus immunoreactivity in individuals with a recent onset of psychotic symptoms. Schizophr Bull 37:101–107

Severance EG, Alaeddini A, Yang S, Halling M, Gressitt KL, Stallings CR et al (2012) Gastrointestinal inflammation and associated immune activation in schizophrenia. Schizophr Res 138:48–53

Severance EG, Gressitt KL, Stallings CR, Origoni AE, Khushalani S, Leweke FM et al (2013) Discordant patterns of bacterial translocation markers and implications for innate immune imbalances in schizophrenia. Schizophr Res 148:130–137

Severance EG, Gressitt KL, Buka SL, Cannon TD, Yolken RH (2014) Maternal complement c1q and increased odds for psychosis in adult offspring. Schizophr Res 159:14–19

Severance EG, Gressitt KL, Alaeddini A, Rohleder C, Enning F, Bumb JM et al (2015a) IgG dynamics of dietary antigens point to cerebrospinal fluid barrier or flow dysfunction in first-episode schizophrenia. Brain Behav Immun 44:148–158

Severance EG, Prandovszky E, Castiglione J, Yolken RH (2015b) Gastroenterology issues in schizophrenia: why the gut matters. Curr Psychiatry Rep 17:27

Severance EG, Gressitt KL, Stallings CR, Katsafanas E, Schweinfurth LA, Savage CL et al (2016a) Candida albicans exposures, sex specificity and cognitive deficits in schizophrenia and bipolar disorder. NPJ Schizophr 2:16018

Severance EG, Xiao J, Jones-Brando L, Sabunciyan S, Li Y, Pletnikov M et al (2016b) Toxoplasma gondii – a gastrointestinal pathogen associated with human brain diseases. Int Rev Neurobiol 131:143–163

Shen Y, Xu J, Li Z, Huang Y, Yuan Y, Wang J et al (2018) Analysis of gut microbiota diversity and auxiliary diagnosis as a biomarker in patients with schizophrenia: a cross-sectional study. Schizophr Res. https://doi.org/10.1016/j.schres.2018.01.002

Shi J, Levinson DF, Duan J, Sanders AR, Zheng Y, Pe'er I et al (2009) Common variants on chromosome 6p22.1 are associated with schizophrenia. Nature 460:753–757

Shirts BH, Prasad KM, Pogue-Geile MF, Dickerson F, Yolken RH, Nimgaonkar VL (2008) Antibodies to cytomegalovirus and herpes simplex virus 1 associated with cognitive function in schizophrenia. Schizophr Res 106:268–274

Smith PM, Garrett WS (2011) The gut microbiota and mucosal t cells. Front Microbiol 2:111

Sommer F, Backhed F (2013) The gut microbiota – masters of host development and physiology. Nat Rev Microbiol 11:227–238

Sorensen HJ, Mortensen EL, Reinisch JM, Mednick SA (2009) Association between prenatal exposure to bacterial infection and risk of schizophrenia. Schizophr Bull 35:631–637

Stefansson H, Ophoff RA, Steinberg S, Andreassen OA, Cichon S, Rujescu D et al (2009) Common variants conferring risk of schizophrenia. Nature 460:744–747

Stilling RM, Dinan TG, Cryan JF (2014) Microbial genes, brain & behaviour – epigenetic regulation of the gut-brain axis. Genes Brain Behav 13:69–86

Suvisaari J, Haukka J, Tanskanen A, Hovi T, Lonqvist J (1999) Association between prenatal exposure to poliovirus infection and adult schizophrenia. Am J Psychiatry 156:1100–1102

Tomasik J, Yolken RH, Bahn S, Dickerson FB (2015) Immunomodulatory effects of probiotic supplementation in schizophrenia patients: a randomized, placebo-controlled trial. Biomark Insights 10:47–54
Tomasik J, Smits SL, Leweke FM, Eljasz P, Pas S, Kahn RS et al (2018) Virus discovery analyses on post-mortem brain tissue and cerebrospinal fluid of schizophrenia patients. Schizophr Res. https://doi.org/10.1016/j.schres.2018.02.012

Torrey EF, Peterson MR (1973) Slow and latent viruses in schizophrenia. Lancet 2:22–24

Torrey EF, Peterson MR (1976) The viral hypothesis of schizophrenia. Schizophr Bull 2:136–146

Torrey EF, Bartko JJ, Lun ZR, Yolken RH (2007) Antibodies to Toxoplasma gondii in patients with schizophrenia: a meta-analysis. Schizophr Bull 33:729–736

Torrey EF, Bartko JJ, Yolken RH (2012) Toxoplasma gondii and other risk factors for schizophrenia: an update. Schizophr Bull 38:642–647

Tsuang M (2000) Schizophrenia: genes and environment. Biol Psychiatry 47:210–220

Watanabe Y, Someya T, Nawa H (2010) Cytokine hypothesis of schizophrenia pathogenesis: evidence from human studies and animal models. Psychiatry Clin Neurosci 64:217–230

Watson AM, Prasad KM, Klei L, Wood JA, Yolken RH, Gur RC et al (2013) Persistent infection with neurotropic herpes viruses and cognitive impairment. Psychol Med 43:1023–1031

Weber NS, Gressitt KL, Cowan DN, Niebuhr DW, Yolken RH, Severance EG (2018) Monocyte activation detected prior to a diagnosis of schizophrenia in the US Military New Onset Psychosis Project (MNOPP). Schizophr Res. https://doi.org/10.1016/j.schres.2017.12.016

Weinberger DR (1987) Implications of normal brain development for the pathogenesis of schizophrenia. Arch Gen Psychiatry 44:660–669

WHO (1949) Manual of the international statistical classification of diseases, injuries and causes of death. World Health Organization, Geneva

Xiao J, Buka SL, Cannon TD, Suzuki Y, Viscidi RP, Torrey EF et al (2009) Serological pattern consistent with infection with type I Toxoplasma gondii in mothers and risk of psychosis among adult offspring. Microbes Infect 11:1011–1018

Yolken RH, Torrey EF (2008) Are some cases of psychosis caused by microbial agents? A review of the evidence. Mol Psychiatry 13:470–479

Yolken RH, Torrey EF, Lieberman JA, Yang S, Dickerson FB (2011) Serological evidence of exposure to Herpes Simplex Virus type 1 is associated with cognitive deficits in the CATIE schizophrenia sample. Schizophr Res 128:61–65

Yolken RH, Severance EG, Sabunciyani S, Gressitt KL, Chen O, Stallings C et al (2015) Metagenomic sequencing indicates that the oropharyngeal phageome of individuals with schizophrenia differs from that of controls. Schizophr Bull 41:1153–1161