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# Autoimmune phenotypes in schizophrenia reveal novel treatment targets

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## ABSTRACT

Typical and atypical antipsychotics are the first-line treatments for schizophrenia, but these classes of drugs are not universally effective, and they can have serious side effects that impact compliance. Antipsychotic drugs generally target the dopamine pathways with some variation. As research of schizophrenia pathophysiology has shifted away from a strictly dopamine-centric focus, the development of new pharmacotherapies has waned. A field of inquiry with centuries-old roots is gaining traction in psychiatric research circles and may represent a new frontier for drug discovery in schizophrenia. At the forefront of this investigative effort is the immune system and its many components, pathways and phenotypes, which are now known to actively engage the brain. Studies in schizophrenia reveal an intricate association of environmentally-driven immune activation in concert with a disrupted genetic template. A consistent conduit through this gene-environmental milieu is the gut-brain axis, which when dysregulated can generate pathological autoimmunity. In this review, we present epidemiological and biochemical evidence in support of an autoimmune component in schizophrenia and depict gut processes and a dysbiotic microbiome as a source and perpetuator of autoimmune dysfunction in the brain. Within this framework, we review the role of infectious agents, inflammation, gut dysbioses and autoantibody propagation on CNS pathologies such as neurotransmitter receptor hypofunction and complement pathway-mediated synaptic pruning. We then review the new pharmacotherapeutic horizon and novel agents directed to impact these pathological conditions. At the core of this discourse is the understanding that schizophrenia is etiologically and pathophysiologically heterogeneous and thus its treatment requires individualized attention with disease state variants diagnosed with objective biomarkers.

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## Contents

1. Introduction	184
2. Autoimmunity in schizophrenia	188
3. Treating autoimmunity in schizophrenia	191
4. Conclusions	193
Acknowledgments	193
References	193

## 1. Introduction

Schizophrenia is a polygenic psychiatric disorder defined by a complex of positive, negative and cognitive symptoms. Positive

*Abbreviations:* BBB, Blood-brain-barrier; CNS, central nervous system; GI, gastrointestinal; GWAS, genome wide association studies; HLA, Human leukocyte antigen; MHC, Major histocompatibility complex; NMDA, *N*-methyl-*D*-aspartate; SCFAs, Small chain fatty acids.

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symptoms include delusions and hallucinations, whereas negative symptoms reflect the absence of an expected response such as blunted affect, anhedonia or loss of social drive. Individuals with schizophrenia also often suffer from cognitive difficulties that impact organized thought processes, concentration, task completion and memory (APA, 2013). The causes of schizophrenia are not known, but the disorder is thought to be a product of gene and environmental factors interacting during critical neurodevelopmental time points (Demjaha, MacCabe, & Murray, 2012; European Network of National Networks studying Gene-Environment Interactions in et al., 2014; Kavanagh, Tansey, O'Donovan, & Owen, 2015; Modinos et al., 2013; Nimgaonkar, Prasad,

Chowdari, Severance, & Yolken, 2017; Schizophrenia Working Group of the Psychiatric Genomics, 2014; Tsuang, 2000). Over the years, research has concentrated on the dopamine receptor, but pharmacological modulation of subtypes of this receptor is not an effective treatment for all cases of schizophrenia. More specifically, although dopamine receptor modifying drugs can be effective for positive symptoms in many, these agents are rarely effective for negative and cognitive symptoms, which account for much of the chronic morbidity of the condition. This research focus beyond the dopamine receptors has broadened to include other neurotransmitter receptor types including serotonergic, cholinergic, glutamatergic, and GABAergic pathway targets, yet the discovery of definitive causative mechanisms for this disease that might effectively guide treatment strategies has remained elusive (Erhart, Marder, & Carpenter, 2006; Marder, 2006).

Schizophrenia is currently treated with typical and atypical antipsychotics. The older, typical, antipsychotics produce a sedative effect and closely target dopamine receptors. Atypical antipsychotics bind dopamine receptors but with less affinity and with additional blockade of the serotonin 5-HT<sub>2A</sub> receptors (Seeman, 2002). The second-generation atypical agents generally overcome some of the extrapyramidal motor side effects associated with the first-generation typical antipsychotics, but themselves can produce metabolic side effects including diabetes mellitus, weight gain and hyperlipidemia (Crossley, Constante, McGuire, & Power, 2010; Uckol & Gaebel, 2008). With much inter-agent and inter-patient variability, both generations of treatments can be effective in reducing positive psychiatric symptoms such as delusions and hallucinations, but there remains a significant proportion of patients who are partially or fully resistant to treatment or who discontinue the medications (Leucht et al., 2009; Muller, 2017). Furthermore, as mentioned, many of the currently available antipsychotics fail to adequately elicit an improvement in negative symptoms or cognition (Meyer, Schwarz, & Muller, 2011; Muller, 2017). The differences in effectiveness and side effect profiles from a meta-analysis as well as from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) and Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CULASS) trials are well discussed by Leucht et al. (2009). In addition, pharmaceutical companies are downsizing psychiatric research budgets, as the currently applied drugs, though flawed, are still the most effective medications that are available. These agents are also becoming accessible generically (Bartfai & Lees, 2011). Technical advances fueled by the deep sequencing revolution and genome wide association studies (GWAS) have not brought about the identification of new genetic loci to direct treatment research efforts or shed light on new mechanisms guiding schizophrenia disease pathophysiology, with one exception that is the focus of our review, the immune system.

Immune system dysregulation in schizophrenia is a consistently replicated physiological target that encompasses gene by environmental interactions (International Schizophrenia et al., 2009; Jones, Mowry, Pender, & Greer, 2005; Kirch, 1993; Knuesel et al., 2014; Meyer, 2013; Muller, 2014; Rothermundt, Arolt, & Bayer, 2001; Severance, Yolken, & Eaton, 2016; Shi et al., 2009; Stefansson et al., 2009; Torrey & Peterson, 1976; Yolken & Torrey, 2008). GWAS studies identified the 6p21–6p22 chromosomal portion that houses the major histocompatibility complex/human leukocyte antigen MHC/HLA and complement C4 loci as one of the most important genetic susceptibility regions for schizophrenia (Corvin & Morris, 2014; International Schizophrenia et al., 2009; Sekar et al., 2016; Shi et al., 2009; Stefansson et al., 2009). The MHC/HLA gene family encodes cell surface proteins that bind and present antigens as either self or non-self to T-cells; thus, any dysfunction thereof predisposes a susceptibility to infectious disease, graft rejection, cancer and autoimmunity. The complement C4 association is interesting because its variation in gene copy numbers may cause abnormal synaptic pruning in schizophrenia, presumably as a consequence of perturbation during normal neurodevelopment and not necessarily as any intrinsic abnormality in immunity (Sekar et al., 2016). Other genetic risk alleles found by GWAS outside of this

chromosomal region also are involved in immune pathways (Network and Pathway Analysis Subgroup of Psychiatric Genomics, 2015). This genetic information, coupled with decades of evidence for environmentally triggered immune risk factors and newfound functions in the brain by classic peripheral immune pathways, all point to an integral immune system role in schizophrenia. Among the dysregulated immune conditions associated with schizophrenia are those with distinct autoimmune components.

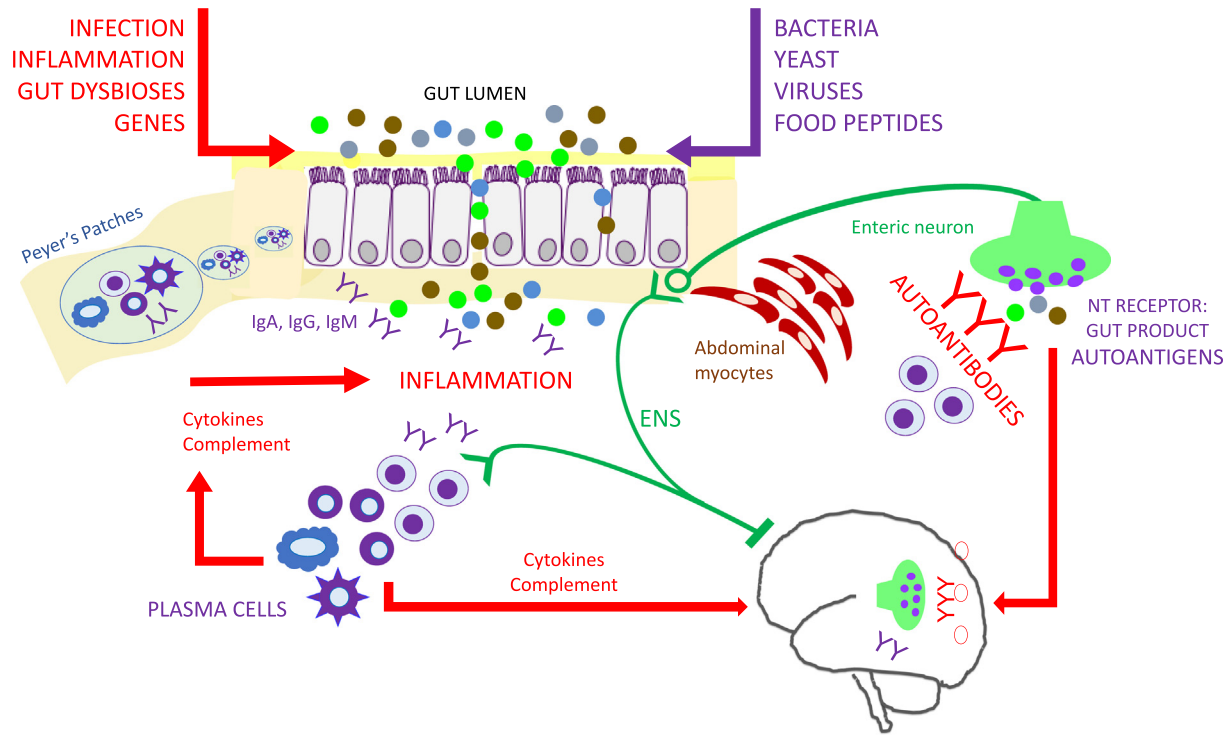
Here we review the autoimmune component of schizophrenia and mechanisms by which this comorbidity could impact central nervous system (CNS) function via the gut-brain axis. An overview of our topic is modelled in Fig. 1. We will first present the basic tenets of autoimmunity in a context that is relevant to our subsequent evaluation of autoimmunity in schizophrenia. We will then discuss the autoimmune phenotype of schizophrenia in terms of risk factors for disease including the role of infection, a peripheral and central inflammatory state, gut dysbioses and the presence of autoantibodies. We will integrate our discussion with mechanisms that contribute to relevant CNS pathologies, including behavioral indices such as severity of psychiatric symptoms and cognitive deficits and biochemical indices such as complement pathway dysfunction and autoimmune-related neurotransmitter receptor hypofunction. In so doing, we bring to light new therapeutic targets and review some of the clinical trials that have already been implemented to test the efficacy of treatment of these immune pathways in schizophrenia.

### 1.1. Autoimmunity and loss of tolerance

The maintenance of good health relies on an immune system that can recognize and destroy non-self-entities including bacteria, viruses and other foreign antigens, as well as remove injured or mutated self-entities such as apoptotic cells and environmentally- or genetically-modified native proteins. Autoimmunity is a complex condition that reflects the inability of a host to differentiate self from non-self. In affected individuals, autoimmunity generally indicates the insufficient establishment of or loss of immune tolerance. Tolerance is a highly regulated process that is dually created centrally and peripherally. Central tolerance is established through primary clonal selection aimed at eliminating immature self-reactive T and B lymphocytes from the thymus and bone marrow, respectively, before mature cells are distributed systemically. Self-reactive lymphocytes can escape into the systemic circulation, and peripheral tolerance refers to the inactivation of these systemic mature auto-reactive T and B cells that are typically concentrated in the body's lymph nodes or non-lymphoid tissues. Methods to control these wayward lymphocytes include their placement into an anergic state or their removal by regulatory T cells (Tregs) (Murphy, Travers, Walport, & Janeway, 2012; Theofilopoulos, Kono, & Baccala, 2017).

When immune tolerance is disrupted, autoimmune diseases ensue. These conditions are characterized by chronic inflammation, autoantibodies, and tissue injury. The autoimmune pathophysiology can occur systemically (systemic lupus erythematosus) or in organ-specific patterns (Hashimoto's thyroiditis – thyroid; type 1 diabetes mellitus – pancreas; rheumatoid arthritis – connective tissue). An imbalanced immune system where over-activated pro-inflammatory effector T cells outnumber the immunosuppressive Tregs can result in autoimmune pathologies, and there are a variety of mechanisms that can bring about this imbalance. One suspected trigger of autoimmunity is infection in genetically susceptible people (Murphy et al., 2012; Theofilopoulos et al., 2017). In a recent study of the Danish Civil Registration System, it was found that hospital admission for infection was a risk factor for 29 autoimmune disorders (Nielsen, Kragstrup, Deleuran, & Benros, 2016).

Infection-mediated loss of tolerance can involve the polyclonal activation of autoreactive T cells, molecular mimicry, uncovering of cryptic antigens and the creation of novel self-reactive antigens. For example, in molecular mimicry, antibodies directed against the infectious



**Fig. 1.** Model of autoimmune phenotypes operating along the gut-brain axis in schizophrenia. As described in the main text, infection, inflammation, gut dysbiosis and autoantibodies are all related to measurable autoimmune features in schizophrenia. These features contribute to permeabilization of the blood-gut barrier, which allows the translocation of gut-based products into circulation. Interactions of these gut products with neurotransmitter receptors located in the enteric nervous system may be one source of autoantibody propagation especially in the presence of inflammation. Systemically, a low-grade inflammatory state is perpetuated as the immune system is activated, including complement and cytokine production pathways. In turn, this inflammation may contribute to a compromised BBB and allow gut-derived products, peripheral immune factors and autoantibodies access to the brain. Immune dysfunction, susceptibility to infections and barrier stabilities in schizophrenia may be under genetic control. In the diagram, immune cells in Peyer's Patches and in systemic circulation include macrophages, dendritic cells, B lymphocytes and T lymphocytes. YY refers to the immunoglobulins IgA, IgG and IgM.

agent or corresponding T cells become cross reactive to self-antigens. New antigenic epitopes can be generated when pathogen-derived proteins bind to a host's cell or tissue or when self-entities undergo post-translational or pathogen-elicited modifications. Infection can also break down the sequestering of tissue-specific antigens that were previously quiescent in areas known as immunologically privileged. These generated autoantibodies initiate the cellular immune machinery to clear perceived invading antigens and thus lead to inflammation, tissue damage, and hypersensitivity that typifies an autoimmune condition (Murphy et al., 2012; Theofilopoulos et al., 2017). Autoantibodies can be pathogenic through binding and inactivation of cell surface receptors and extracellular molecules and the formation of immune complexes that collect and cause tissue damage. Autoantibodies generated by the mother also have the potential of affecting fetal development as part of antibody transfers across the placenta (Lleo, Invernizzi, Gao, Podda, & Gershwin, 2010). It is possible that these autoantibodies and their potential to bind to important brain proteins may underlie some neuropsychiatric symptoms.

### 1.2. The gut as a source of autoimmunity

As described later, low grade central and peripheral inflammation is an emerging risk factor for the development of schizophrenia (Bechter, 2013; Bechter et al., 2010), but the source of this inflammation is not known and likely has multiple origins in different people. The largest immune organ in the body is the gastrointestinal (GI) tract which serves as a critical hub regulating self and non-self interactions via the gut-associated lymphoid tissue (GALT). As such, the GALT functions to convey immune tolerance to a complex community of commensal microbes, externally-derived dietary products, and the host's own cellular machinery, while simultaneously protecting the body from

destructive pathogens and other dangerous antigens. (Chistiakov, Bobryshev, Kozarov, Sobenin, & Orekhov, 2014; Dinan & Cryan, 2015; Sandhya, Danda, Sharma, & Scaria, 2016; Wekerle, 2017). Members of the gut microbiome include bacteria, viruses, archaea and fungi, which comprise a functional system whose goal it is to extract, metabolize and absorb nutrients to fuel and maintain a healthy body. These microbes and downstream products, however, also have important immunomodulatory roles. When functioning correctly, they dynamically control the immune response and inflammatory status of the GI tract. The breakdown of tryptophan, for example, leads to a broad range of kynurenine-related metabolites that function as both pro- and anti-inflammatory triggers and are involved with excitatory neurotransmission (Cervenka, Agudelo, & Ruas, 2017). Bacterial metabolites and structures such as short chain fatty acids (SCFAs) and polysaccharide moieties function diversely to maintain an immune homeostasis with pro-inflammatory Th17 effects that are dampened by anti-inflammatory Treg cell-mediated immunosuppression (Wekerle, 2017). Importantly, many of these microbial metabolites are neuromodulatory and either are themselves, or else trigger the production of, neurotransmitters and neuropeptides such as dopamine, acetylcholine, gamma-aminobutyric acid, serotonin and brain-derived neurotrophic factor (Cryan & Dinan, 2012; Rieder, Wisniewski, Alderman, & Campbell, 2017).

A homeostatic microbiome can become imbalanced, or dysbiotic, by many intrinsic or extrinsic factors including diet, pharmaceuticals, toxic chemicals, infectious agents and even by the genetics of the host (Abegunde, Muhammad, Bhatti, & Ali, 2016; Sandhya et al., 2016; Wu et al., 2011). During this dysbiosis, microbial control of inflammation shifts toward a pro-inflammatory Th1, Th2 and Th17 dominance and suppression of anti-inflammatory Treg cells (Chistiakov et al., 2014; Hornig, 2013; Wekerle, 2017). In response, there is an increase in the expression of antimicrobial proteins,

downregulation of inflammatory pathways, and an increase in the production of mucus to protect epithelial surfaces and repair damaged intestinal tissue and cellular barriers (Ismail & Hooper, 2005; Round, O'Connell, & Mazmanian, 2010; Smith & Garrett, 2011; Sommer & Backhed, 2013). When commensal bacteria (and invading pathogens) do breach the GI mucosa and gut-vasculature barrier, the setting is prime for the generation of an autoimmune state with the creation of an inflammatory environment that both develops from and fosters the genesis of autoantibodies.

Microbial dysbiosis has a hypothesized role in the etiology of autoimmune-based human inflammatory bowel disorders including Crohn's disease and ulcerative colitis (Powell, Walker, & Talley, 2017; Theofilopoulos et al., 2017). Similarly, the gut is in constant contact with food-derived antigens that, in a setting when tolerance has not been sufficiently established, can also trigger autoimmunity. Tolerance to the food load also involves microbial maintenance of epithelial cellular barriers, efficient digestion of food proteins and immune mediation by regulatory T and dendritic cells (Steele, Mayer, & Berin, 2012). A GI disorder with an autoimmune mechanism directed against food antigens is celiac disease. Celiac disease is characterized by a hypersensitivity autoimmune reaction directed against a wheat gluten antigen combined to an enzyme necessary for its metabolism, tissue transglutaminase, in individuals with a genetic predisposition as evidenced by specific HLA-DQ types. Increasingly, a psychiatric comorbidity is being recognized in individuals with autoimmune GI disorders (Fadgyas-Stanculete, Buga, Popa-Wagner, & Dumitrascu, 2014; Filipovic & Filipovic, 2014; Gupta, Masand, Kaplan, Bhandary, & Hendricks, 1997; Vaknin, Eliakim, Ackerman, & Steiner, 2004; Vu, Kushnir, Cassell, Gyawali, & Sayuk, 2014). Conversely, there is a long history of data demonstrating GI inflammation in individuals with psychiatric disorders (Buscaino, 1953; Hemmings, 2004; Severance, Prandovszky, Castiglione, & Yolken, 2015).

### 1.3. The brain as a target of autoimmunity

Autoimmune conditions of the brain can arise via such varied means as injury-induced cytokine release, pathogen- and tumor-directed antibodies that are cross-reactive to brain proteins, T-cells that are exposed to previously inaccessible brain antigens, and genes that confer a susceptibility to immune dysfunction (Pilli, Zou, Tea, Dale, & Brilot, 2017; Wekerle, 2017). CNS-related autoimmune disorders include multiple sclerosis, Amyotrophic lateral sclerosis (ALS), limbic encephalitis, seizures, Rasmussen's Encephalitis, Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) and anti- *N*-methyl-*D*-aspartate (NMDA) receptor encephalitis (Dalmau, Geis, & Graus, 2017; Diamond, Honig, Mader, Brimberg, & Volpe, 2013; Pilli et al., 2017). In spite of a varied etiology, many autoimmune encephalopathies are similarly characterized by an inflammatory state and the presence of antibodies directed against such brain structures as neuronal surface receptors and synaptic proteins (Dalmau et al., 2017; Diamond et al., 2013; Newman et al., 2016). As research in this field progresses, the intricate and extensive role that peripheral immunity has within the CNS is becoming better understood and appreciated.

The CNS has long been considered an immune-privileged organ and thus impervious to processes involving peripheral immune cells. Structural protection comes from the blood brain barrier (BBB), an endothelial cell-vascular interface reinforced with tight junction proteins and astrocyte processes, which has been thought to prevent peripheral immune factors and cells from entering the brain. Recent data bring to question a more contentious issue regarding the requirement that the integrity of the BBB be compromised in order for autoimmune features to affect the CNS. BBB permeability would presumably be required for autoantibodies generated peripherally to be active in the brain, as well as for the CNS entry of inflammatory molecules or other immune entities (Pollak et al., 2018). It is becoming evident that subsets of lymphocytes are able to gain access to and take up residence in the

CNS in spite of an intact BBB, and further, these B and T cells may become active in the presence of microbial infection (Wekerle, 2017). The perceived impenetrability of this structural and immune barrier in the brain was further disputed with the discovery of lymphatic vessels lining the dural sinuses and connecting the CSF with deep cervical lymph nodes; in these vessels were T cells suggesting that this conduit between the CNS and lymph nodes provides evidence that the CNS is a site accessible to immunosurveillance (Louveau et al., 2015). Nevertheless, inflammation renders the BBB more permeable and therefore, there are likely numerous autoimmune conditions that are accelerated when a BBB has been inappropriately breached (Hammer et al., 2014), such as during pathogen infection. Interestingly, in germ-free experimental mouse studies, the absence of gut microbes was associated with a dysfunctional BBB, altered myelination of cortical neurons, cognitive deficits and behavioral changes (Blander, Longman, Iliev, Sonnenberg, & Artis, 2017; Sharon, Sampson, Geschwind, & Mazmanian, 2016).

The wide range of types of antigens that bring about similar immune effects suggests it is the immune system response or dysregulation thereof rather than a specific pathogen or food exposure that contributes to neuropsychiatric disease. The immune system response can take the form of adaptive immunity, where an antigen-specific response elicits the machinery to generate immunological memory through clonal selection of lymphocytes. The immune response can also be innate, a form characterized by less specificity and immediate cellular defense to clear invading pathogens, or antigens identified as foreign (Murphy et al., 2012). The complement pathway bridges innate and adaptive immunity and when initially activated forms immune complexes to aid clearing of foreign antigens, damaged cells, and autoantigens from circulation. Defects of the complement pathway lead to increased susceptibility to infection and to autoimmune disorders. Complement deficits result in the accumulation of apoptotic debris, immune complex deposits, inflammation and tissue damage. Lingering apoptotic waste is a source for autoantigens especially during inflammation in genetically susceptible individuals, and subsequent T cell activation can lead to autoreactive B cells and autoantibodies (Walport, 2001a, 2001b). Systemic Lupus Erythematosus (SLE), for example, is an autoimmune disease characterized by systemic autoimmune symptoms that result from tissue injury in multiple organs due to high levels of immune complex deposits. SLE is associated with alterations in the levels of multiple complement proteins including C1q and C4. C1q is a first-line antigen recognition protein that forms immune complexes with antigens bound to antibodies; C4 is found further downstream from C1q in the classic pathway and also as part of the PAMP- or DAMP-initiated lectin pathway, in both cases involved in enzymatic reactions to assemble the C3-convertase and eventual activation of the membrane attack complex (Ballanti et al., 2013; Martin & Blom, 2016; Walport, 2001a, 2001b).

Intriguingly in recent discoveries over the last decade, this peripheral complement pathway was found to be active in the brain. As described in rodent models, complement proteins functioned in synapse formation and elimination during neuronal development as well as in response to the presence of brain pathogens in adults (Bialas & Stevens, 2013; Boulanger, 2009; Fourgeaud & Boulanger, 2007; Hong et al., 2016; Lui et al., 2016; Presumey, Bialas, & Carroll, 2017; Ransohoff & Stevens, 2011; Schafer et al., 2012; Stephan et al., 2013; Stevens et al., 2007; Vasek et al., 2016). The subsequent identification of C4-related polymorphisms as genetic risk factors for schizophrenia (Sekar et al., 2016) has potentially important implications for autoimmune studies of schizophrenia and may represent a nexus molecular pathway by which genetic and environmental etiologies for the disorder can be reconciled (Nimgaonkar et al., 2017). With respect to schizophrenia, the timing of exposure to an infectious disease with maternal generation of antibodies during the prenatal or early postnatal period is a topic that has been the focus of numerous investigations, the results of which generally support neurodevelopmental hypotheses for

schizophrenia etiology (Allswede, Buka, Yolken, Torrey, & Cannon, 2016; Blomstrom et al., 2012; Brown et al., 2004; Brown et al., 2004; Brown, Cohen, Greenwald, & Susser, 2000; Buka et al., 2008; Ellman, Yolken, Buka, Torrey, & Cannon, 2009; Karlsson et al., 2012; Mortensen et al., 2010; Pedersen, Stevens, Pedersen, Norgaard-Pedersen, & Mortensen, 2011; Severance, Gressitt, Buka, Cannon, & Yolken, 2014; Xiao et al., 2009). The precise activation of complement in response to a maternal antibody load implicates a mechanism of inappropriate fetal activation of synaptic pruning as an etiological pathway to schizophrenia.

## 2. Autoimmunity in schizophrenia

As described to this point, autoimmunity can materialize through multiple mechanisms that reflect the body's failure to accurately recognize its own cellular make-up. Emerging data indicate that these pathologies may very well impact the brain. A similar dysregulation of adaptive and cellular immunity is increasingly demonstrated in schizophrenia, suggesting that this disorder, although not a classic autoimmune disease, may share some common, potentially treatable, physiological features. Early records examining the associations between autoimmune disorders and schizophrenia document the discovery of an inverse correlation in prevalence between rheumatoid arthritis and schizophrenia, and this relationship was also more recently replicated (Chen et al., 2012; Eaton, Hayward, & Ram, 1992; Gorwood et al., 2004; Sellgren, Frisell, Lichtenstein, Landen, & Askling, 2014; Torrey & Yolken, 2001; Trevathan & Tatum, 1953). Other investigations, including some recent large-scale birth registry studies, found a positive association between an array of autoimmune disorders (including multiple sclerosis, systemic lupus erythematosus, autoimmune thyrotoxicosis, autoimmune hepatitis and psoriasis) and a diagnosis of schizophrenia or psychosis (Benros, Eaton, & Mortensen, 2014; Chen et al., 2012; Eaton et al., 2006; Gilvarry et al., 1996; Wright et al., 1996). In addition, it has also been found that a history of infection further contributed to elevate the risk of autoimmune disorders on the development of schizophrenia (Benros et al., 2011). Similarly, having a history of an infection or having a family member with schizophrenia also significantly elevated the risk for developing an autoimmune disease (Benros et al., 2014). Very recently, an analysis of this registry data indicated that the combination of a history of infections and exposure to anti-infective agents such as antibiotics further augmented the risk for developing schizophrenia (Kohler et al., 2017).

It is likely that in certain cases, autoimmune disorders and schizophrenia may be the result of a genetically-encoded insufficient or over-active immune response triggered by exposure to an environmental factor such as infection. Data from studies of the microbiome also suggest that the genesis of autoimmunity can occur at least in part when the gut is dysbiotic (de Oliveira, Leite, Higuchi, Gonzaga, & Mariano, 2017; Fung, Olson, & Hsiao, 2017; Thaiss, Zmora, Levy, & Elinav, 2016). An intestinal origin for autoimmunity also reconciles numerous risk factors for the development of schizophrenia, which in turn supports the existence of a gut-brain connection. As such, similarly faulty genetic templates perhaps involving variations of mutations in MHC, HLA or complement loci in autoimmune disorders and schizophrenia may result in a dysregulated immune response to not only pathogens but to a wide array of environmentally- and endogenously-derived antigens. The reaction against these antigens provokes inflammation, a hallmark characteristic of the autoimmune state and often observed in people with schizophrenia (Bechter, 2013; Dickerson et al., 2016; Fillman et al., 2013; Miller, Buckley, Seabolt, Mellor, & Kirkpatrick, 2011; Severance et al., 2012). Again, of interest with respect to brain disorders are the many components of the complement pathway which are not only part of inflammation-generating trajectories but also, as mentioned, have newly-discovered functions in synapse formation and pruning. Autoantibodies also prime and perpetuate the autoimmune inflammatory state. If these autoantibodies

are directed against important brain proteins such as neurotransmitter receptors, neuronal function can be greatly compromised. In this section, we review the evidence in support of pathogen exposures, inflammation, the gut-brain axis and autoantibodies as autoimmune phenotypes in schizophrenia.

### 2.1. Pathogen exposures

There is a long history of research and support for infection as a process leading to autoimmune disorders (Ercolini & Miller, 2009; Nielsen et al., 2016); therefore, it is not surprising that exposure to pathogens has been posited as an autoimmune risk factor for the development of schizophrenia (Hornig, 2013; Torrey & Peterson, 1976; Yolken & Torrey, 2008). Among the documented infectious disease agents and types of infections that have been associated with schizophrenia are the protozoan *Toxoplasma gondii*, influenza viruses, cytomegalovirus and other human herpesviruses, Borna disease virus, endogenous retroviruses, coronaviruses, urinary tract infections, Chlamydia, and Candida yeast infections (Arias et al., 2012; Hornig, 2013; Karlsson et al., 2001; Karlsson, Schroder, Bachmann, Bottmer, & Yolken, 2004; Leweke et al., 2004; Miller et al., 2013; Severance et al., 2011; Severance et al., 2016; Torrey et al., 2006; Torrey, Bartko, Lun, & Yolken, 2007; Torrey, Bartko, & Yolken, 2012; Yolken & Torrey, 2008). In some studies, pathogen exposures were associated with a decrease in cognitive function and progressive gray matter loss (Nimgaonkar & Yolken, 2012; Prasad et al., 2011; Prasad, Watson, Dickerson, Yolken, & Nimgaonkar, 2012; Schretlen et al., 2010; Severance, Gressitt, et al., 2016; Shirts et al., 2008; Watson et al., 2013; Yolken, Torrey, Lieberman, Yang, & Dickerson, 2011). The focus of this review is on identifying autoimmune conditions in people with schizophrenia with a direction toward identification of new treatments; however, it should be noted that there is also a large literature base about prenatal exposures to specific microbes and to the infectious disease process as a risk factor for the future development of schizophrenia (Blomstrom et al., 2012; Brown et al., 2000; Brown, Begg, et al., 2004; Brown & Derkits, 2010; Brown, Hooton, et al., 2004; Buka et al., 2008; Ellman et al., 2009; Estes & McAllister, 2016; Mortensen et al., 2010; Pedersen et al., 2011; Xiao et al., 2009).

Perhaps the most consistently replicated finding of a pathogen exposure associated with a diagnosis of schizophrenia involves the parasitic pathogen, *T. gondii* (Arias et al., 2012; Monroe, Buckley, & Miller, 2015; Torrey et al., 2007; Torrey et al., 2012). Only in recent years has this connection been regarded in the context of *T. gondii* as a gut pathogen showing significant associations with gut-based antigens and inflammatory processes in people with schizophrenia (Severance, Alaedini, et al., 2012; Severance, Yolken, & Eaton, 2016). Indeed, *T. gondii* is used routinely in experimental rodents to model inflammatory bowel diseases (Craven et al., 2012; Grainger et al., 2013; Hand et al., 2012; Heimesaat et al., 2006). Thus, as an inflammation-generating, neurotropic parasite able to permeabilize endothelial cell barriers, *T. gondii* is uniquely equipped to pathologically impact the brain directly resulting in glial cell activation or indirectly via the facilitated entry of systemic immune and gut-derived factors to the CNS. In a mouse model, we demonstrated extensive *T. gondii*-generated complement activation in brains in the vicinity of the parasite and in proximity to synapses (Xiao et al., 2016). In a recent translational study, we found parallel increases in mice and humans of autoantibodies directed against the NMDA receptor in those who had been exposed to *T. gondii*, with corresponding elevations of surrogate markers of compromised blood-gut-barrier and BBB (Kannan et al., 2017). Results from this and other studies also further documented the effects of parasite exposure on clinical endpoints such as decreased cognition, suicidal behavior and severity of psychotic symptoms (Dickerson et al., 2017; Eshili et al., 2016; Hamdani et al., 2017; Kannan et al., 2017; Lindgren et al., 2018).

## 2.2. Inflammation

Just as schizophrenia is not a classic autoimmune disorder, it is also not a classic inflammatory disorder. In schizophrenia, the detectable inflammation has been ascribed to be of a low-grade nature with peripheral and central inflammatory states measured using a variety of biomarkers in different research labs (Bechter, 2013; Catts, Wong, Fillman, Fung, & Shannon Weickert, 2014; Dickerson et al., 2016; Fillman et al., 2013; Fillman et al., 2016; Fillman, Sinclair, Fung, Webster, & Shannon Weickert, 2014; Kirkpatrick & Miller, 2013; Miller et al., 2011; Muller, 2016; Severance et al., 2013; Severance, Alaedini, et al., 2012). In most cases, the source of this inflammation in these studies is not known, but it is evident in the form of pro- and anti-inflammatory cytokine dysregulation, disrupted tryptophan and kynurenine metabolism, exposure to microbial pathogens and antigens, food hypersensitivities, complement activation, post-mortem pathologies and brain imaging. A large meta-analysis of cytokines in schizophrenia provided strong evidence for upregulation of proinflammatory cytokines associated with schizophrenia and particularly of IL-6, IFN-gamma, and TNF-alpha compared to controls (Miller et al., 2011). Interestingly, those patients receiving antipsychotic medication showed significantly decreased levels of IL-6 and IFN gamma suggesting an immunosuppressive effect of these drugs; such an effect was previously demonstrated by other investigators for haloperidol and clozapine (Leykin, Mayer, & Shinitzky, 1997; Muller, 2017). Simultaneous increases in IL12 and IL-2 receptors in schizophrenia, however, suggest the cytokine network is dysregulated and not necessarily uniformly pro-inflammatory in direction.

As noted earlier, complement activation is part of the body's inflammatory defense response culminating in the launching of the membrane attack complex. Altered peripheral complement components in schizophrenia include C1, C3, and C4, although not all of the studies reported consistent findings (Arakelyan et al., 2011; Boyajyan, Khoyetsyan, Tsakanova, & Sim, 2008; Kucharska-Mazur et al., 2014; Mayilyan, 2012; Mayilyan, Weinberger, & Sim, 2008; Santos Soria, Moura Gubert, Cereser, Gama, & Kapczinski, 2012; Severance et al., 2012). C4 is also upregulated centrally with postmortem human brains samples showing increased RNA expression in schizophrenia compared to controls (Sekar et al., 2016). As noted, C4 polymorphisms have been identified as conferring a genetic susceptibility for schizophrenia with copy number variations impacting levels of gene expression (Mayilyan, 2012; Mayilyan, Dodds, Boyajyan, Soghoyan, & Sim, 2008; Sekar et al., 2016). Preliminary evidence in a study of twins with schizophrenia implicated peripheral expression of complement genes C5 and SERPING1 with cortical thinning (Allswede et al., 2018). While centrally-derived complement activity has implications for brain biochemistry and synaptic pruning, chronic peripheral inflammation also has brain effects and was associated with cognitive impairment in schizophrenia (Bulzacka et al., 2016). As we posit in the next section, a logical possible source of this inflammation derives from a gut microbiome that is imbalanced; this imbalance may cause the translocation of microbes, microbial products, antigenic food products across the gut vasculature, and instigate a low level of inflammation and autoimmune-generating potential (Severance, Yolken, & Eaton, 2016).

## 2.3. Gut dysbiosis

As discussed earlier, an imbalanced GI environment is a prime venue for the production of autoantigens. A leading autoimmune disorder with often replicated ties to schizophrenia is, in fact, celiac disease (Baldwin, 1980; Bender, 1953; Dohan, 1970, 1973, 1980; Eaton et al., 2004; Graff & Handford, 1961). As we discussed earlier, people with celiac disease have an intolerance to wheat gluten which when ingested causes the body to launch an autoimmune attack against what it perceives to be a novel antigenic complex of gluten bound to cell-derived tissue transglutaminase in the small intestine (Alaedini & Green, 2008;

Green et al., 2005; Guandalini & Assiri, 2014). Gluten antibodies have also been shown to bind synapse-related brain proteins (Alaedini et al., 2007; Briani et al., 2008; Hadjivassiliou et al., 2002). This connection between gluten exposure and psychiatric disorders was first hypothesized by FC Dohan who observed that psychiatric hospitalization rates in Europe strongly correlated with the amount of wheat consumption, which varied considerably during and immediately after World War II (Dohan, 1966a, 1966b). Since then, numerous studies and meta-analyses have examined the association of food antigens with schizophrenia and with varied results (Cascella et al., 2011; Dickerson et al., 2010; Jin et al., 2010; McLean, Wilson, St Clair, Mustard, & Wei, 2017; Reichelt & Landmark, 1995; Reichelt & Stensrud, 1998; Samaroo et al., 2010; Severance et al., 2010). In our studies, these gluten antibody profiles correlated with measures of GI inflammation (Severance et al., 2013; Severance, Alaedini, et al., 2012; Severance, Gressitt, et al., 2012). Interestingly, in a recent clinical study, antigliadin antibodies were found to predict brain inflammation as measured via proton magnetic resonance spectroscopy (Rowland et al., 2017). Celiac disease is marked by strong HLA associations, pathogenic CD4+ and autoantibody generation. As such, celiac disease represents the classic interaction of genes, the environment and immunology (Hardy & Tye-Din, 2016). Similar operative mechanisms may be present in certain people with schizophrenia who suffer from gluten sensitivities.

Inflammatory bowel diseases are among the autoimmune disorders that are found with increased frequency in schizophrenia (Gupta et al., 1997; Severance, Prandovszky, et al., 2015). Likewise as we have indicated, there are emerging data that people diagnosed with these GI disorders have increased rates of psychiatric symptoms (Fadgyas-Stanculete et al., 2014; Filipovic & Filipovic, 2014; Gupta et al., 1997; Vaknin et al., 2004; Vu et al., 2014). GI disturbances related to mental illnesses are recorded as early as the first and second centuries when Hippocrates and later Galen advocated the practice of treating the gut in order to improve brain function (Severance, Prandovszky, et al., 2015). Since then, the search for a physiological basis for the gut-brain connection has resurfaced periodically, particularly starting in the 19th century, and interest in this topic is currently at an all-time high. The historical precedence of GI studies of mental illness is important, because of a present misbelief that the GI comorbidities are primarily the result of medications. While intestinal motility is impaired by the anticholinergic side effects of antipsychotics, GI dysfunction not attributable to medications has been documented in numerous studies, including those that predate the introduction of antipsychotic medications which occurred in the 1950s and those that examine various GI-related biomarkers in antipsychotic-naïve patients (Severance, Prandovszky, et al., 2015). A pre-antipsychotic era study of post mortem tissue reported 50–92% of the schizophrenia group had extensive bowel inflammation (Buscaino, 1953; Hemmings, 2004). In our studies, food antigen exposures, yeast exposures and bacterial dysbiosis are all entities that contribute to GI-related inflammation in individuals with schizophrenia (Severance et al., 2010, 2013; Severance, Alaedini, et al., 2012; Severance, Gressitt, et al., 2016). Parallel studies in antipsychotic naïve individuals support that the biomarker patterns are specific to the disease state and not the result of immune effects of the drug. These biomarker studies also document the translocation of gut-based products such as food peptides and microbial products into systemic circulation at increased rates in people with schizophrenia compared to controls. As discussed earlier, it is known that GI inflammation produces an environment that has deleterious effects on the gut vasculature barrier. We found evidence for compromised endothelial barrier pathologies in the gut and CNS, which were associated with schizophrenia. In people with intact endothelial barriers, gut-derived food antigen antibodies found peripherally in serum should not be associated with those found centrally in the CSF. In people with schizophrenia, we found strong correlations between serum and CSF antibodies, which were not present in control individuals without a psychiatric disorder (Severance et al., 2015).

Gut-derived inflammation can be the product or source of a gut microbiome that is out of balance. The gut microbiome itself has not been yet extensively studied in schizophrenia, but initial deep sequencing studies of microbial taxa suggest altered patterns of diversity associated with disease compared to controls (Castro-Nallar et al., 2015; Schwarz et al., 2018; Yolken et al., 2015). In the oropharyngeal microbiome, species of lactic acid bacteria, *Lactobacilli* and *Bifidobacterium*, known to regulate chronic inflammation, were more abundant in schizophrenia compared to controls (Castro-Nallar et al., 2015). Interestingly, levels of the viral phage, *Lactobacillus* phage phiadh, were also altered in schizophrenia and correlated with levels of its corresponding bacterial host, *Lactobacillus gasseri* (Yolken et al., 2015). A study of the fecal microbiome also pointed toward elevations of *Lactobacillus* bacteria in individuals with first episode psychosis compared to controls and importantly indicated that these levels were related to the severity of psychotic symptoms and response to treatment (Schwarz et al., 2018). These few studies of the microbiome as well as those documenting microbial translocation collectively indicate that gut dysbioses are putatively prevalent in schizophrenia (Dickerson, Severance, & Yolken, 2017). Further studies aimed to elucidate the functional consequences of this microbial dysbiosis on CNS endpoints such as psychiatric symptoms, cognition and treatment resistance are desperately needed.

Thus, inflammation in the intestinal tract and associated compromise of the gut-blood cytological barrier has varied implications for people with psychiatric disorders who may have co-existing autoimmune conditions. Microbial and related products in the bloodstream lead to systemic immune activation, a potentially pathological state that may be already aggravated in individuals who have genetically-encoded immune dysfunctions. Endothelial barrier permeability not only impacts the GI-vasculature interface but provides a means by which gut-derived products might penetrate the blood-brain barrier, a cytological architecture that is structurally similar. These faulty barriers may be particularly important if autoantibodies generated in the inflammatory gut environment were able to cross a compromised BBB. An intestinal system in flux may predispose to autoimmunity by means of a wide array of neurotransmitter targets found in the enteric nervous system that are identical to those found in the brain.

#### 2.4. Autoantibodies

Understanding the role of autoantibodies that are reactive against brain proteins is a longstanding subject of studies that examine autoimmunity in psychiatric disorders (Boehme, Cottrell, Dohan, & Hillegeass, 1973; Durell & Archer, 1976; Fessel, 1962a, 1962b; Glebov, 1972; Gurevich, 1969; Heath, 1967; Heath & Krupp, 1967; Heath, Krupp, Byers, & Liljekvist, 1967a; Heath, Krupp, Byers, & Liljekvist, 1967b; Jones et al., 2005; Kirch, 1993; Lehmann-Facijs, 1937; Mellso, Whittingham, & Ungar, 1973; Stamboliev, 1970; Stoimenov, 1969). A recent meta-analysis recorded a significant elevation of 20 different autoantibodies in persons with schizophrenia compared with controls (Ezeoke, Mellor, Buckley, & Miller, 2013). In schizophrenia, autoantibodies directed to a number of brain proteins have been examined, and particularly but not exclusively, the target has been the neurotransmitter receptors: cholinergic muscarinic receptors, nicotinic acetylcholine receptors, dopamine D2 receptors, mu-opioid receptors, serotonin receptors, AMPA receptors, glutamate receptors, gamma-Aminobutyric acid (GABA) receptors, glutamic acid decarboxylase (GAD), and potassium channel receptors (Deakin, Lennox, & Zandi, 2014; Ezeoke et al., 2013; Jones et al., 2005; Masdeu et al., 2012). These studies also highlight other brain-related entities that may be regulated by autoantibodies including neuregulin-2, human endogenous retroviruses (HERVs), cardiolipin, DNA, histones, and mitochondria. The rationale for studying neurotransmitter receptors is based on the idea that these autoantibodies bind and suppress the activity or otherwise block and contribute to receptor hypofunction.

Of note, cell surface targets such as neurotransmitter receptors are presumably more accessible than intracellular targets such as DNA and mitochondria.

NMDA receptor hypofunction has been a longheld hypothesis for schizophrenia etiology with evidence that its blockage in healthy people precipitates some of the symptoms of schizophrenia (Gilmour et al., 2012). Positive associations of NMDA receptor autoantibodies and schizophrenia have not, however, been uniformly replicated suggesting the possibility that autoantibody presence may not be solely disease associated (Ando et al., 2016; Castillo-Gomez et al., 2017; Dahm et al., 2014; de Witte et al., 2015; Deakin et al., 2014; Dickerson et al., 2012; Haussleiter et al., 2012; Masdeu et al., 2012; Masopust et al., 2015; Pearlman & Najjar, 2014; Pollak, McCormack, Peakman, Nicholson, & David, 2014; Rhoads, Guirgis, McKnight, & Duchemin, 2011; Steiner et al., 2013; Steiner et al., 2014; Timucin, Ozdemir, & Parlak, 2016; Zandi et al., 2011). For example, these putatively pathogenic anti-NMDA receptor antibodies and other brain-directed antibodies were found to be present in multiple non-psychiatric control groups (Castillo-Gomez et al., 2017; Glass et al., 2017). As the autoantibody presence in controls may also be significant, it is possible that these autoantibodies may serve some regulatory function. It is additionally a possibility that a two-hit hypothesis is in effect; for these autoantibodies to be pathogenic, access through the BBB is required. As discussed with respect to the parasite, *T. gondii*, infection may be a potent agent of both barrier permeabilization and autoantibody generation (Kannan et al., 2017). In this review, we have focused on *T. gondii* as the perpetrator of autoimmunity, but other infectious disease agents may also produce autoantibodies, including HIV (Arboleya et al., 2016).

The alpha7 nicotinic acetylcholine receptor represents an interesting autoimmune target because it introduces the putative contribution of the enterically-located vagus nerve and thus another gut-brain connection. The vagus nerve carries information between the enteric nervous system and the CNS. It is hypothesized that in a certain subset of patients, the vagus nerve when stimulated can control peripheral and central inflammation through modulation of nicotinic acetylcholine receptor subtypes (Corsi-Zuelli et al., 2017). Thus, if autoantibodies are present against this receptor, as several studies of schizophrenia have found (Chandley, Miller, Kwasigroch, Wilson, & Miller, 2009; Mukherjee et al., 1994), suppressed inflammation or dysregulated anti-inflammatory modulation may ensue. This set of studies further implicates the enteric nervous system as a rich autoantibody source for relevant brain targets, as the enteric nervous system is equipped with much the same extensive array of neurotransmitter receptors that are found in the brain.

Finally, with respect to autoantibodies, we address the timing of exposure to these potentially pathological agents, particularly for the fetus. A large repertoire of work in rodents documents the role of maternal immune activation as detrimental to fetal brain biochemistry (Brown & Derkits, 2010; Estes & McAllister, 2016). Among the pathways studied, complement is found to be elevated peripherally as well as centrally following infection of the mother (Han, Zhang, & Hashimoto, 2017; Severance et al., 2012). Results from human studies also support a neurodevelopmental role for maternal immune activation in conferring risk to the development of schizophrenia or psychosis in adult offspring (Allswede et al., 2016; Brown & Derkits, 2010; Estes & McAllister, 2016). A large high profile study of the Swedish birth registry demonstrated elevated gluten antibodies in mothers whose children went on to develop psychosis as adults (Karlsson et al., 2012). Because we had previously found that C1q bound and formed immune complexes with gluten at increased rates in schizophrenia compared to controls, we examined maternal C1q levels in a birth cohort from the National Collaborative Perinatal Project and also found elevated levels of C1q in mothers whose children went on to develop psychosis (Severance et al., 2014). In this study, maternal C1q levels were significantly correlated with gluten, HSV-2 and adenovirus. In a rodent model of maternal immune activation, C1q was elevated in the prefrontal cortex of adult



offspring from mothers treated with poly(I:C) during pregnancy (Han et al., 2017). Placental transfer of maternal antibodies is a primary means of conferring offspring immunity. Indeed, in recent work, autoantibodies to the contactin-associated protein-like 2 (CASPR2), a protein important in brain development, have been isolated from mothers of children with neurodevelopmental disorders, with some variation (Brimberg et al., 2016; Coutinho et al., 2017). Modelling of antibody capping of CASPR2 in mice during pregnancy resulted in offspring with significant microglial activation, synaptic loss, structural insufficiencies of the cortex and hippocampus and behavioral abnormalities (Brimberg et al., 2016; Coutinho et al., 2017). Thus, the presence maternally of autoantibodies to important brain proteins including complement and neurotransmitter receptors may be a very tangible threat to the developing fetus.

### 3. Treating autoimmunity in schizophrenia

By studying the comorbid physiological conditions present in individuals with schizophrenia, we are offered clues to the cellular and pathway deficiencies that could be evaluated for treatment. As described in this review, the immune system has many complexities that when dysregulated can result in an autoimmune state. As such, this immune network represents a novel group of therapeutic targets that may be relevant to the study of brain disorders. The intricacies of the immune system and the poly-genic and poly-environmental heterogeneity of the schizophrenia disorder, itself, however, reinforces the likelihood that any one treatment approach will not be relevant for every patient. It will be critical to pre-identify those subsets of patients who are experiencing specific autoimmune characteristics and to diagnose these comorbidities with appropriate biomarkers so that an effective individualized treatment approach can be designed and implemented. It will be additionally important to develop biomarkers of treatment response and side effects (Fond et al., 2015). At the present time, the treatments described below are best considered as potential adjuncts to currently employed antipsychotics. In this section, we review some of the evidence in support of varied therapeutic approaches to treat autoimmune-derived abnormalities in schizophrenia. Given the overlapping mechanisms of some of the treated pathological conditions, certain therapeutic approaches may be appropriate for managing multiple autoimmune conditions.

#### 3.1. Anti-infective agents

##### 3.1.1. Antibiotics

Minocycline is a tetracycline antibiotic that has been evaluated in several clinical trials as an adjunctive treatment to antipsychotics and was associated with improvement of certain psychiatric symptoms and cognition (Chaudhry et al., 2012; Kelly et al., 2015; Levkovitz et al., 2010; Liu et al., 2014; Miyaoka et al., 2008), with several meta-analyses supporting its safety and efficacy (Solmi et al., 2017; Xiang et al., 2017). Interestingly, the effects of minocycline in schizophrenia may not be solely a result of its direct anti-microbial activity. Minocycline may also inhibit some of the detrimental effects of microglial activation including free radical generation and impaired adult neurogenesis (Mattei et al., 2014). Other antibiotics such as azithromycin and D-cycloserine have been tested in small studies with mixed results and remain candidates for follow-up studies when biomarkers are available to identify the most appropriate patients (Dickerson, Stallings, Boronow, Origoni, & Yolken, 2009; Goff, 2016; Schade & Paulus, 2016). The mechanism of action of D-cycloserine may be especially informative for schizophrenia hypotheses linked to dysfunction of the NMDA receptor, as D-cycloserine is a known partial agonist at the glycine modulatory site of this receptor (Goff, 2016; McBain, Kleckner, Wyrick, & Dingledine, 1989). More experimental data are also needed to determine the role of antibiotics in beneficially or detrimentally modulating gut microbiota and thus the gut-brain axis.

##### 3.1.2. Anti-virals

Several antiviral agents have been tested as adjunctive therapies including valacyclovir in various patient populations pre-screened for seropositivity to certain viruses, with mixed findings. In the first study, a significant improvement in psychiatric symptoms by valacyclovir was evident in individuals who were seropositive for cytomegalovirus but not for those who were seropositive for other herpesviruses (Dickerson, Boronow, Stallings, Origoni, & Yolken, 2003). In a placebo-controlled follow-up study, no differences in psychiatric symptoms were evident between the two treatment groups (Dickerson et al., 2009).

##### 3.1.3. Anti-protozoal agents

No clinical trials to date have demonstrated a change in psychiatric symptoms or cognition with therapy aimed to treat *T. gondii* infections (Chorlton, 2017). Although anti-malarial compounds involving artemisinin derivatives did not show a significant effect on psychiatric endpoints in two studies (Dickerson et al., 2011; Wang et al., 2014), a reduction of antibodies directed to the food antigen, gluten, was found in the treatment group compared to placebo (Dickerson et al., 2011).

#### 3.2. Anti-inflammatories

Because inflammation has been documented in many individuals with schizophrenia and because it can create a physiological state that predisposes susceptible individuals to autoimmunity, it is possible that anti-inflammatory pharmacotherapy may be beneficial (Meyer et al., 2011). Agents of therapeutic potential include COX-1&2 inhibitors, N-acetylcysteine, statins, or use of monoclonal antibodies as cytokine blockers (Miller & Buckley, 2016; Muller, 2017).

##### 3.2.1. COX inhibitors

Acetylsalicylic acid (aspirin) is a COX-1 and -2 inhibitor shown to significantly lower positive psychiatric scores in smaller studies as well as meta-analyses (Laan et al., 2010; Nitta et al., 2013; Sommer et al., 2014). The COX-2 inhibitor celecoxib administered as an adjunct to antipsychotic agents also resulted in improvement of symptoms/cognition compared to risperidone alone in several study trials, although most benefit was observed in earlier disease stages (Akhondzadeh et al., 2007; Marini et al., 2016; Muller, 2016; Muller et al., 2002; Muller et al., 2010). However, this benefit by celecoxib was not confirmed in two meta-analyses of anti-inflammatory agents (Nitta et al., 2013; Sommer et al., 2014), but appeared efficacious in improving psychotic symptoms in first-episode schizophrenia in a third meta-analysis (Zheng et al., 2017).

##### 3.2.2. N-acetylcysteine

Oxidative stress, as evidenced by a shift in balance in favor of pro-versus anti-oxidants, results in disrupted redox signaling, which is a phenotype increasingly associated with schizophrenia (Do, Cuenod, & Hensch, 2015). Biomarkers of oxidative stress such as glutathione, glutathione peroxidase, and superoxide dismutase are thought to reflect this disruption, and alterations of these biomarkers have been recorded in schizophrenia and in psychosis (Coughlin et al., 2013; Coughlin et al., 2017; Langbein et al., 2017; Nucifora et al., 2017; Zeni-Graiff et al., 2017; Zhang, Catts, & Shannon Weickert, 2017). N-acetylcysteine, a precursor of glutathione which has potent anti-oxidant as well as anti-inflammatory properties, was found with some variation to significantly improve psychiatric symptom severity and cognition in a variety of psychiatric disorders including schizophrenia (Berk et al., 2008; Chen, Chibnall, & Nasrallah, 2016; Conus et al., 2018; Farokhnia et al., 2013; Minarini et al., 2017; Nitta et al., 2013; Sommer et al., 2014; Zheng et al., 2018). N-acetylcysteine is interesting because of its multiplicity of effects on cytokine generation and removal and its role in glutamatergic and dopaminergic neurotransmission (Bumb, Enning, & Leweke, 2015; Sommer et al., 2014).

### 3.2.3. Statins

Adjunctive pravastatin, a cholesterol lowering medication, was found to significantly lower positive psychiatric scores from baseline to 6 weeks, although the benefit was not maintained through 12 weeks (Vincenzi et al., 2014). A trend toward some benefit in symptom reduction was also observed for simvastatin and the serotonin (5-HT<sub>3</sub>) receptor antagonist, ondansetron (Chaudhry et al., 2014). Adjunctive treatment with another statin, lovastatin, was not associated with improvement in psychiatric symptoms (Ghanizadeh, Rezaee, Dehbozorgi, Berk, & Akhondzadeh, 2014). A meta-analysis of adjunctive statin therapy in schizophrenia indicated a favorable improvement of psychiatric symptoms associated with treatment (Shen et al., 2018).

### 3.2.4. Cytokine blockers

Based on results from several small studies, potential cytokine targets that might be promising in schizophrenia include monoclonal antibodies directed against IL6 and its receptor (tocilizumab) and against tumor necrosis factor (infliximab) (Miller & Buckley, 2016). In people with inflammatory bowel disease, for example, the anti-tumor necrosis factor- $\alpha$  aided in the reduction of mucosal inflammation (Pache, Rogler, & Felley, 2009). Several trials of monoclonal antibodies for the treatment of schizophrenia are underway.

### 3.2.5. Complement modulators

Inflammation in schizophrenia may be related to dysregulation of the complement system that, when coupled with complement function in the brain, make this pathway a prime candidate to harness for adjunctive treatments in schizophrenia. Therapeutic strategies have focused on inhibiting complement activation which has been primarily successful with targets in the terminal pathway (Barnum, 2017a, 2017b). Barnum (2017a, 2017b) provides comprehensive reviews on the progress and history of targeting the complement pathway using small molecules, siRNA inhibitors and antibodies. The anti-C5 antibody, eculizumab, for example, has favorable safety and effectiveness results for managing other indications (Hillmen et al., 2013). The end result is blocked formation of the membrane attack complex, so complement pathways upstream from C5 would remain intact. Targeted development of complement inhibitors for autoimmunity are in progress (Morgan & Harris, 2015). For schizophrenia, it will be important to understand precisely how and which complement components are dysfunctional peripherally and in the brain in order for an effective complement-based treatment to be designed.

## 3.3. Gut dysbiosis correction

The operative rationale for correcting microbial imbalances is that decreasing gut inflammation and resolving a source autoimmunity will eliminate a sequence of pathologies such as compromised barrier permeability and inappropriate immune activation. In this way, progress may be made toward therapeutics that will improve psychiatric symptoms and cognition. Several approaches thus fall into this category including use of prebiotics, short chain fatty acids (SCFAs), probiotics, fecal transplants and various combinations thereof. Most studies with this objective have been performed in experimental rodent models, but results from a number of human clinical studies also show promise.

### 3.3.1. Prebiotics & SCFAs

Prebiotics are specialized plant products used to stimulate the colonization of the intestinal tract with beneficial bacteria but that are not metabolized by the host. SCFAs are metabolites generated from the fermentation of these fibers by gut microbes. SCFAs modulate inflammatory and metabolic pathways and are likely able to cross the BBB (Joseph, Depp, Shih, Cadenhead, & Schmid-Schonbein, 2017). Joseph et al. (2017) proposed that a diet enriched with fiber in conjunction with SCFAs, such as the Mediterranean diet, might improve immune outcomes that are dysregulated in schizophrenia. Intestinal

permeability may also be improved with the SCFAs propionate and butyrate, and the polyunsaturated fatty acids, omega-3 fatty acids (Michielan & D'Inca, 2015). Satogami, Takahashi, Yamada, Ukai, and Shinosaki (2017) showed that reduced omega-3 levels in the blood were associated with significant cognitive impairment in individuals with schizophrenia, but a number of trials of omega-3 supplementation in schizophrenia have been negative (Chen, Chibnall, & Nasrallah, 2015; Fenton, Dickerson, Boronow, Hibbeln, & Knable, 2001; Qiao et al., 2017; Satogami et al., 2017). Results from a rodent study showed that a diet enriched for the microbial metabolites acetate and butyrate increased regulatory T cell densities, improved gut barrier cohesion and reduced diabetogenic cytokines such as IL21 (Marino et al., 2017).

### 3.3.2. Probiotics & fecal transplantation

Probiotics are supplements containing live beneficial gut bacteria and sometimes yeast, administered with the rationale that these microorganisms will themselves re-establish a balanced microbiome. Probiotics have been evaluated in schizophrenia in three analyses of a placebo-controlled study. It was found that probiotics (*Lactobacillus rhamnosus* strain GG and *Bifidobacterium animalis* subsp. Lactis strain Bb12) given once per day improved GI symptoms, altered IL-17-mediated immune and intestinal epithelial pathways and was associated with decreased antibody levels against the opportunistic pathogen *Candida albicans* (Dickerson et al., 2014; Severance, Gressitt, et al., 2016; Tomasik, Yolken, Bahn, & Dickerson, 2015). In these analyses, probiotics did not deliver a benefit for improvement of residual psychotic symptoms. Interestingly an impact on psychiatric symptoms by probiotics was suggested only in those who did not have evidence of a *C. albicans* infection. Fecal transplantation also involves the re-priming of a dysfunctional gut microbiome with live bacteria from a healthy donor, usually performed for the purposes of treating *Clostridium difficile* infections. It is also experimentally used in autoimmune diseases and has shown promise in inflammatory bowel diseases (Millan, Laffin, & Madsen, 2017; Weingarden & Vaughn, 2017). Case reports also describe its benefit for treating autism, Parkinson's disease, multiple sclerosis and chronic fatigue syndrome (Evrinsel & Ceylan, 2016).

### 3.3.3. Other considerations

Dietary modification to avoid a high animal protein and high carbohydrate content is essential for improving the microbiome composition toward a healthy balance (Fond et al., 2015; Statovci, Aguilera, MacSharry, & Melgar, 2017). The dietary avoidance of gluten is the standard treatment of celiac disease and gluten intolerance. Gluten-free diets in people with schizophrenia in fact were found to be associated with a decreased prevalence of thyroid autoantibodies (Toscano et al., 2000; Ventura et al., 2000). Pharmacological agents in development to treat celiac disease include gluten degrading enzymes, (ALV003 and AN-PEP), which are in clinical trials and show promise in reducing symptoms and gluten T-cell responses (Mitea et al., 2008; Siegel et al., 2012; Tye-Din et al., 2010). Zonulin inhibitors such as larazotide are also in development to block gluten transit across the intestinal barrier and have demonstrated improved symptoms, fewer autoantibodies and reduced pro-inflammatory state patients with celiac disease (Parzanese et al., 2017). In mice, an endogenous serine protease inhibitor, elafin, has been shown to normalize inflammation and restore intestinal barrier function (Galipeau et al., 2014), while the compound, sevelamer, available to treat symptoms of chronic kidney disease, binds bacterial proteins and prevents their translocation from the gut into circulation (Kristoff et al., 2014). Some of these compounds are in the beginning stages of preclinical development and thus will require extensive safety, efficacy and other regulatory testing before clinical trials are considered.

### 3.4. Autoantibody clearance

Therapeutic strategies to diminish the effects of autoantibodies involve plasmapheresis to remove the antibodies from systemic circulation or immunosuppression to offset the actual production of antibodies. Plasmapheresis in schizophrenia with the objective to eliminate autoantibodies has been tested with limited success in small studies with very select patients and in case reports (Kramina et al., 2015; Schulz et al., 1983). Directed pharmacotherapy to rejuvenate the receptor can be successful if the autoantibody target, such as the identity of a specific neurotransmitter receptor, is known. Autoantibodies directed against the glutamate system in schizophrenia are best exemplified by the multitude of studies that examine NMDA receptors, as described earlier. Hypofunction of this receptor is a hypothesized mechanism underlying schizophrenia symptoms with the presence of autoantibodies that will bind and internalize the receptor lending support to this rationale. This target is attractive because of the numerous agents currently available that are known to modulate this receptor. Some promising research has been implicated by agents that enhance NMDA receptor function via stimulation of the glycine modulatory site (D-serine, D-cycloserine and bitopertin), although with some mixed results in terms of the treatment of schizophrenia (Alberati et al., 2012; Bugarski-Kirola et al., 2016; Bugarski-Kirola et al., 2017; Heresco-Levy et al., 2015; Kantrowitz et al., 2017; Umbricht et al., 2014). The use of immunotherapy including steroids, intravenous immunoglobulin, and plasma exchange demonstrated promising improvements in symptoms and reductions in autoantibodies in a case series of individuals with NMDA receptor autoantibody-related psychosis, a finding that will be further investigated in randomized placebo-controlled trials (Zandi et al., 2014). Pharmacological strategies to increase NMDA receptor function in schizophrenia are well-reviewed elsewhere (Balu, 2016).

### 4. Conclusions

Here we presented evidence in support of an autoimmune component of schizophrenia in the context of mechanistic or impacted pathways in order to better understand how to formulate novel treatment strategies. Currently, we cannot advocate or suggest any compound to replace antipsychotics. New clinical trials that examine the safety and efficacy of adjunctive therapies in carefully identified individuals who demonstrate specific comorbidities or evidence of inflammation are needed.

As we have discussed in the context of the autoimmune phenotype of schizophrenia, a number of moieties potentially treatable by immunomodulatory agents emerge including pathogens, inflammation, gut dysbioses, and effects from autoantibodies. It is likely that a combination of approaches may offer the most effective evaluation of adjunctive therapies. For example, in patients presenting with GI symptoms, the genetic screening for HLA subtypes coupled with antibody studies might identify a subset of patients who would benefit from an approach to treat celiac disease and gluten intolerance. Microbiome screening of fecal samples coupled with blood tests using biomarkers of microbial dysbioses could identify those who might benefit from probiotics and other gut-related treatments. Genetic screening for complement deficits could identify people with C4 gene susceptibilities and who might be candidates for complement activation or inhibition-based treatment.

For a long time, treating schizophrenia has been focused on dopamine since this pathway is most likely central to the physiological and therapeutic puzzle of schizophrenia. Very recently, it has been discovered that dopamine participates in signaling between immune cells, in a similar manner to synapse communications in the brain. Papa et al. (2017) report that human specialized T cells transfer dopamine to B cells in order to boost the production of antibodies to clear infection (Papa et al., 2017). Might it be that genetically encoded dopamine deficiencies contribute to immune cell dysfunction in schizophrenia?

Likewise, could genetically encoded immune dysfunction contribute to dysregulated dopamine pathways in the brain? As we learn more about the intricate mechanisms governing the immune-brain interface, the development of individualized treatments will become more practical. The development of such modalities will go a long way toward reducing the enormous social and economic costs associated with schizophrenia.

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