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Role of Immune and Autoimmune Dysfunction in Schizophrenia

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INTRODUCTION

Schizophrenia is a debilitating and complex brain disorder of unknown etiology. Complicating our understanding of the causes and pathophysiology of schizophrenia is the likelihood that what we call schizophrenia is actually a heterogeneous assemblage of etiological conditions across a broad spectrum (Arnedo et al., 2014). Reigning evidence supports a schizophrenia etiopathogenesis arising from and perpetuated by a multi-sourced genetic by environmental interaction (Demjaha, MacCabe, & Murray, 2012; Modinos et al., 2013; van Os et al., 2014; Tsuang, 2000). Although schizophrenia is highly heritable, the disease is polygenic, and gene studies to date have identified an enormous number of susceptibility loci (Kavanagh, Tansey, O'Donovan, & Owen, 2014; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Thus, the disease is thought to manifest when one or more of many possible genetic predispositions co-occurs with exposure to one or more of many possible environmental factors. Relevant environmental factors can derive from a diversity of sources including exposures to infection, food-derived antigens, stress, smoking, cannabinoids, pollutants, and other toxins (Allen, Liu, Pelkowski, et al., 2014; Allen, Liu, Weston, et al., 2014; Fine, Zhang, & Stevens, 2014; Fineberg & Ellman, 2013; Fraga et al., 2011; Severance, Yolken, & Eaton, 2014; Suarez-Pinilla, Lopez-Gil, & Crespo-Facorro, 2014; Yolken & Torrey, 2008; Zhang et al., 2014). If these exposures coincide with critical periods of fetal and neonatal brain maturation, there is the potential to aberrantly impact important brain processes including neural migration, synaptogenesis, myelination, and synaptic pruning. Coinciding

with these neurodevelopmental landmarks are events crucial for the instigation and maturation of innate and adaptive immunity.

A possible role for immune system dysregulation in schizophrenia etiopathogenesis would reconcile both genetic and environmental hypotheses. A number of genetic loci found to associate with schizophrenia involve immune functions directly or implicate biological pathways that can influence immune function. For example, a consistently replicated locus for association with schizophrenia is the 6p22 chromosomal region that houses the major histocompatibility (MHC) locus and human leukocyte antigens (Corvin & Morris, 2014; Purcell et al., 2009; Shi et al., 2009; Stefansson et al., 2009). The MHC/human leukocyte gene family functions to identify self and nonself entities and any dysfunction of these genes can render susceptibility to infectious disease, graft rejection, cancer, and autoimmunity. Environmental triggers that show consistently replicated associations with schizophrenia are also those that result in immune activation. Exposures to infectious pathogens, food antigens, and autoantigens have been especially well-studied risk factors for the development of schizophrenia, and special consideration is afforded to the timing, intensity, and type of immune activation elicited by these exposures (Jones, Mowry, Pender, & Greer, 2005; Kirch, 1993; Knuesel et al., 2014; Meyer, 2013; Muller, 2014; Rothermundt, Arolt, & Bayer, 2001; Severance, Yolken, et al., 2014; Torrey & Peterson, 1976; Yolken & Torrey, 2008).

The focus of this chapter is to review some of the evidence in support of an immune and autoimmune dysfunction in the etiology, pathogenesis, and

pathophysiology of schizophrenia. From a historical perspective, a recurrent immune theme predominated the early literature with a particular emphasis on schizophrenia-associated immunoglobulins and anti-brain antibodies. These ideas still formulate the basis of current immune topics in schizophrenia, but over the years the scope has widened beyond the adaptive immune system to encompass also innate immunity. Advances in our understanding of inflammation and mediators of both the adaptive and innate immune system and their functional roles in standard brain physiology provide an important context by which schizophrenia might arise as the result of the coupling of immune and neurodevelopmental dysregulation.

PRIMER ON BASIC IMMUNOLOGY

The focus of this review on immune system aberrations in schizophrenia requires a review of basic knowledge of the major molecules and cells involved in the highly regulated balance of interacting innate and adaptive immune pathways. The function of the immune system is to protect the organism from disease and allow distinction between self and nonself entities, a process that is generally classified into the innate (non-specific, always present) and adaptive (specific, triggered) immune systems. The innate immune system is composed of physical epithelial barriers, monocytes/macrophages, dendritic cells, natural killer cells, and circulating plasma proteins. Microbial invaders or compromised cells interact with recognition receptors found on monocytes/macrophages and dendritic cells. Pattern recognition receptors can be cytoplasmic, membrane-bound, and secreted and include Toll-like receptors, complement receptors, nucleotide-binding oligomerization domain (NOD)-like receptors, pentraxins, and C-reactive protein. The adaptive immune system is composed of two immune response types: humoral (antibody) immunity and T-lymphocyte-mediated immunity. During activation of the adaptive immune system, binding of the invading antigen to B lymphocytes precipitates its differentiation into plasma cells that produce immunoglobulin antibodies specifically targeted to the invading antigen (Alberets, 2008; Rothermundt et al., 2001). The complement system acts in conjunction with the humoral immune system to form immune complexes with the antibody bound antigens and clear these from the body (Walport, 2001a, 2001b). Upon binding to monocytes/macrophages, pathogenic and other antigens also trigger the T-cell cascade, where T cells differentiate into cytotoxic T cells, T-helper cells, and natural killer cells. The lysis of cells containing the invading antigen is accompanied by the production of pro- and anti-inflammatory cytokines, signaling

proteins that function in immune regulation (Alberets, 2008; Rothermundt et al., 2001).

Dysregulation of any of these molecules, proteins, or cells at any stage of these pathways irrespective of a genetic or environmental origin can result in disorders of the immune system, which generally can take the form of inflammatory diseases, immunodeficiency, autoimmunity, or some forms of neoplasia. For complex psychiatric disorders such as schizophrenia, it is also necessary to understand how perturbations of these immune processes might impact the brain. Because schizophrenia is thought to originate as a result of aberrant neurodevelopment, it is important to note that for a number of these classic immune factors, including complement, MHC, Toll-like receptors, and pentraxins, additional functions in the developing brain are continuously being identified (Benoit & Tenner, 2011; Bialas & Stevens, 2013; Boulanger, 2009; Fourgeaud & Boulanger, 2007; Frodl & Amico, 2014; Garate et al., 2013; Nagyoszi et al., 2010; Pribiag & Stellwagen, 2014; Stephan et al., 2013; Stevens et al., 2007; Trotta, Porro, Calvello, & Panaro, 2014). It is also becoming increasingly evident that circulating endogenous peripheral immune entities may directly access the central nervous system (CNS) as a result of directed regulation or compromised endothelial barriers. At the same time, it is possible that invading or resident pathogens or their products could directly exert detriment to the CNS by similarly penetrating these barriers. As such, the spectrum of psychiatric dysfunctions known as schizophrenia may be the compilation of different stages of an immunoneurological intersection gone awry from both external and internal pathological molecules and pathways.

HISTORICAL PERSPECTIVE OF THE IMMUNE-SCHIZOPHRENIA ASSOCIATION

Early observations prepared a foundation for the studies of today where the role of immune activation is no longer questioned but understood to be the most parsimonious etiological explanation that encompasses a gene by environment landscape of schizophrenia. In this section, we will review the history of these immune associations and especially illuminate adaptive humoral immune system dysregulation because immunoglobulin abnormalities were the focus of early investigations (Kirch, 1993; Rothermundt et al., 2001). Although many of these early studies are inconsistent regarding the impact of any single infectious pathogen or autoimmune reaction against brain tissue, these investigations offer snapshots of how the immune process might be relevant to and influence brain function. Importantly, they bring to light issues that are still relevant today and that

are now studied without previous restrictions such as unrecognized disease heterogeneity, constricted study designs, and limited laboratory technologies.

Activation of the adaptive immune system and specifically of humoral immunity generally is manifested by changes in the levels of immunoglobulin antibodies with respect to the disease state. Schizophrenia-associated changes in the levels of plasma and cerebrospinal fluid (CSF) proteins were repeated findings that implicated immunoglobulins and solidified the idea that in schizophrenia, either an infectious or an autoimmune process might be occurring (Amkraut, Solomon, Allansmith, McClellan, & Rappaport, 1973; Bock & Rafaelsen, 1974; Burian, Kubikova, & Krejcova, 1964; Durell & Archer, 1976; Fessel, 1962a, 1962b; Gammack & Hector, 1965; Hendrie, Paraskevas, & Varsamis, 1972; Selecki, Todd, Westwood, & Kraus, 1964; Solomon, Allansmith, McCellan, & Amkraut, 1969; Strahilevitz & Davis, 1970). Of particular interest were reports that people with schizophrenia who had elevated immunoglobulin levels were also the least likely to show clinical improvement over the course of hospitalization compared with those with lower immunoglobulin levels (Amkraut et al., 1973).

An infectious disease component contribution to psychotic mental disorders is often first attributed to Esquirol (1845), who suggested that the dissemination of psychoses unfolds similarly to an epidemic-like process (Esquirol, 1845). This observation was followed by other reports of psychotic epidemics in the decades following World War I and the 1918 influenza epidemic (Kirch, 1993; Menninger, 1919, 1926; Torrey & Peterson, 1973, 1976). The possible role of an antigen derived from a pathogenic organism such as a virus or bacteria took root in various forms and the early years of the viral hypothesis of schizophrenia is well-reviewed by Torrey and Peterson (1973, 1976) and Kirch (1993), with exposures to neurotropic viruses such as herpes simplex virus 1, measles, and rubella figuring prominently (Kirch, 1993; Torrey & Peterson, 1973, 1976).

There was also an extensive literature base primarily from the 1940s to 1950s that describe a variety of antibody reactions in people with schizophrenia including the Rosenow antibody-antigen skin reaction. This reaction was based on a hypothesis that several brain diseases such as epilepsy and schizophrenia were the result of alpha-hemolytic streptococci as measured by a cutaneous reaction to a streptococcal antibody or antigen that was obtained and cultured from nasopharynx samples (Rosenow, 1948). Results from these studies were varied, with some showing greater immune response (cutaneous reaction) associated with schizophrenia and others showing no difference (Gurassa & Fleischhacker, 1958; Rosenow, 1948). We will revisit this idea of a pathogen-derived viral or bacterial source of immune activation in schizophrenia in its current form in a later

section, because it is still a relevant hypothesis that is being explored with the benefit of modern tools such as high throughput sequencing.

Meanwhile, early literature on the topic of autoimmunity received similar effort and attention. One very early study of postmortem brain tissue identified the presence of autoantibodies to brain proteins and launched the idea that schizophrenia and other psychoses may have an autoimmune basis (Lehmann-Facijs, 1937). This theme continued in later decades when the role of autoantibodies to brain proteins was actively studied and disputed (Boehme, Cottrell, Dohan, & Hillegass, 1973; Durell & Archer, 1976; Fessel, 1962a, 1962b; Heath, 1967; Heath & Krupp, 1967; Heath, Krupp, Byers, & Lijekvist, 1967a, 1967b; Jones et al., 2005; Kirch, 1993; Mellisop, Whittingham, & Ungar, 1973). In some of these studies, the observation again came that levels of anti-brain antibodies seemed to correlate with the intensity of psychotic symptoms and were generally higher during the early disease state and during acute attacks (Glebov, 1972; Gurevich, 1969; Stamboliev, 1970; Stoimenov, 1969).

WHERE ARE WE TODAY WITH THE ADAPTIVE IMMUNE HYPOTHESES?

Dysregulation of the adaptive immune system and especially of humoral immunity still figures prominently in today's literature examining immune-based hypotheses for schizophrenia. Speculation that medication is behind changes in immune marker levels is unavoidable; however, studies of patients who are antipsychotic naive or who have a recent onset of the disease support specific immune activation early in the course of disease, even before medication is administered (Beumer et al., 2012; Drexhage et al., 2010; Drexhage et al., 2011; Leonard, Schwarz, & Myint, 2012; Miller, Mellor, & Buckley, 2012; Mondelli & Howes, 2014; Severance, Alaedini, et al., 2012; Severance, Gressitt, et al., 2012; Severance et al., 2013b; Steiner et al., 2012; Stojanovic et al., 2014). Next we describe some current evidence available regarding schizophrenia-specific immune responses to external antigens and autoantigens.

Pathogens

Exposure to infectious disease pathogens during the pre- and postnatal period as defined by an antibody response is significantly associated with the future development of or current status of schizophrenia (Arias et al., 2012; Brown & Derkits, 2010; Buka, Cannon, Torrey, & Yolken, 2008; Fellerhoff, Laumbacher, Mueller, Gu, & Wank, 2007; Mortensen et al., 2010; Niebuhr et al., 2008; Xiao et al., 2009; Yolken et al., 2001; Yolken & Torrey, 2008). We include both pre- and postnatal

exposure references in this section and in a later section will review the implications on neurodevelopment of strictly maternal-occurring immune activation from a variety of sources including pathogens. Pathogenic microorganisms are relevant to schizophrenia pathophysiology because they or their products can be neurotropic as well as cytotoxic or because the process of immune system activation is pathogenic in schizophrenia. Certain viruses known to be neurotropic include the herpes simplex viruses, cytomegalovirus, and Epstein-Barr virus; these viruses are also of interest because their life cycle can contain a latent state from which they can be periodically reactivated (Kirch, 1993; Torrey & Peterson, 1973, 1976). To date, the strongest association of an infectious disease agent with schizophrenia is *Toxoplasma gondii*, a neurotropic parasite, and this relationship is well-reviewed in numerous analyses and meta-analyses (Arias et al., 2012; Monroe, Buckley, & Miller, 2014; Torrey, Bartko, Lun, & Yolken, 2007; Torrey, Bartko, & Yolken, 2012). Other pathogens that have shown significant associations with schizophrenia and psychoses also include Epstein-Barr virus, measles, polio, influenza, coronaviruses, human herpesvirus 2, Borna disease virus, human endogenous retrovirus, and *Chlamydomphila* spp (Arias et al., 2012; Brown, Begg, et al., 2004; Dickerson, Stallings, Origoni, Copp, et al., 2010; Karlsson et al., 2001; Karlsson, Schroder, Bachmann, Bottmer, & Yolken, 2004; Khandaker, Stochl, Zammit, Lewis, & Jones, 2014; Mednick, Machon, Huttunen, & Bonett, 1988; Perron et al., 2012; Prasad, Shirts, Yolken, Keshavan, & Nimgaonkar, 2007; Severance et al., 2011; Suvisaari, Haukka, Tanskanen, Hovi, & Lonnqvist, 1999).

Of note, exposure to the process of infection may be as or more important than the virulence or neurotropism of any single pathogen. A large study of the Swedish national birth registry suggested that exposure to viral CNS infections during childhood could result in the later development of schizophrenia (Dalman et al., 2008). Unlike other investigations, this study did not support a link of bacterial infections with the development of subsequent psychoses. A different study, however, found that urinary tract infections (likely of bacterial origin) were found to occur with increased prevalence in schizophrenia and associated with acute relapse of psychosis (Graham, Carson, Ezeoke, Buckley, & Miller, 2014; Miller et al., 2013). Other conditions typically characterized by bacterial infection (sinusitis, tonsillitis, and pneumonia) were associated with the development of schizophrenia in the prenatal exposure scenario, as were genital and other reproductive infections (Babulas, Factor-Litvak, Goetz, Schaefer, & Brown, 2006; Sorensen, Mortensen, Reinisch, & Mednick, 2009).

It is expected that if schizophrenia in some people is the result of a specific virus or parasite, then evidence in the form of DNA sequences would be found in the

brain. These data, however, have thus far been elusive. The ability to efficiently search for this needle in a haystack came several years ago with the advent of high-throughput sequencing. The infancy of this field has not yet uncovered evidence for a causative pathogen, but ongoing investigations have brought about findings in unexpected places, including microbes associated with the gut microbiome.

Food Antigens

The connection between food sensitivity and propensity for schizophrenia was pioneered by F. Curtis Dohan, who hypothesized that wheat gluteins and bovine milk caseins were broken down into bioactive exorphins that could penetrate through gut barriers, enter systemic circulation, and have access to the CNS. His work was based on observations of celiac disease overlap with schizophrenia, with strong correlations of hospitalization rates for schizophrenia with wheat availability during wartime and improvement of psychotic symptoms following removal of wheat and dairy products from the diet (Dohan, 1969, 1970, 1973, 1980; Dohan, Harper, Clark, Rodrigue, & Zigas, 1984). A recent resurgence in this field is exemplified by the numerous antibody studies that confirm an increased immune response directed at these food antigens, including a role for maternal antibodies to food antigens and the possible presence of an antigen-specific immune reaction up to 2 years before diagnosis of the disease (Casella et al., 2011; Dickerson, Stallings, Origoni, Vaughan, et al., 2010; Jackson et al., 2012; Karlsson et al., 2012; Lachance & McKenzie, 2014; Niebuhr et al., 2011; Samaroo et al., 2010; Severance et al., 2010; Severance, Gressitt, et al., 2012). The presence of food-derived exorphins or antibodies against them have been documented in the CSF of individuals with a variety of psychoses including schizophrenia and coupled with a propensity for blood-brain and CSF-brain barrier defects might implicate a neurotropic role of these peptides in the etiology or pathophysiology of the disease (Axelsson, Martensson, & Alling, 1982; Bauer & Kornhuber, 1987; Kirch et al., 1992; Lindstrom, Besev, Gunne, & Terenius, 1986; Lindstrom et al., 1984).

Autoantigens

Autoimmune disease epidemiology and schizophrenia have been strongly linked for some time, with the first vestiges of the association coming in the form of findings suggestive of an inverse correlation between rheumatoid arthritis and schizophrenia (Benros, Eaton, & Mortensen, 2014; Eaton, Hayward, & Ram, 1992; Torrey & Yolken, 2001). Observations of a co-occurring psychosis with a number of autoimmune diseases including celiac disease, multiple sclerosis, systemic

lupus erythematosus, autoimmune thyrotoxicosis, autoimmune hepatitis, and psoriasis also lent credence to the idea of an interrelated component of autoimmunity and the brain (Benros et al., 2014; Eaton et al., 2006). Celiac disease perhaps provides the strongest association with schizophrenia and reinforces the idea that for some, immune activation and autoimmunity have roots in the gut (Baldwin, 1980; Dohan, 1970, 1973, 1980; Eaton et al., 2004). Celiac disease is a disease whereby the ingestion of wheat gluten launches an immune reaction that damages the epithelial lining of the small intestine through an autoimmune attack on tissue transglutaminase that breaks down the gluten peptide (Alaedini & Green, 2008; Green et al., 2005; Guandalini & Assiri, 2014).

In the same way that the type of pathogen infection is probably not as important as the infectious process itself in causing brain pathologies such as schizophrenia, the specific type of autoimmune disease may not be the primary determinant of brain pathology. Instead, the occurrence of a state of autoimmunity and its association with schizophrenia is rather likely to be a suggestion of the pathophysiology or faulty mechanism that is at work, perhaps as a disjunctive operation of an immune system pathway that has failed to function. Large Danish population-based studies, in fact, confirm that individuals or first-degree family members who had any history of an autoimmune disease have a 45% increased relative risk for schizophrenia (Eaton et al., 2006). The autoimmune link with schizophrenia was further solidified in an even larger investigation of this registry, and interestingly, this risk was further elevated in those with a history of an infection (Benros et al., 2011). This finding is not surprising given the fairly established literature base supporting the idea that exposure to infectious agents generates an autoimmune response (Ercolini & Miller, 2009).

As mentioned in a previous section, documenting and characterizing autoantibodies directed at brain proteins has been intriguing researchers for decades with generally mixed results. Among the many autoantigens analyzed for an association with schizophrenia and psychosis are *N*-methyl-*D*-aspartate (NMDA) receptors (Deakin, Lennox, & Zandi, 2014; Ezeoke, Mellor, Buckley, & Miller, 2013; Jones et al., 2005; Masdeu et al., 2012; Muller, 2014; Pearlman & Najjar, 2014; Steiner et al., 2014; Steiner et al., 2013). This NMDA receptor antibody quest was fueled by findings that antibodies to the NMDA receptor were elevated in women with ovarian teratoma and psychoses-related encephalitis (Dalmau et al., 2007). Other targets of autoimmune investigations include Neuregulin-2, human endogenous retroviruses, cholinergic muscarinic receptors, nicotinic acetylcholine receptors, dopamine D2 receptors, mu-opioid receptors, serotonin receptors, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors, gamma-aminobutyric acid receptors, glutamic acid decarboxylase, potassium

channel receptors, cardiolipin, DNA, histones, and mitochondria (Deakin et al., 2014; Ezeoke et al., 2013; Jones et al., 2005; Masdeu et al., 2012). An increased understanding of the underlying immunopathological processes and an improved characterization of reactive epitopes involved in disease pathogenesis might improve the predictive value of autoantibody assays and provide for reliable markers of disease susceptibility.

MOVING TOWARD INNATE IMMUNITY AND “THE PROCESS OF IMMUNE ACTIVATION”

The Gut, Inflammation, and Endothelial Barrier Dysfunction

A movement away from schizophrenia as a solely brain-centric disease is an active one in psychiatric research circles where an increasing awareness of the importance of the gastrointestinal (GI) tract, the body's largest immune organ, may share a bidirectional pathway with the brain. The strong association between food-based sensitivities and schizophrenia implicates the GI tract as an important site to search for immunological dysfunction. Food antigen sensitivity is but one of a number of risk factors for schizophrenia that are related to gut inflammation, and this immunoglobulin G (IgG) sensitivity joins other gut-related risk factors such as endothelial barrier defects, celiac disease, and exposure to *T. gondii* (Severance, Yolken, et al., 2014). Research at this interface has shown in translational models that intestinal inflammation is a significant comorbidity of schizophrenia, and markers of this inflammation correlate with antibodies to food antigens such as gluten and casein at heightened rates in people with schizophrenia (Severance, Alaedini, et al., 2012; Severance, Yolken, et al., 2014). It has been demonstrated in rodent models that the schizophrenia-associated pathogen *T. gondii* has many effects on the gut and during infection allows the passage of gluten peptides to translocate into circulation and provoke an antibody response (Severance, Kannan, et al., 2012). In the presence of compromised epithelial and endothelial barriers, not only do food-based peptides but also bacteria and other related harmful substances cross into the systemic circulation and generate more inflammation and propagate autoimmunity. Markers of bacterial translocation are elevated in schizophrenia and also found to correlate with the antibody response to food antigens (Severance et al., 2013a). Thus gut-based inflammation can be added to the growing list of studies that implicate both peripheral and CNS inflammatory pathways associated with schizophrenia (Dickerson et al., 2013; Drexhage et al., 2010; Fillman et al., 2013; Fillman, Sinclair, Fung, Webster, & Shannon

Weickert, 2014; Gibney & Drexhage, 2013; Leonard et al., 2012; Linderholm et al., 2012; Miller, Buckley, Seabolt, Mellor, & Kirkpatrick, 2011; Miller et al., 2012; Monji et al., 2013; Muller, 2014; Muller, Myint, & Schwarz, 2012; Torrey et al., 2012; Yolken & Torrey, 2008).

The burgeoning field of gut brain axis analyses is the subject of investigations directed at the understanding of how gut microbes might impact neuronal connections in the CNS. Importantly, the gut microbiome functions to regulate the immune system. The ability of intestinal epithelial cells to actively respond to microbes is mediated by innate immune pattern recognition receptors (Toll-like receptors), NOD-like receptors, and helicases expressed on cell surfaces. During times of mucosal stress, gut homeostasis becomes disrupted (Stockinger, Hornef, & Chassin, 2011). Although there are numerous reports of autism-related altered communities of the intestinal microbiome (Adams, Johansen, Powell, Quig, & Rubin, 2011; Finegold et al., 2010; Finegold, Downes, & Summanen, 2012; Kang et al., 2013; Parracho, Bingham, Gibson, & McCartney, 2005; Williams et al., 2011; Williams, Hornig, Parekh, & Lipkin, 2012), studies of the microbiome in schizophrenia are scant. Preliminary clinical studies report altered pharyngeal and intestinal microbiomes in individuals with schizophrenia as compared to controls (Yolken & Dickerson, 2014). Some insight can be gleaned from rodent studies, where manipulations of gut microbiota do in fact result in behavioral, biochemical, and molecular changes (Collins, Surette, & Bercik, 2012; Foster & McVey Neufeld, 2013; Hsiao et al., 2013; Stilling, Dinan, & Cryan, 2014). Diaz-Heijtz et al. (2011), for example, illustrated that behavioral effects accompanied changes in synaptic markers, synaptophysin and PSD95, in the striatum (Diaz Heijtz et al., 2011). In these rodent studies, animal phenotypes were recovered with manipulations of gnotobiotic (germ-free) animals, vagotomy, probiotics, and/or antibiotics.

The ability of an extrinsically or intrinsically derived microbe, cell, protein, or other product normally found in peripheral circulation to enter to the CNS renders discussion of epithelial and endothelial barriers an important topic. Barrier permeability of the gut, blood–brain barrier, or blood–CSF barrier (Axelsson et al., 1982; Bauer & Kornhuber, 1987; Kirch et al., 1992) can arise from a variety of environmental factors or from genetic mutations in the many biological pathways that impact this cellular architecture. Barrier structures are composed of tight junctions (zonula occludens) that occur between the epithelial cells of the GI lumen of the GI tract; similar tight junction structures comprise the blood–brain barrier (Deli, 2009; Jong & Huang, 2005). The CSF–brain and CSF–blood barrier are slightly different, but these interfaces at the choroid plexus and arachnoid membrane are also relevant areas of access to the brain from the CSF (Lattera, Keep, Betz, & Goldstein, 1999). For schizophrenia, CNS barrier dysfunction has been evaluated

in studies of CSF dynamics and is often attributed to a low-grade, systemic inflammation (Bauer & Kornhuber, 1987; Bechter, 2013; Bechter et al., 2010; Kirch et al., 1992; Severance, Gressitt, Alaedini, et al., 2015). In conjunction with analyses of plasma and CSF protein dynamics, it has been possible to detect evidence for barrier defects or restricted flow, as is particularly evident by the high prevalence of plasma-derived albumin. Abnormal measures of plasma-derived albumin in the CSF are noteworthy because the CNS does not synthesize albumin and its elevation would require transport across the blood–brain or blood–CSF barrier (Tibbling, Link, & Ohman, 1977). An increased albumin ratio can be indicative of either an anatomical barrier defect or a decreased CSF flow rate, a dysfunction with numerous physiological causes (Reiber, 1994; Whedon & Glassey, 2009). The presence of pathological CNS structures such as choroid plexus calcification, arachnoid cysts, and decreased brain volume all can disrupt CSF flow patterns and all of these conditions have been previously associated with psychoses and schizophrenia (Arango et al., 2012; Kuloglu, Caykoylu, Yilmaz, & Ekinci, 2008; Lattera et al., 1999; Marinescu, Udristoiu, & Marinescu, 2013; Narr et al., 2003; Reiber, 1994; Rimol et al., 2012; Sandyk, 1993; Shiga et al., 2012; Veijola et al., 2014; Whedon & Glassey, 2009).

Although a systemic state of inflammation that might impact barrier integrities is most likely the result of immune activation from an environmental source, cellular barrier proteins and related biological pathways may also be the result of genetic associations. Specific barrier-related genes that have been significantly associated with schizophrenia include the tight junction protein claudin-5, cytoskeletal elements such as actin, haptoglobin, and nitric oxide synthetase (Burghardt, Grove, & Ellingrod, 2014; Hall, Trent, Thomas, O'Donovan, & Owen, 2014; Horvath & Mirnics, 2014; Maes et al., 2001; Sun et al., 2004; Wan et al., 2007; Wei & Hemmings, 2005; Yang et al., 2006; Ye et al., 2005; Zhao et al., 2014).

The Maternal–Fetal Environment

The etiology and pathogenesis of schizophrenia likely stem from aberrant neurodevelopment (Lewis & Levitt, 2002; Piper et al., 2012; Rapoport, Giedd, & Gogtay, 2012). Perinatal-occurring environmental disturbances such as maternal stress, infection, or obstetric complications may interact adversely in genetically predisposed offspring to impact neural migration, synaptogenesis, myelination, and synaptic pruning (Knuesel et al., 2014). Epidemiological and preclinical studies clearly indicate that exposure to maternal immune activity is associated with pathological brain development and thus maternal immune activation has become a strong risk factor for the development of schizophrenia (Bauman et al., 2014; Brown & Derkits, 2010; Canetta et al., 2014; Garbett, Hsiao, Kalman, Patterson, & Mirnics, 2012; Meyer, 2013;

Shi, Smith, et al., 2009). Specifically, maternal exposure to cytomegalovirus, herpes simplex virus type 2, influenza, rubella, *T. gondii*, and wheat gluteins have all been documented to increase the risk of development of psychosis or schizophrenia (Blomstrom et al., 2012; Brown, Begg, et al., 2004; Brown, Cohen, Greenwald, & Susser, 2000; Brown, Hooton, et al., 2004; 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; Xiao et al., 2009). This repertoire was recently expanded to include exposure to general inflammation and innate immunity based on measures of C-reactive protein and complement C1q (Canetta et al., 2014; Severance, Gressitt, Buka, Cannon, & Yolken, 2014). In this section, we will review the timelines of brain and immune development and review the evidence where these trajectories might intersect and result in brain disorders (Figure 1).

Neural development is a highly regulated process and since molecules and proteins of the immune system are continually being found to participate in mechanisms of normal brain development, any immune overactivation, or failure of the immune system to activate will impact brain circuitry. The immune environment during pregnancy is a complex balance aimed at preserving

immune protection of both sides of the maternal–fetal interface. Several good reviews are available of how this interface is skewed maternally toward inhibiting fetal immunity and regulating and maintaining a protective Th2 environment over the pro-inflammatory cytotoxic Th1 immune response needed to fight infectious disease (Belderbos, Levy, Meyaard, & Bont, 2013; Morein, Blomqvist, & Hu, 2007). Maternal immunity is antibody based and functions to maintain immune tolerance in the fetus and breast-feeding neonate. As a result, all antibodies including autoantibodies are passed to the offspring during this period. Furthermore, while under maternal immune protection, the antigen recognition system of the fetus is immature. Once maternal-derived immune factors are depleted, the immune system of the neonate must be redirected to become competent, including a more active Th1 component. Maturation of the innate and adaptive immune systems is a process that occurs from the fetal stage through adulthood (Belderbos et al., 2013; Knuesel et al., 2014; Morein et al., 2007).

Molecules and proteins of the immune system are intrinsically intertwined with important brain processes during development. These processes include initial proliferation of glia and neurons, consequent migration, programmed cell death, formation of synapses,

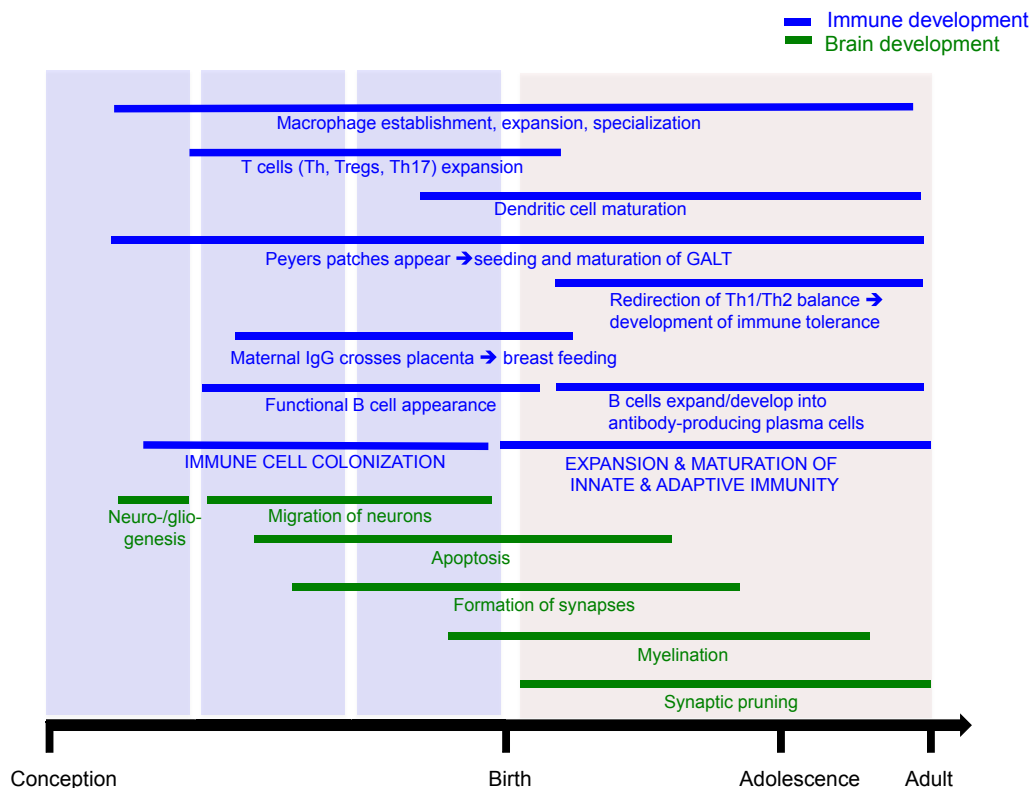


FIGURE 1 Developmental timelines of the brain and the immune system. Complex disorders such as schizophrenia are thought to arise when one or more neurodevelopmental processes are interrupted because of genetic and/or environmental factors. Various immune molecules, proteins, and cells such as C1q and major histocompatibility complex function in the brain during neurodevelopment, suggesting that any disruption in the immune system during pregnancy or postnatally has the ability to compound synaptic misconnections. *Compiled from Belderbos et al. (2013), Diert et al. (2010), Knuesel et al. (2014), and Morein et al. (2007).*

myelination, and synapse pruning with the overall endpoint to establish functional neuronal circuits (Knuesel et al., 2014). Here, we present the case of complement C1q as an example of an immune molecule that is highly active in the developing brain and that is also implicated in schizophrenia-associated gene and environmental studies. In the developing immune system, relevant processes include immune cell appearance, colonization, expansion, and maturation. Complement C1q and MHC1 were some of the first immune molecules identified to function in synapse development and pruning in the brain (Boulanger, 2009; Fourgeaud & Boulanger, 2007; Huh et al., 2000; Shatz, 2009; Stevens et al., 2007). Complement pathway-related genes that have been associated with schizophrenia include the C1QB gene, complement control-related genes, and complement surface receptor gene CD46 (Havik et al., 2011; Zakharyan et al., 2011). Biologically, complement-containing circulating immune complexes were elevated in individuals with schizophrenia compared to controls and a primary antigenic component of these immune complexes was often found to be casein or gluten (Arakelyan et al., 2011; Boyajyan, Khoyetsyan, Tsakanova, & Sim, 2008; Mailian, Boiadzhian, Sogoian, Sim, & Manukian, 2005; Mayilyan, Weinberger, & Sim, 2008; Severance, Gressitt, et al., 2012; Vetlugina, Logvinovich, Maslennikova, & Vasil'eva, 1984). Finally, elevated levels of maternal C1q IgG have been found to increase the odds for psychosis in offspring (Severance, Gressitt, Buka, et al., 2014). Given that maternal IgG antibodies begin transfer to the fetus at 13 weeks' gestation and approach maternal levels at time of birth (Malek, Sager, Kuhn, Nicolaides, & Schneider, 1996; Simister, 2003), this study introduces the interesting possibility that autoantibodies to C1q present in the mother might interact with fetal C1q during critical periods of brain development. Specifically, if the process of normal C1q-mediated synapse formation and pruning is interrupted, synaptic connections will presumably be permanently altered in the developing brain either through overpruning or through underpruning. Other studies have connected the presence of maternal autoantibodies and with the development of autism spectrum disorders where maternal autoantibodies have been found to recognize brain proteins critical to the neurodevelopmental process (Braunschweig et al., 2013; Brimberg, Sadiq, Gregersen, & Diamond, 2013).

CONCLUDING REMARKS

This chapter provides an introduction into some of the mechanisms by which the immune system might be involved in the development of schizophrenia. If schizophrenia has an immune component, and if evidence indicates a primary rather than secondary role in disease pathogenesis, then interventions that target the immune system are warranted. Toward this end, one purpose of

this review was to emphasize the very diverse and multiple ways in which the immune system might impact schizophrenia. Its etiology, pathogenesis, and pathophysiology may not just be a function of exposure to an infectious agent or food antigen or dysfunctional innate immunity. Therefore, designing a treatment strategy to an extraordinarily heterogeneous disease is difficult. It is extremely important to be able to identify the subsets of people who have immune-related conditions and fully characterize what kind of immune anomaly is present. Only in this manner can tailored treatments be evaluated. In the future, therapeutic strategies might involve monoclonal or monospecific antibodies to antagonize or inactivate antigenic or other protein targets or use of other immunosuppressive treatments. The rapid advance in the use of monoclonal antibodies for the treatment of autoimmune disorders provides hope that such therapies can also have a major impact on schizophrenia as well. Dietary interventions have been successful in some instances clinically, and developmental compounds aimed to normalize gut function and endothelial barriers in other capacities appear promising (Freeman, 2013; Jackson et al., 2012; Kristoff et al., 2014; Whiteley et al., 2010, 2012). An improved understanding of the role of immune activation in schizophrenia may lead, not only to an improved understanding of disease pathogenesis but also to a new methods for the prevention and treatment of this devastating disorder.

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References

- Adams, J. B., Johansen, L. J., Powell, L. D., Quig, D., & Rubin, R. A. (2011). Gastrointestinal flora and gastrointestinal status in children with autism – comparisons to typical children and correlation with autism severity. *BMC Gastroenterology*, *11*, 22. <http://dx.doi.org/10.1186/1471-230X-11-22>.
- Alaedini, A., & Green, P. H. (2008). Autoantibodies in celiac disease. [Review] *Autoimmunity*, *41*(1), 19–26. <http://dx.doi.org/10.1080/08916930701619219>.
- Alberts, B. (2008). *Molecular biology of the cell* (5th ed.). New York: Garland Science.
- Allen, J. L., Liu, X., Pelkowski, S., Palmer, B., Conrad, K., Oberdorster, G., et al. (2014). Early postnatal exposure to ultrafine particulate matter air pollution: persistent ventriculomegaly, neurochemical disruption, and glial activation preferentially in male mice. [Research Support, N.I.H., Extramural] *Environmental Health Perspectives*, *122*(9), 939–945. <http://dx.doi.org/10.1289/ehp.1307984>.
- Allen, J. L., Liu, X., Weston, D., Prince, L., Oberdorster, G., Finkelstein, J. N., & Cory-Slechta, D. A. (2014). Developmental exposure to concentrated ambient ultrafine particulate matter air pollution in mice results in persistent and sex-dependent behavioral neurotoxicity and glial activation. [Research Support, N.I.H., Extramural] *Toxicological Sciences: An Official Journal of the Society of Toxicology*, *140*(1), 160–178. <http://dx.doi.org/10.1093/toxsci/kfu059>.

- Amkraut, A., Solomon, G. F., Allansmith, M., McClellan, B., & Rappaport, M. (1973). Immunoglobulins and improvement in acute schizophrenic reactions. *Archives of General Psychiatry*, 28(5), 673–677.
- Arakelyan, A., Zakharyan, R., Khoyetsyan, A., Poghosyan, D., Aroutiounian, R., Mrazek, F., et al. (2011). Functional characterization of the complement receptor type 1 and its circulating ligands in patients with schizophrenia. *BMC Clinical Pathology*, 11, 10. <http://dx.doi.org/10.1186/1472-6890-11-10>.
- Arango, C., Rapado-Castro, M., Reig, S., Castro-Fornieles, J., Gonzalez-Pinto, A., Otero, S., et al. (2012). Progressive brain changes in children and adolescents with first-episode psychosis. [Comparative Study Multicenter Study Research Support, Non-U.S. Gov't] *Archives of General Psychiatry*, 69(1), 16–26. <http://dx.doi.org/10.1001/archgenpsychiatry.2011.150>.
- 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. [Meta-Analysis Review] *Schizophrenia Research*, 136(1–3), 128–136. <http://dx.doi.org/10.1016/j.schres.2011.10.026>.
- Arnedo, J., Svrakic, D. M., Del Val, C., Romero-Zaliz, R., Hernandez-Cuervo, H., Fanous, A. H., et al. (2014). Uncovering the hidden risk architecture of the schizophrenias: confirmation in three independent genome-wide association studies. *American Journal of Psychiatry*. <http://dx.doi.org/10.1176/appi.ajp.2014.14040435>.
- Axelsson, R., Martensson, E., & Alling, C. (1982). Impairment of the blood–brain barrier as an aetiological factor in paranoid psychosis. [Research Support, Non-U.S. Gov't] *The British Journal of Psychiatry: The Journal of Mental Science*, 141, 273–281.
- Babulas, V., Factor-Litvak, P., Goetz, R., Schaefer, C. A., & Brown, A. S. (2006). Prenatal exposure to maternal genital and reproductive infections and adult schizophrenia. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't] *American Journal of Psychiatry*, 163(5), 927–929. <http://dx.doi.org/10.1176/appi.ajp.163.5.927>.
- Baldwin, J. (1980). Schizophrenia and physical disease: a preliminary analysis of the data from the Oxford Record Linkage Study. In G. Hemmings (Ed.), *Biochemistry of schizophrenia and addiction*. Lancaster, England: MTP Press. (Reprinted from: Not in File).
- Bauer, K., & Kornhuber, J. (1987). Blood-cerebrospinal fluid barrier in schizophrenic patients. *European Archives of Psychiatry and Neurological Sciences*, 236(5), 257–259.
- Bauman, M. D., Iosif, A. M., Smith, S. E., Bregere, C., Amaral, D. G., & Patterson, P. H. (2014). Activation of the maternal immune system during pregnancy alters behavioral development of rhesus monkey offspring. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't] *Biological Psychiatry*, 75(4), 332–341. <http://dx.doi.org/10.1016/j.biopsych.2013.06.025>.
- Bechter, K. (2013). Updating the mild encephalitis hypothesis of schizophrenia. [Review] *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, 42, 71–91. <http://dx.doi.org/10.1016/j.pnpbp.2012.06.019>.
- Bechter, K., Reiber, H., Herzog, S., Fuchs, D., Tumani, H., & Maxeiner, H. G. (2010). Cerebrospinal fluid analysis in affective and schizophrenic spectrum disorders: identification of subgroups with immune responses and blood-CSF barrier dysfunction. [Research Support, Non-U.S. Gov't] *Journal of Psychiatric Research*, 44(5), 321–330. <http://dx.doi.org/10.1016/j.jpsychires.2009.08.008>.
- Belderbos, M. E., Levy, O., Meyaard, L., & Bont, L. (2013). Plasma-mediated immune suppression: a neonatal perspective. [Review] *Pediatric Allergy and Immunology: Official Publication of the European Society of Pediatric Allergy and Immunology*, 24(2), 102–113. <http://dx.doi.org/10.1111/pai.12023>.
- Benoit, M. E., & Tenner, A. J. (2011). Complement protein C1q-mediated neuroprotection is correlated with regulation of neuronal gene and microRNA expression. [Comparative Study Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, Non-P.H.S.] *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 31(9), 3459–3469. <http://dx.doi.org/10.1523/JNEUROSCI.3932-10.2011>.
- Benros, M. E., Eaton, W. W., & Mortensen, P. B. (2014). The epidemiologic evidence linking autoimmune diseases and psychosis. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't] *Biological Psychiatry*, 75(4), 300–306. <http://dx.doi.org/10.1016/j.biopsych.2013.09.023>.
- Benros, M. E., Nielsen, P. R., Nordentoft, M., Eaton, W. W., Dalton, S. O., & Mortensen, P. B. (2011). Autoimmune diseases and severe infections as risk factors for schizophrenia: a 30-year population-based register study. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't] *American Journal of Psychiatry*, 168(12), 1303–1310. <http://dx.doi.org/10.1176/appi.ajp.2011.11030516>.
- Beumer, W., Drexhage, R. C., De Wit, H., Versnel, M. A., Drexhage, H. A., & Cohen, D. (2012). Increased level of serum cytokines, chemokines and adipokines in patients with schizophrenia is associated with disease and metabolic syndrome. [Research Support, Non-U.S. Gov't] *Psychoneuroendocrinology*, 37(12), 1901–1911. <http://dx.doi.org/10.1016/j.psyneuen.2012.04.001>.
- Bialas, A. R., & Stevens, B. (2013). TGF-beta signaling regulates neuronal C1q expression and developmental synaptic refinement. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't] *Nature Neuroscience*, 16(12), 1773–1782. <http://dx.doi.org/10.1038/nn.3560>.
- Blomstrom, A., Karlsson, H., Wicks, S., Yang, S., Yolken, R. H., & Dalman, C. (2012). Maternal antibodies to infectious agents and risk for non-affective psychoses in the offspring – a matched case-control study. [Research Support, Non-U.S. Gov't] *Schizophrenia Research*, 140(1–3), 25–30. <http://dx.doi.org/10.1016/j.schres.2012.06.035>.
- Bock, E., & Rafaelsen, O. J. (1974). Schizophrenia: proteins in blood and cerebrospinal fluid. A review. [Review] *Danish Medical Bulletin*, 21(3), 93–105.
- Boehme, D. H., Cottrell, J. C., Dohan, F. C., & Hilleagass, L. M. (1973). Fluorescent antibody studies of immunoglobulin binding by brain tissues. Demonstration of cytoplasmic fluorescence by direct and indirect testing in schizophrenic and nonschizophrenic subjects. *Archives of General Psychiatry*, 28(2), 202–207.
- Boulanger, L. M. (2009). Immune proteins in brain development and synaptic plasticity. *Neuron*, 64(1), 93–109. <http://dx.doi.org/10.1016/j.neuron.2009.09.001> pii:S0896-6273(09)00678-3.
- Boyajyan, A., Khoyetsyan, A., Tsakanova, G., & Sim, R. B. (2008). Cryoglobulins as indicators of upregulated immune response in schizophrenia. *Clinical Biochemistry*, 41(6), 355–360. <http://dx.doi.org/10.1016/j.clinbiochem.2007.11.014> pii:S0009-9120(07)00478-X.
- Braunschweig, D., Krakowiak, P., Duncanson, P., Boyce, R., Hansen, R. L., Ashwood, P., et al. (2013). Autism-specific maternal autoantibodies recognize critical proteins in developing brain. *Translational Psychiatry*, 3, e277. <http://dx.doi.org/10.1038/tp.2013.50>.
- Brimberg, L., Sadiq, A., Gregersen, P. K., & Diamond, B. (2013). Brain-reactive IgG correlates with autoimmunity in mothers of a child with an autism spectrum disorder. *Molecular Psychiatry*. <http://dx.doi.org/10.1038/mp.2013.101>.
- Brown, A. S., Begg, M. D., Gravenstein, S., Schaefer, C. A., Wyatt, R. J., Bresnahan, M., et al. (2004). Serologic evidence of prenatal influenza in the etiology of schizophrenia. [Comparative Study] *Archives of General Psychiatry*, 61(8), 774–780. <http://dx.doi.org/10.1001/archpsyc.61.8.774>.
- Brown, A. S., Cohen, P., Greenwald, S., & Susser, E. (2000). Non-affective psychosis after prenatal exposure to rubella. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.] *The American Journal of Psychiatry*, 157(3), 438–443.
- Brown, A. S., & Derkits, E. J. (2010). Prenatal infection and schizophrenia: a review of epidemiologic and translational studies. [Research Support, N.I.H., Extramural Review] *The American Journal of Psychiatry*, 167(3), 261–280. <http://dx.doi.org/10.1176/appi.ajp.2009.09030361>.
- Brown, A. S., Hooton, J., Schaefer, C. A., Zhang, H., Petkova, E., Babulas, V., et al. (2004). Elevated maternal interleukin-8 levels and risk of schizophrenia in adult offspring. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.] *The American Journal of Psychiatry*, 161(5), 889–895.

- Buka, S. L., Cannon, T. D., Torrey, E. F., & Yolken, R. H. (2008). Maternal exposure to herpes simplex virus and risk of psychosis among adult offspring. [Multicenter Study Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't] *Biological Psychiatry*, 63(8), 809–815. <http://dx.doi.org/10.1016/j.biopsych.2007.09.022>.
- Burghardt, K., Grove, T., & Ellingrod, V. (2014). Endothelial nitric oxide synthetase genetic variants, metabolic syndrome and endothelial function in schizophrenia. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, Non-P.H.S.] *Journal of Psychopharmacology*, 28(4), 349–356. <http://dx.doi.org/10.1177/0269881113516200>.
- Burian, L., Kubikova, A., & Krejčova, O. (1964). Human antiglobulins in the serum of schizophrenic patients. *Ceskoslovenska Psychiatrie*, 60, 26–29.
- Canetta, S., Sourander, A., Surcel, H. M., Hinkka-Yli-Salomaki, S., Leiviska, J., Kellendonk, C., et al. (2014). Elevated maternal C-reactive protein and increased risk of schizophrenia in a national birth cohort. *American Journal of Psychiatry*. <http://dx.doi.org/10.1176/appi.ajp.2014.13121579>.
- Cascella, N. G., Kryszak, D., Bhatti, B., Gregory, P., Kelly, D. L., Mc Evoy, J. P., et al. (2011). Prevalence of celiac disease and gluten sensitivity in the United States clinical antipsychotic trials of intervention effectiveness study population. *Schizophrenia Bulletin*, 37(1), 94–100. <http://dx.doi.org/10.1093/schbul/sbp055>.
- Collins, S. M., Surette, M., & Bercik, P. (2012). The interplay between the intestinal microbiota and the brain. [Research Support, Non-U.S. Gov't Review] *Nature Reviews Microbiology*, 10(11), 735–742. <http://dx.doi.org/10.1038/nrmicro2876>.
- Corvin, A., & Morris, D. W. (2014). Genome-wide association studies: findings at the major histocompatibility complex locus in psychosis. *Biological Psychiatry*, 75(4), 276–283. <http://dx.doi.org/10.1016/j.biopsych.2013.09.018>.
- 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 Swedish subjects. [Comparative Study Research Support, Non-U.S. Gov't] *American Journal of Psychiatry*, 165(1), 59–65. <http://dx.doi.org/10.1176/appi.ajp.2007.07050740>.
- Dalmau, J., Tuzun, E., Wu, H. Y., Masjuan, J., Rossi, J. E., Voloschin, A., et al. (2007). Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. [Clinical Trial Comparative Study Research Support, N.I.H., Extramural] *Annals of Neurology*, 61(1), 25–36. <http://dx.doi.org/10.1002/ana.21050>.
- Deakin, J., Lennox, B. R., & Zandi, M. S. (2014). Antibodies to the N-methyl-D-aspartate receptor and other synaptic proteins in psychosis. [Review] *Biological Psychiatry*, 75(4), 284–291. <http://dx.doi.org/10.1016/j.biopsych.2013.07.018>.
- Deli, M. A. (2009). Potential use of tight junction modulators to reversibly open membranous barriers and improve drug delivery. *Biochimica et Biophysica Acta-Biomembranes*, 1788(4), 892–910. <http://dx.doi.org/10.1016/j.bbamem.2008.09.016>.
- Demjaha, A., MacCabe, J. H., & Murray, R. M. (2012). How genes and environmental factors determine the different neurodevelopmental trajectories of schizophrenia and bipolar disorder. *Schizophrenia Bulletin*, 38(2), 209–214. <http://dx.doi.org/10.1093/schbul/sbr100>.
- Diaz Heijtz, R., Wang, S., Anuar, F., Qian, Y., Bjorkholm, B., Samuelsson, A., et al. (2011). Normal gut microbiota modulates brain development and behavior. *Proceedings of the National Academy of Sciences of the United States of America*, 108(7), 3047–3052. <http://dx.doi.org/10.1073/pnas.1010529108>. Epub 2011 Jan 31. PMID: 21282636.
- Dickerson, F., Stallings, C., Origoni, A., Copp, C., Khushalani, S., & Yolken, R. (2010). Antibodies to measles in individuals with recent onset psychosis. [Research Support, Non-U.S. Gov't] *Schizophrenia Research*, 119(1–3), 89–94. <http://dx.doi.org/10.1016/j.schres.2009.12.010>.
- Dickerson, F., Stallings, C., Origoni, A., Vaughan, C., Khushalani, S., Leister, F., et al. (2010). Markers of gluten sensitivity and celiac disease in recent-onset psychosis and multi-episode schizophrenia. *Biological Psychiatry*, 68(1), 100–104. <http://dx.doi.org/10.1016/j.biopsych.2010.03.021> pii:S0006-3223(10)00250-7.
- Dickerson, F., Stallings, C., Origoni, A., Vaughan, C., Khushalani, S., Yang, S., et al. (2013). C-reactive protein is elevated in schizophrenia. [Research Support, Non-U.S. Gov't] *Schizophrenia Research*, 143(1), 198–202. <http://dx.doi.org/10.1016/j.schres.2012.10.041>.
- Dietert, R. R., DeWitt, J. C., Germolec, D. R., & Zelikoff, J. T. (2010). Breaking patterns of environmentally influenced disease for health risk reduction: immune perspectives. *Environmental Health Perspectives*, 118(8), 1091–1099. <http://dx.doi.org/10.1289/ehp.1001971>. Epub 2010 May 18. Review. PMID: 20483701.
- Dohan, F. C. (1969). Is celiac disease a clue to the pathogenesis of schizophrenia? *Mental Hygiene*, 53(4), 525–529.
- Dohan, F. C. (1970). Coeliac disease and schizophrenia. *Lancet*, 1(7652), 897–898.
- Dohan, F. C. (1973). Coeliac disease and schizophrenia. *British Medical Journal*, 3(5870), 51–52.
- Dohan, F. C. (1980). Coeliac disease and schizophrenia. *The New England Journal of Medicine*, 302(22), 1262.
- Dohan, F. C., Harper, E. H., Clark, M. H., Rodrigue, R. B., & Zigas, V. (1984). Is schizophrenia rare if grain is rare? *Biological Psychiatry*, 19(3), 385–399.
- Drexhage, R. C., Knijff, E. M., Padmos, R. C., Heul-Nieuwenhuijzen, L., Beumer, W., Versnel, M. A., et al. (2010). The mononuclear phagocyte system and its cytokine inflammatory networks in schizophrenia and bipolar disorder. *Expert Review of Neurotherapeutics*, 10(1), 59–76. <http://dx.doi.org/10.1586/ern.09.144>.
- Drexhage, R. C., Weigelt, K., van Beveren, N., Cohen, D., Versnel, M. A., Nolen, W. A., et al. (2011). Immune and neuroimmune alterations in mood disorders and schizophrenia. [Research Support, Non-U.S. Gov't Review] *International Review of Neurobiology*, 101, 169–201. <http://dx.doi.org/10.1016/B978-0-12-387718-5.00007-9>.
- Durell, J., & Archer, E. G. (1976). Plasma proteins in schizophrenia: a review. [Research Support, U.S. Gov't, Non-P.H.S. Review] *Schizophrenia Bulletin*, 2(1), 147–159.
- Eaton, W., Hayward, C., & Ram, R. (1992). Schizophrenia and rheumatoid arthritis: a review. *Schizophrenia Research*, 6, 181–192.
- Eaton, W., Mortensen, P. B., Agerbo, E., Byrne, M., Mors, O., & Ewald, H. (2004). Coeliac disease and schizophrenia: population based case control study with linkage of Danish national registers. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.] *British Medical Journal*, 328(7437), 438–439. <http://dx.doi.org/10.1136/bmj.328.7437.438>.
- Eaton, W. W., Byrne, M., Ewald, H., Mors, O., Chen, C. Y., Agerbo, E., et al. (2006). Association of schizophrenia and autoimmune diseases: linkage of Danish national registers. [Comparative Study Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't] *The American Journal of Psychiatry*, 163(3), 521–528. <http://dx.doi.org/10.1176/appi.ajp.163.3.521>.
- Ellman, L. M., Yolken, R. H., Buka, S. L., Torrey, E. F., & Cannon, T. D. (2009). Cognitive functioning prior to the onset of psychosis: the role of fetal exposure to serologically determined influenza infection. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't] *Biological Psychiatry*, 65(12), 1040–1047. <http://dx.doi.org/10.1016/j.biopsych.2008.12.015>.
- Ercolini, A. M., & Miller, S. D. (2009). The role of infections in autoimmune disease. [Review] *Clinical & Experimental Immunology*, 155(1), 1–15. <http://dx.doi.org/10.1111/j.1365-2249.2008.03834.x>.
- Esquirol, J. E. (1845). *Mental maladies, a treatise on insanity*. Philadelphia, PA: Lea and Blanchard.
- Ezeoke, A., Mellor, A., Buckley, P., & Miller, B. (2013). A systematic, quantitative review of blood autoantibodies in schizophrenia. [Review] *Schizophrenia Research*, 150(1), 245–251. <http://dx.doi.org/10.1016/j.schres.2013.07.029>.

- Fellerhoff, B., Laumbacher, B., Mueller, N., Gu, S., & Wank, R. (2007). Associations between Chlamydia infections, schizophrenia and risk of HLA-A10. [Comparative Study/Research Support, Non-U.S. Gov't] *Molecular Psychiatry*, 12(3), 264–272. <http://dx.doi.org/10.1038/sj.mp.4001925>.
- Fessel, W. J. (1962a). Autoimmunity and mental illness. A preliminary report. *Archives of General Psychiatry*, 6, 320–323.
- Fessel, W. J. (1962b). Blood proteins in functional psychoses. A review of the literature and unifying hypothesis. *Archives of General Psychiatry*, 6, 132–148.
- Fillman, S. G., Cloonan, N., Catts, V. S., Miller, L. C., Wong, J., McCrossin, T., et al. (2013). Increased inflammatory markers identified in the dorsolateral prefrontal cortex of individuals with schizophrenia. *Molecular Psychiatry*, 18(2), 206–214. <http://dx.doi.org/10.1038/mp.2012.110>.
- Fillman, S. G., Sinclair, D., Fung, S. J., Webster, M. J., & Shannon Weickert, C. (2014). Markers of inflammation and stress distinguish subsets of individuals with schizophrenia and bipolar disorder. *Translational Psychiatry*, 4, e365. <http://dx.doi.org/10.1038/tp.2014.8>.
- Fine, R., Zhang, J., & Stevens, H. E. (2014). Prenatal stress and inhibitory neuron systems: implications for neuropsychiatric disorders. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't] *Molecular Psychiatry*, 19(6), 641–651. <http://dx.doi.org/10.1038/mp.2014.35>.
- Fineberg, A. M., & Eilman, L. M. (2013). Inflammatory cytokines and neurological and neurocognitive alterations in the course of schizophrenia. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Review] *Biological Psychiatry*, 73(10), 951–966. <http://dx.doi.org/10.1016/j.biopsych.2013.01.001>.
- Finogold, S. M., Dowd, S. E., Gontcharova, V., Liu, C., Henley, K. E., Wolcott, R. D., et al. (2010). Pyrosequencing study of fecal microflora of autistic and control children. *Anaerobe*, 16(4), 444–453. <http://dx.doi.org/10.1016/j.anaerobe.2010.06.008>.
- Finogold, S. M., Downes, J., & Summanen, P. H. (2012). Microbiology of regressive autism. [Review] *Anaerobe*, 18(2), 260–262. <http://dx.doi.org/10.1016/j.anaerobe.2011.12.018>.
- Foster, J. A., & McVey Neufeld, K. A. (2013). Gut-brain axis: how the microbiome influences anxiety and depression. [Research Support, Non-U.S. Gov't] *Trends in Neurosciences*, 36(5), 305–312. <http://dx.doi.org/10.1016/j.tins.2013.01.005>.
- Fourgeaud, L., & Boulanger, L. M. (2007). Synapse remodeling, compliments of the complement system. [Comment] *Cell*, 131(6), 1034–1036. <http://dx.doi.org/10.1016/j.cell.2007.11.031>.
- Fraga, D. B., Deroza, P. F., Ghedim, F. V., Steckert, A. V., De Luca, R. D., Silverio, A., et al. (2011). Prenatal exposure to cigarette smoke causes persistent changes in the oxidative balance and in DNA structural integrity in rats submitted to the animal model of schizophrenia. [Research Support, Non-U.S. Gov't] *Journal of Psychiatric Research*, 45(11), 1497–1503. <http://dx.doi.org/10.1016/j.jpsychires.2011.06.007>.
- Freeman, H. J. (2013). Non-dietary forms of treatment for adult celiac disease. [Review] *World Journal of Gastrointestinal Pharmacology and Therapeutics*, 4(4), 108–112. <http://dx.doi.org/10.4292/wjgpt.v4.i4.108>.
- Frodl, T., & Amico, F. (2014). Is there an association between peripheral immune markers and structural/functional neuroimaging findings? *Progress in Neuropsychopharmacology & Biological Psychiatry*, 48, 295–303. <http://dx.doi.org/10.1016/j.pnpbp.2012.12.013>.
- Gammack, D. B., & Hector, R. I. (1965). A Study of Serum Proteins in Acute Schizophrenia. *Clinical Science*, 28, 469–475.
- Garate, I., Garcia-Bueno, B., Madrigal, J. L., Caso, J. R., Alou, L., Gomez-Lus, M. L., et al. (2013). Stress-induced neuroinflammation: role of the Toll-like receptor-4 pathway. [Research Support, Non-U.S. Gov't] *Biological Psychiatry*, 73(1), 32–43. <http://dx.doi.org/10.1016/j.biopsych.2012.07.005>.
- Garbett, K. A., Hsiao, E. Y., Kalman, S., Patterson, P. H., & Mirnics, K. (2012). Effects of maternal immune activation on gene expression patterns in the fetal brain. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't] *Translational Psychiatry*, 2, e98. <http://dx.doi.org/10.1038/tp.2012.24>.
- Gibney, S. M., & Drexhage, H. A. (2013). Evidence for a dysregulated immune system in the etiology of psychiatric disorders. *Journal of Neuroimmune Pharmacology: The Official Journal of the Society on NeuroImmune Pharmacology*, 8(4), 900–920. <http://dx.doi.org/10.1007/s11481-013-9462-8>.
- Glebov, V. S. (1972). Clinico-immunologic correlations in the period of development of therapeutical remissions in continuous forms of schizophrenia. *Zhurnal nevropatologii i psikiatrii imeni S.S. Korsakova*, 72(8), 1191–1195.
- Graham, K. L., Carson, C. M., Ezeoke, A., Buckley, P. F., & Miller, B. J. (2014). Urinary tract infections in acute psychosis. [Research Support, Non-U.S. Gov't] *The Journal of Clinical Psychiatry*, 75(4), 379–385. <http://dx.doi.org/10.4088/JCP.13m08469>.
- Green, P. H., Alaedini, A., Sander, H. W., Brannagan, T. H., 3rd, Latov, N., & Chin, R. L. (2005). Mechanisms underlying celiac disease and its neurologic manifestations. [Review] *Cellular and Molecular Life Sciences*, 62(7–8), 791–799. <http://dx.doi.org/10.1007/s00018-004-4109-9>.
- Guandalini, S., & Assiri, A. (2014). Celiac disease: a review. [Review] *JAMA Pediatrics*, 168(3), 272–278. <http://dx.doi.org/10.1001/jamapediatrics.2013.3858>.
- Gurassa, W. P., & Fleischhacker, H. H. (1958). An investigation of the Rosenow antibody antigen skin reaction in schizophrenia. *Journal of Neurology, Neurosurgery, and Psychiatry*, 21(2), 141–145.
- Gurevich, Z. P. (1969). Incomplete anti-tissue autoantibodies in schizophrenia. *Zhurnal nevropatologii i psikiatrii imeni S.S. Korsakova*, 69(11), 1683–1687.
- Hall, J., Trent, S., Thomas, K. L., O'Donovan, M. C., & Owen, M. J. (2014). Genetic risk for schizophrenia: convergence on synaptic pathways involved in plasticity. [Review] *Biological Psychiatry*. <http://dx.doi.org/10.1016/j.biopsych.2014.07.011>.
- Havik, B., Le Hellard, S., Rietschel, M., Lybaek, H., Djurovic, S., Mattheisen, M., et al. (2011). The complement control-related genes CSMD1 and CSMD2 associate to schizophrenia. *Biological Psychiatry*, 70(1), 35–42. <http://dx.doi.org/10.1016/j.biopsych.2011.01.030> pii:S0006-3223(11)00122-3.
- Heath, R. G. (1967). Schizophrenia: pathogenetic theories. *International Journal of Psychiatry*, 3(5), 407–410.
- Heath, R. G., & Krupp, I. M. (1967). Schizophrenia as an immunologic disorder. I. Demonstration of antibody globulins by fluorescent antibody techniques. *Archives of General Psychiatry*, 16(1), 1–9.
- Heath, R. G., Krupp, I. M., Byers, L. W., & Liljekvist, J. I. (1967a). Schizophrenia as an immunologic disorder. 3. Effects of antimonkey and antihuman brain antibody on brain function. *Archives of General Psychiatry*, 16(1), 24–33.
- Heath, R. G., Krupp, I. M., Byers, L. W., & Liljekvist, J. I. (1967b). Schizophrenia as an immunologic disorder. II. Effects of serum protein fractions on brain function. *Archives of General Psychiatry*, 16(1), 10–23.
- Hendrie, H. C., Paraskevas, F., & Varsamis, J. (1972). Gamma globulin levels in psychiatric patients. *Canadian Psychiatric Association Journal*, 17(2), 93–97.
- Horvath, S., & Mirnics, K. (2014). Immune system disturbances in schizophrenia. [Research Support, N.I.H., Extramural Review] *Biological Psychiatry*, 75(4), 316–323. <http://dx.doi.org/10.1016/j.biopsych.2013.06.010>.
- Hsiao, E. Y., McBride, S. W., Hsien, S., Sharon, G., Hyde, E. R., McCue, T., et al. (2013). Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, Non-P.H.S.] *Cell*, 155(7), 1451–1463. <http://dx.doi.org/10.1016/j.cell.2013.11.024>.
- Huh, G. S., Boulanger, L. M., Du, H., Riquelme, P. A., Brotz, T. M., & Shatz, C. J. (2000). Functional requirement for class I MHC in CNS development and plasticity. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.] *Science*, 290(5499), 2155–2159.

- Jackson, J., Eaton, W., Cascella, N., Fasano, A., Warfel, D., Feldman, S., et al. (2012). A gluten-free diet in people with schizophrenia and anti-tissue transglutaminase or anti-gliadin antibodies. [Letter] *Schizophrenia Research*, 140(1–3), 262–263. <http://dx.doi.org/10.1016/j.schres.2012.06.011>.
- Jones, A. L., Mowry, B. J., Pender, M. P., & Greer, J. M. (2005). Immune dysregulation and self-reactivity in schizophrenia: do some cases of schizophrenia have an autoimmune basis? [Review] *Immunology and Cell Biology*, 83(1), 9–17. <http://dx.doi.org/10.1111/j.1440-1711.2005.01305.x>.
- Jong, A., & Huang, S. H. (2005). Blood–brain barrier drug discovery for central nervous system infections. *Current Drug Targets – Infectious Disorders*, 5(1), 65–72.
- Kang, D. W., Park, J. G., Ilhan, Z. E., Wallstrom, G., Labaer, J., Adams, J. B., et al. (2013). Reduced incidence of Prevotella and other fermenters in intestinal microflora of autistic children. [Research Support, Non-U.S. Gov't] *PLoS One*, 8(7), e68322. <http://dx.doi.org/10.1371/journal.pone.0068322>.
- Karlsson, H., Bachmann, S., Schroder, J., McArthur, J., Torrey, E. F., & Yolken, R. H. (2001). Retroviral RNA identified in the cerebrospinal fluids and brains of individuals with schizophrenia. [Research Support, Non-U.S. Gov't] *Proceedings of the National Academy of Sciences of the United States of America*, 98(8), 4634–4639. <http://dx.doi.org/10.1073/pnas.061021998>.
- Karlsson, H., Blomstrom, A., Wicks, S., Yang, S., Yolken, R. H., & Dalman, C. (2012). Maternal antibodies to dietary antigens and risk for nonaffective psychosis in offspring. *The American Journal of Psychiatry*. <http://dx.doi.org/10.1176/appi.ajp.2012.11081197>.
- Karlsson, H., Schroder, J., Bachmann, S., Bottmer, C., & Yolken, R. H. (2004). HERV-W-related RNA detected in plasma from individuals with recent-onset schizophrenia or schizoaffective disorder. [Letter] *Molecular Psychiatry*, 9(1), 12–13. <http://dx.doi.org/10.1038/sj.mp.4001439>.
- Kavanagh, D. H., Tansey, K. E., O'Donovan, M. C., & Owen, M. J. (2014). Schizophrenia genetics: emerging themes for a complex disorder. *Molecular Psychiatry*. <http://dx.doi.org/10.1038/mp.2014.148>.
- Khandaker, G. M., Stochl, J., Zammit, S., Lewis, G., & Jones, P. B. (2014). Childhood Epstein-Barr Virus infection and subsequent risk of psychotic experiences in adolescence: a population-based prospective serological study. [Research Support, Non-U.S. Gov't] *Schizophrenia Research*, 158(1–3), 19–24. <http://dx.doi.org/10.1016/j.schres.2014.05.019>.
- Kirch, D. G. (1993). Infection and autoimmunity as etiologic factors in schizophrenia: a review and reappraisal. [Review] *Schizophrenia Bulletin*, 19(2), 355–370.
- Kirch, D. G., Alexander, R. C., Suddath, R. L., Papadopoulos, N. M., Kaufmann, C. A., Daniel, D. G., et al. (1992). Blood-CSF barrier permeability and central nervous system immunoglobulin G in schizophrenia. *Journal of Neural Transmission. General Section*, 89(3), 219–232.
- Knuesel, I., Chicha, L., Britschgi, M., Schobel, S. A., Bodmer, M., Hellings, J. A., et al. (2014). Maternal immune activation and abnormal brain development across CNS disorders. [Review] *Nature Reviews. Neurology*, 10(11), 643–660. <http://dx.doi.org/10.1038/nrneurol.2014.187>.
- Kristoff, J., Haret-Richter, G., Ma, D., Ribeiro, R. M., Xu, C., Cornell, E., et al. (2014). Early microbial translocation blockade reduces SIV-mediated inflammation and viral replication. *The Journal of Clinical Investigation*, 124(6), 2802–2806. <http://dx.doi.org/10.1172/JCI75090>.
- Kuloglu, M., Caykoylu, A., Yilmaz, E., & Ekinci, O. (2008). A left temporal lobe arachnoid cyst in a patient with schizophrenia-like psychosis: a case report. [Case Reports Letter] *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, 32(5), 1353–1354. <http://dx.doi.org/10.1016/j.pnpbp.2008.04.014>.
- Lachance, L. R., & McKenzie, K. (2014). Biomarkers of gluten sensitivity in patients with non-affective psychosis: a meta-analysis. *Schizophrenia Research*, 152(2–3), 521–527. <http://dx.doi.org/10.1016/j.schres.2013.12.001>.
- Laterra, J., Keep, R., Betz, L. A., & Goldstein, G. (1999). *Blood-cerebrospinal fluid barrier*. Philadelphia: Lippincott-Raven.
- Lehmann-Facius, H. (1937). Über die Liequordiagnose der Schizophrenien. *Klinische Wochenschrift*, 16, 1646–1648.
- Leonard, B. E., Schwarz, M., & Myint, A. M. (2012). The metabolic syndrome in schizophrenia: is inflammation a contributing cause? [Review] *Journal of Psychopharmacology*, 26(5 Suppl.), 33–41. <http://dx.doi.org/10.1177/0269881111431622>.
- Lewis, D. A., & Levitt, P. (2002). Schizophrenia as a disorder of neurodevelopment. [Research Support, U.S. Gov't, P.H.S. Review] *Annual Review of Neuroscience*, 25, 409–432. <http://dx.doi.org/10.1146/annurev.neuro.25.112701.142754>.
- Linderholm, K. R., Skogh, E., Olsson, S. K., Dahl, M. L., Holtze, M., Engberg, G., et al. (2012). Increased levels of kynurenine and kynurenic acid in the CSF of patients with schizophrenia. [Research Support, U.S. Gov't, Non-P.H.S.] *Schizophrenia Bulletin*, 38(3), 426–432. <http://dx.doi.org/10.1093/schbul/sbq086>.
- Lindstrom, L. H., Besev, G., Gunne, L. M., & Terenius, L. (1986). CSF levels of receptor-active endorphins in schizophrenic patients: correlations with symptomatology and monoamine metabolites. [Research Support, Non-U.S. Gov't] *Psychiatry Research*, 19(2), 93–100.
- Lindstrom, L. H., Nyberg, F., Terenius, L., Bauer, K., Besev, G., Gunne, L. M., et al. (1984). CSF and plasma beta-casomorphin-like opioid peptides in postpartum psychosis. [Comparative Study Research Support, Non-U.S. Gov't] *The American Journal of Psychiatry*, 141(9), 1059–1066.
- Maes, M., Delanghe, J., Bocchio Chiavetto, L., Bignotti, S., Tura, G. B., Pioli, R., et al. (2001). Haptoglobin polymorphism and schizophrenia: genetic variation on chromosome 16. *Psychiatry Research*, 104(1), 1–9.
- Mailian, K. R., Boiadzian, A. S., Sogoian, A. F., Sim, R. B., & Manukian, L. A. (2005). Concentration and protein composition of circulating immune complexes in the blood of patients with schizophrenia and subjects with positive familial history of disease. *Zhurnal nevrologii i psikiatrii imeni S.S. Korsakova*, 105(4), 55–60.
- Malek, A., Sager, R., Kuhn, P., Nicolaidis, K. H., & Schneider, H. (1996). Evolution of maternofetal transport of immunoglobulins during human pregnancy. [Research Support, Non-U.S. Gov't] *American Journal of Reproductive Immunology*, 36(5), 248–255.
- Marinescu, I., Udristoiu, I., & Marinescu, D. (2013). Choroid plexus calcification: clinical, neuroimaging and histopathological correlations in schizophrenia. *Romanian Journal of Morphology and Embryology = Revue Roumaine de Morphologie et Embryologie*, 54(2), 365–369.
- Masdeu, J. C., Gonzalez-Pinto, A., Matute, C., Ruiz De Azua, S., Palomino, A., De Leon, J., et al. (2012). Serum IgG antibodies against the NR1 subunit of the NMDA receptor not detected in schizophrenia. [Letter] *American Journal of Psychiatry*, 169(10), 1120–1121. <http://dx.doi.org/10.1176/appi.ajp.2012.12050646>.
- Mayilyan, K. R., Weinberger, D. R., & Sim, R. B. (2008). The complement system in schizophrenia. *Drug News & Perspectives*, 21(4), 200–210. <http://dx.doi.org/10.1358/dnp.2008.21.4.1213349>.
- Mednick, S. A., Machon, R. A., Huttunen, M. O., & Bonett, D. (1988). Adult schizophrenia following prenatal exposure to an influenza epidemic. [Research Support, U.S. Gov't, P.H.S.] *Archives of General Psychiatry*, 45(2), 189–192.
- Mellsop, G., Whittingham, S., & Ungar, B. (1973). Schizophrenia and autoimmune serological reactions. *Archives of General Psychiatry*, 28(2), 194–196.
- Menninger, K. A. (1919). Psychoses associated with influenza. *Journal of the American Medical Association*, 72, 235–241.

- Menninger, K. A. (1926). Influenza and schizophrenia: an analysis of post-influenza "dementia praecox" as of 1918 and five years later. *American Journal of Psychiatry*, 5, 469–529.
- Meyer, U. (2013). Developmental neuroinflammation and schizophrenia. [Research Support, Non-U.S. Gov't Review] *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, 42, 20–34. <http://dx.doi.org/10.1016/j.pnpbp.2011.11.003>.
- Miller, B. J., Buckley, P., Seabolt, W., Mellor, A., & Kirkpatrick, B. (2011). Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. [Meta-Analysis Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't] *Biological Psychiatry*, 70(7), 663–671. <http://dx.doi.org/10.1016/j.biopsych.2011.04.013>.
- Miller, B. J., Graham, K. L., Bodenheimer, C. M., Culpepper, N. H., Waller, J. L., & Buckley, P. F. (2013). A prevalence study of urinary tract infections in acute relapse of schizophrenia. [Research Support, Non-U.S. Gov't] *The Journal of Clinical Psychiatry*, 74(3), 271–277. <http://dx.doi.org/10.4088/JCP.12m08050>.
- Miller, B. J., Mellor, A., & Buckley, P. (2012). Total and differential white blood cell counts, high-sensitivity C-reactive protein, and the metabolic syndrome in non-affective psychoses. *Brain, Behavior, and Immunity*, 31, 82–89. <http://dx.doi.org/10.1016/j.bbi.2012.08.016>.
- Modinos, G., Iyegbe, C., Prata, D., Rivera, M., Kempton, M. J., Valmaggia, L. R., et al. (2013). Molecular genetic gene-environment studies using candidate genes in schizophrenia: a systematic review. [Research Support, Non-U.S. Gov't] *Schizophrenia Research*, 150(2–3), 356–365. <http://dx.doi.org/10.1016/j.schres.2013.09.010>.
- Mondelli, V., & Howes, O. (2014). Inflammation: its role in schizophrenia and the potential anti-inflammatory effects of antipsychotics. [Editorial] *Psychopharmacology*, 231(2), 317–318. <http://dx.doi.org/10.1007/s00213-013-3383-3>.
- Monji, A., Kato, T. A., Mizoguchi, Y., Horikawa, H., Seki, Y., Kasai, M., et al. (2013). Neuroinflammation in schizophrenia especially focused on the role of microglia. [Review] *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, 42, 115–121. <http://dx.doi.org/10.1016/j.pnpbp.2011.12.002>.
- Monroe, J. M., Buckley, P. F., & Miller, B. J. (2014). Meta-analysis of Anti-*Toxoplasma gondii* IgM antibodies in acute psychosis. *Schizophrenia Bulletin*. <http://dx.doi.org/10.1093/schbul/sbu159>.
- Morein, B., Blomqvist, G., & Hu, K. (2007). Immune responsiveness in the neonatal period. [Review] *Journal of Comparative Pathology*, 137(Suppl. 1), S27–S31. <http://dx.doi.org/10.1016/j.jcpa.2007.04.008>.
- Mortensen, P. B., Pedersen, C. B., Hougaard, D. M., Norgaard-Petersen, B., Mors, O., Borglum, A. D., & Yolken, R. H. (2010). A Danish National Birth Cohort study of maternal HSV-2 antibodies as a risk factor for schizophrenia in their offspring. [Research Support, Non-U.S. Gov't] *Schizophrenia Research*, 122(1–3), 257–263. <http://dx.doi.org/10.1016/j.schres.2010.06.010>.
- Muller, N. (2014). Immunology of schizophrenia. [Review] *Neuro-immunomodulation*, 21(2–3), 109–116. <http://dx.doi.org/10.1159/000356538>.
- Muller, N., Myint, A. M., & Schwarz, M. J. (2012). Inflammation in schizophrenia. [Review] *Advances in Protein Chemistry and Structural Biology*, 88, 49–68. <http://dx.doi.org/10.1016/B978-0-12-398314-5.00003-9>.
- Nagyoszi, P., Wilhelm, I., Farkas, A. E., Fazakas, C., Dung, N. T., Hasko, J., et al. (2010). Expression and regulation of toll-like receptors in cerebral endothelial cells. [Research Support, Non-U.S. Gov't] *Neurochemistry International*, 57(5), 556–564. <http://dx.doi.org/10.1016/j.neuint.2010.07.002>.
- Narr, K. L., Sharma, T., Woods, R. P., Thompson, P. M., Sowell, E. R., Rex, D., et al. (2003). Increases in regional subarachnoid CSF without apparent cortical gray matter deficits in schizophrenia: modulating effects of sex and age. [Research Support, U.S. Gov't, P.H.S.] *The American Journal of Psychiatry*, 160(12), 2169–2180.
- Niebuhr, D. W., Li, Y., Cowan, D. N., Weber, N. S., Fisher, J. A., Ford, G. M., et al. (2011). Association between bovine casein antibody and new onset schizophrenia among US military personnel. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, Non-P.H.S.] *Schizophrenia Research*, 128(1–3), 51–55. <http://dx.doi.org/10.1016/j.schres.2011.02.005>.
- Niebuhr, D. W., Millikan, A. M., Cowan, D. N., Yolken, R., Li, Y., & Weber, N. S. (2008). Selected infectious agents and risk of schizophrenia among U.S. military personnel. [Comparative Study Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, Non-P.H.S.] *The American Journal of Psychiatry*, 165(1), 99–106. <http://dx.doi.org/10.1176/appi.ajp.2007.06081254>.
- Parracho, H. M., Bingham, M. O., Gibson, G. R., & McCartney, A. L. (2005). Differences between the gut microflora of children with autistic spectrum disorders and that of healthy children. [Comparative Study Research Support, Non-U.S. Gov't] *Journal of Medical Microbiology*, 54(Pt 10), 987–991. <http://dx.doi.org/10.1099/jmm.0.46101-0>.
- Pearlman, D. M., & Najjar, S. (2014). Meta-analysis of the association between N-methyl-D-aspartate receptor antibodies and schizophrenia, schizoaffective disorder, bipolar disorder, and major depressive disorder. *Schizophrenia Research*, 157(1–3), 249–258. <http://dx.doi.org/10.1016/j.schres.2014.05.001>.
- Pedersen, M. G., Stevens, H., Pedersen, C. B., Norgaard-Pedersen, B., & Mortensen, P. B. (2011). Toxoplasma infection and later development of schizophrenia in mothers. [Research Support, Non-U.S. Gov't] *The American Journal of Psychiatry*, 168(8), 814–821. <http://dx.doi.org/10.1176/appi.ajp.2011.10091351>.
- 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. [Research Support, Non-U.S. Gov't] *Translational Psychiatry*, 2, e201. <http://dx.doi.org/10.1038/tp.2012.125>.
- Piper, M., Beneyto, M., Burne, T. H., Eyles, D. W., Lewis, D. A., & McGrath, J. J. (2012). The neurodevelopmental hypothesis of schizophrenia: convergent clues from epidemiology and neuropathology. [Review] *The Psychiatric Clinics of North America*, 35(3), 571–584. <http://dx.doi.org/10.1016/j.psc.2012.06.002>.
- Prasad, K. M., Shirts, B. H., Yolken, R. H., Keshavan, M. S., & Nimgaonkar, V. L. (2007). Brain morphological changes associated with exposure to HSV1 in first-episode schizophrenia. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't] *Molecular Psychiatry*, 12(1), 105–113, 101. <http://dx.doi.org/10.1038/sj.mp.4001915>.
- Pribrig, H., & Stellwagen, D. (2014). Neuroimmune regulation of homeostatic synaptic plasticity. [Research Support, Non-U.S. Gov't] *Neuropharmacology*, 78, 13–22. <http://dx.doi.org/10.1016/j.neuropharm.2013.06.008>.
- Purcell, S. M., Wray, N. R., Stone, J. L., Visscher, P. M., O'Donovan, M. C., Sullivan, P. F., et al. (2009). Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature*, 460(7256), 748–752. <http://dx.doi.org/10.1038/nature08185>.
- Rapoport, J. L., Giedd, J. N., & Gogtay, N. (2012). Neurodevelopmental model of schizophrenia: update 2012. [Review] *Molecular Psychiatry*, 17(12), 1228–1238. <http://dx.doi.org/10.1038/mp.2012.23>.
- Reiber, H. (1994). Flow rate of cerebrospinal fluid (CSF) – a concept common to normal blood-CSF barrier function and to dysfunction in neurological diseases. *Journal of the Neurological Sciences*, 122(2), 189–203.
- Rimol, L. M., Nesvag, R., Hagler, D. J., Jr., Bergmann, O., Fennema-Notestine, C., Hartberg, C. B., et al. (2012). Cortical volume, surface area, and thickness in schizophrenia and bipolar disorder. [Research Support, Non-U.S. Gov't] *Biological Psychiatry*, 71(6), 552–560. <http://dx.doi.org/10.1016/j.biopsych.2011.11.026>.
- Rosenow, E. C. (1948). Bacteriologic, etiologic, and serologic studies in epilepsy and schizophrenia; cutaneous reactions to intradermal injection of streptococcal antibody and antigen. *Postgraduate Medicine*, 3(5), 367–376.

- Rothermundt, M., Arolt, V., & Bayer, T. A. (2001). Review of immunological and immunopathological findings in schizophrenia. [Research Support, Non-U.S. Gov't Review] *Brain, Behavior, and Immunity*, 15(4), 319–339. <http://dx.doi.org/10.1006/brbi.2001.0648>.
- Samaroo, D., Dickerson, F., Kasarda, D. D., Green, P. H., Briani, C., Yolken, R. H., et al. (2010). Novel immune response to gluten in individuals with schizophrenia. *Schizophrenia Research*, 118(1–3), 248–255. <http://dx.doi.org/10.1016/j.schres.2009.08.009> pii:S0920-9964(09)00385-5.
- Sandyk, R. (1993). Choroid plexus calcification as a possible marker of hallucinations in schizophrenia. *The International Journal of Neuroscience*, 71(1–4), 87–92.
- Schizophrenia Working Group of the Psychiatric Genomics Consortium. (2014). Biological insights from 108 schizophrenia-associated genetic loci. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't] *Nature*, 511(7510), 421–427. <http://dx.doi.org/10.1038/nature13595>.
- Selecki, B. R., Todd, P., Westwood, A. P., & Kraus, J. A. (1964). Cerebrospinal fluid and serum protein profiles in deteriorated epileptics, mental defectives with epilepsy, and schizophrenics. *The Medical Journal of Australia*, 2, 751–753.
- Severance, E. G., Alaedini, A., Yang, S., Halling, M., Gressitt, K. L., Stallings, C. R., et al. (2012). Gastrointestinal inflammation and associated immune activation in schizophrenia. [Research Support, Non-U.S. Gov't] *Schizophrenia Research*, 138(1), 48–53. <http://dx.doi.org/10.1016/j.schres.2012.02.025>.
- Severance, E. G., Dickerson, F. B., 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. *Schizophrenia Research*, 118(1–3), 240–247. <http://dx.doi.org/10.1016/j.schres.2009.12.030> pii:S0920-9964(09)00621-5.
- Severance, E. G., Dickerson, F. B., Viscidi, R. P., Bossis, L., Stallings, C. R., Origoni, A. E., et al. (2011). Coronavirus immunoreactivity in individuals with a recent onset of psychotic symptoms. *Schizophrenia Bulletin*, 37(1), 101–107. <http://dx.doi.org/10.1093/schbul/sbp052>.
- Severance, E. G., Gressitt, K. L., Alaedini, A., Rohleder, C., Enning, F., Bumb, J. M., et al. (2015). IgG dynamics of dietary antigens point to cerebrospinal fluid barrier or flow dysfunction in first-episode schizophrenia. *Brain, Behavior, and Immunity*, 44, 148–158. <http://dx.doi.org/10.1016/j.bbi.2014.09.009>. Epub 2014 Sep 20. PMID: 25241021.
- Severance, E. G., Gressitt, K. L., Buka, S. L., Cannon, T. D., & Yolken, R. H. (2014). Maternal complement C1q and increased odds for psychosis in adult offspring. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't] *Schizophrenia Research*, 159(1), 14–19. <http://dx.doi.org/10.1016/j.schres.2014.07.053>.
- Severance, E. G., Gressitt, K. L., Halling, M., Stallings, C. R., Origoni, A. E., Vaughan, C., et al. (2012). Complement C1q formation of immune complexes with milk caseins and wheat gluteins in schizophrenia. *Neurobiology of Disease*, 48(3), 447–453. <http://dx.doi.org/10.1016/j.nbd.2012.07.005>.
- Severance, E. G., Gressitt, K. L., Stallings, C. R., Origoni, A. E., Khushalani, S., Leweke, F. M., et al. (2013a). Discordant patterns of bacterial translocation markers and implications for innate immune imbalances in schizophrenia. [Multicenter Study Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't] *Schizophrenia Research*, 148(1–3), 130–137. <http://dx.doi.org/10.1016/j.schres.2013.05.018>.
- Severance, E. G., Gressitt, K. L., Stallings, C. R., Origoni, A. E., Khushalani, S., Leweke, F. M., et al. (2013b). Discordant patterns of bacterial translocation markers and implications for innate immune imbalances in schizophrenia. *Schizophrenia Research*. <http://dx.doi.org/10.1016/j.schres.2013.05.018>.
- Severance, E. G., Kannan, G., Gressitt, K. L., Xiao, J., Alaedini, A., Pletnikov, M. V., & Yolken, R. H. (2012). Anti-gluten immune response following *Toxoplasma gondii* infection in mice. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't] *PLoS One*, 7(11), e50991. <http://dx.doi.org/10.1371/journal.pone.0050991>.
- Severance, E. G., Yolken, R. H., & Eaton, W. W. (2014). Autoimmune diseases, gastrointestinal disorders and the microbiome in schizophrenia: more than a gut feeling. [Review] *Schizophrenia Research*. <http://dx.doi.org/10.1016/j.schres.2014.06.027>.
- Shatz, C. J. (2009). MHC class I: an unexpected role in neuronal plasticity. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't] *Neuron*, 64(1), 40–45. <http://dx.doi.org/10.1016/j.neuron.2009.09.044>.
- Shi, J., Levinson, D. F., Duan, J., Sanders, A. R., Zheng, Y., Pe'er, I., et al. (2009). Common variants on chromosome 6p22.1 are associated with schizophrenia. *Nature*, 460(7256), 753–757. <http://dx.doi.org/10.1038/nature08192>.
- Shi, L., Smith, S. E., Malkova, N., Tse, D., Su, Y., & Patterson, P. H. (2009). Activation of the maternal immune system alters cerebellar development in the offspring. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't] *Brain, Behavior, and Immunity*, 23(1), 116–123. <http://dx.doi.org/10.1016/j.bbi.2008.07.012>.
- Shiga, T., Wada, A., Kunii, Y., Itagaki, S., Sakuma, J., Yabe, H., et al. (2012). Effective surgical intervention for schizophrenia-like symptoms and low event-related potentials caused by arachnoid cyst. [Case Reports Letter] *Psychiatry and Clinical Neurosciences*, 66(6), 536–537. <http://dx.doi.org/10.1111/j.1440-1819.2012.02371.x>.
- Simister, N. E. (2003). Placental transport of immunoglobulin G. [Research Support, U.S. Gov't, P.H.S. Review] *Vaccine*, 21(24), 3365–3369.
- Solomon, G. F., Allansmith, M., McCellan, B., & Amkraut, A. (1969). Immunoglobulins in psychiatric patients. *Archives of General Psychiatry*, 20(3), 272–277.
- Sorensen, H. J., Mortensen, E. L., Reinisch, J. M., & Mednick, S. A. (2009). Association between prenatal exposure to bacterial infection and risk of schizophrenia. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't] *Schizophrenia Bulletin*, 35(3), 631–637. <http://dx.doi.org/10.1093/schbul/sbn121>.
- Stamboliev, P. N. (1970). Immunoelectrophoretic analysis of serum during development of schizophrenia. *Zhurnal neoropatologii i psikhiiatrii imeni S.S. Korsakova*, 70(9), 1339–1343.
- Stefansson, H., Ophoff, R. A., Steinberg, S., Andreassen, O. A., Cichon, S., Rujescu, D., et al. (2009). Common variants conferring risk of schizophrenia. *Nature*, 460(7256), 744–747. <http://dx.doi.org/10.1038/nature08186>.
- Steiner, J., Bernstein, H. G., Schiltz, K., Muller, U. J., Westphal, S., Drexhage, H. A., et al. (2012). Immune system and glucose metabolism interaction in schizophrenia: a chicken-egg dilemma. *Progress in Neuropsychopharmacology & Biological Psychiatry*, 48, 287–294. <http://dx.doi.org/10.1016/j.pnpbp.2012.09.016>.
- Steiner, J., Teegen, B., Schiltz, K., Bernstein, H. G., Stoecker, W., & Bogerts, B. (2014). Prevalence of N-methyl-D-aspartate receptor autoantibodies in the peripheral blood: healthy control samples revisited. *JAMA Psychiatry*, 71(7), 838–839. <http://dx.doi.org/10.1001/jamapsychiatry.2014.469>.
- Steiner, J., Walter, M., Glanz, W., Sarnyai, Z., Bernstein, H. G., Vielhaber, S., et al. (2013). Increased prevalence of diverse N-methyl-D-aspartate glutamate receptor antibodies in patients with an initial diagnosis of schizophrenia: specific relevance of IgG NR1a antibodies for distinction from N-methyl-D-aspartate glutamate receptor encephalitis. *JAMA Psychiatry*, 70(3), 271–278. <http://dx.doi.org/10.1001/2013.jamapsychiatry.86>.
- Stephan, A. H., Madison, D. V., Mateos, J. M., Fraser, D. A., Lovelett, E. A., Coutellier, L., et al. (2013). A dramatic increase of C1q protein in the CNS during normal aging. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't] *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 33(33), 13460–13474. <http://dx.doi.org/10.1523/JNEUROSCI.1333-13.2013>.
- Stevens, B., Allen, N. J., Vazquez, L. E., Howell, G. R., Christopherson, K. S., Nouri, N., et al. (2007). The classical complement cascade mediates CNS synapse elimination. *Cell*, 131(6), 1164–1178. <http://dx.doi.org/10.1016/j.cell.2007.10.036> pii:S0092-8674(07)01355-4.

- Stilling, R. M., Dinan, T. G., & Cryan, J. F. (2014). Microbial genes, brain & behaviour – epigenetic regulation of the gut-brain axis. [Research Support, Non-U.S. Gov't] *Genes, Brain, and Behavior*, 13(1), 69–86. <http://dx.doi.org/10.1111/gbb.12109>.
- Stockinger, S., Hornef, M. W., & Chassin, C. (2011). Establishment of intestinal homeostasis during the neonatal period. [Research Support, Non-U.S. Gov't Review] *Cellular and Molecular Life Sciences*, 68(22), 3699–3712. <http://dx.doi.org/10.1007/s00018-011-0831-2>.
- Stoimenov, I. A. (1969). Relationship between forms and symptoms of schizophrenia and the presence of brain antibodies in the blood serum. *Vestnik Akademii Meditsinskikh Nauk SSSR*, 24(4), 67–70.
- Stojanovic, A., Martorell, L., Montalvo, I., Ortega, L., Monseny, R., Vilella, E., et al. (2014). Increased serum interleukin-6 levels in early stages of psychosis: associations with at-risk mental states and the severity of psychotic symptoms. *Psychoneuroendocrinology*, 41, 23–32. <http://dx.doi.org/10.1016/j.psyneuen.2013.12.005>.
- Strahilevitz, M., & Davis, S. D. (1970). Increased IgA in schizophrenic patients. *Lancet*, 2(7668), 370.
- Suarez-Pinilla, P., Lopez-Gil, J., & Crespo-Facorro, B. (2014). Immune system: a possible nexus between cannabinoids and psychosis. *Brain, Behavior, and Immunity*, 40, 269–282. <http://dx.doi.org/10.1016/j.bbi.2014.01.018>.
- Sun, Z. Y., Wei, J., Xie, L., Shen, Y., Liu, S. Z., Ju, G. Z., et al. (2004). The CLDN5 locus may be involved in the vulnerability to schizophrenia. [Research Support, Non-U.S. Gov't] *European Psychiatry: The Journal of the Association of European Psychiatrists*, 19(6), 354–357. <http://dx.doi.org/10.1016/j.eurpsy.2004.06.007>.
- Suvisaari, J., Haukka, J., Tanskanen, A., Hovi, T., & Lonnqvist, J. (1999). Association between prenatal exposure to poliovirus infection and adult schizophrenia. [Research Support, Non-U.S. Gov't] *American Journal of Psychiatry*, 156(7), 1100–1102.
- Tibbling, G., Link, H., & Ohman, S. (1977). Principles of albumin and IgG analyses in neurological disorders. I. Establishment of reference values. [Clinical Trial Comparative Study] *Scandinavian Journal of Clinical and Laboratory Investigation*, 37(5), 385–390. <http://dx.doi.org/10.1080/00365517709091496>.
- Torrey, E. F., Bartko, J. J., Lun, Z. R., & Yolken, R. H. (2007). Antibodies to *Toxoplasma gondii* in patients with schizophrenia: a meta-analysis. [Meta-Analysis] *Schizophrenia Bulletin*, 33(3), 729–736. <http://dx.doi.org/10.1093/schbul/sbl050>.
- Torrey, E. F., Bartko, J. J., & Yolken, R. H. (2012). *Toxoplasma gondii* and other risk factors for schizophrenia: an update. *Schizophrenia Bulletin*, 38(3), 642–647. <http://dx.doi.org/10.1093/schbul/sbs043>.
- Torrey, E. F., & Peterson, M. R. (1973). Slow and latent viruses in schizophrenia. *Lancet*, 2(7819), 22–24.
- Torrey, E. F., & Peterson, M. R. (1976). The viral hypothesis of schizophrenia. *Schizophrenia Bulletin*, 2(1), 136–146.
- Torrey, E. F., & Yolken, R. H. (2001). The schizophrenia-rheumatoid arthritis connection: infectious, immune, or both? *Brain, Behavior, and Immunity*, 15(4), 401–410.
- Trotta, T., Porro, C., Calvello, R., & Panaro, M. A. (2014). Biological role of Toll-like receptor-4 in the brain. [Review] *Journal of Neuroimmunology*, 268(1–2), 1–12. <http://dx.doi.org/10.1016/j.jneuroim.2014.01.014>.
- Tsuang, M. (2000). Schizophrenia: genes and environment. [Review] *Biological Psychiatry*, 47(3), 210–220.
- van Os, J., Rutten, B. P., Myin-Germeys, I., Delespaul, P., Viechtbauer, W., van Zelst, C., & Mirjanic, T. (2014). Identifying gene-environment interactions in schizophrenia: contemporary challenges for integrated, large-scale investigations. [Research Support, Non-U.S. Gov't] *Schizophrenia Bulletin*, 40(4), 729–736. <http://dx.doi.org/10.1093/schbul/sbu069>.
- Veijola, J., Guo, J. Y., Moilanen, J. S., Jaaskelainen, E., Miettunen, J., Kyllonen, M., et al. (2014). Longitudinal changes in total brain volume in schizophrenia: relation to symptom severity, cognition and antipsychotic medication. *PLoS One*, 9(7), e101689. <http://dx.doi.org/10.1371/journal.pone.0101689>.
- Vetlugina, T. P., Logvinovich, G. V., Maslennikova, S. N., & Vasil'eva, O. A. (1984). Circulating immune complexes in the serum of mental patients and healthy subjects. *Zhurnal nevrologii i psikiatrii imeni S.S. Korsakova*, 84(3), 422–426.
- Walport, M. J. (2001a). Complement. First of two parts. [Review] *The New England Journal of Medicine*, 344(14), 1058–1066. <http://dx.doi.org/10.1056/NEJM200104053441406>.
- Walport, M. J. (2001b). Complement. Second of two parts. [Research Support, Non-U.S. Gov't Review] *The New England Journal of Medicine*, 344(15), 1140–1144. <http://dx.doi.org/10.1056/NEJM200104123441506>.
- Wan, C., La, Y., Zhu, H., Yang, Y., Jiang, L., Chen, Y., et al. (2007). Abnormal changes of plasma acute phase proteins in schizophrenia and the relation between schizophrenia and haptoglobin (Hp) gene. [Clinical Trial Research Support, Non-U.S. Gov't] *Amino Acids*, 32(1), 101–108. <http://dx.doi.org/10.1007/s00726-005-0292-8>.
- Wei, J., & Hemmings, G. P. (2005). A study of the combined effect of the CLDN5 locus and the genes for the phospholipid metabolism pathway in schizophrenia. *Prostaglandins, Leukotrienes, and Essential Fatty Acids*, 73(6), 441–445. <http://dx.doi.org/10.1016/j.plefa.2005.08.003>.
- Whedon, J. M., & Glassey, D. (2009). Cerebrospinal fluid stasis and its clinical significance. [Review] *Alternative Therapies in Health and Medicine*, 15(3), 54–60.
- Whiteley, P., Haracopos, D., Knivsberg, A. M., Reichelt, K. L., Parlar, S., Jacobsen, J., et al. (2010). The ScanBrit randomised, controlled, single-blind study of a gluten- and casein-free dietary intervention for children with autism spectrum disorders. *Nutritional Neuroscience*, 13(2), 87–100. <http://dx.doi.org/10.1179/147683010X12611460763922>.
- Whiteley, P., Shattock, P., Knivsberg, A. M., Seim, A., Reichelt, K. L., Todd, L., et al. (2012). Gluten- and casein-free dietary intervention for autism spectrum conditions. *Frontiers in Human Neuroscience*, 6, 344. <http://dx.doi.org/10.3389/fnhum.2012.00344>.
- Williams, B. L., Hornig, M., Buie, T., Bauman, M. L., Cho Paik, M., Wick, I., et al. (2011). Impaired carbohydrate digestion and transport and mucosal dysbiosis in the intestines of children with autism and gastrointestinal disturbances. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, Non-P.H.S.] *PLoS One*, 6(9), e24585. <http://dx.doi.org/10.1371/journal.pone.0024585>.
- Williams, B. L., Hornig, M., Parekh, T., & Lipkin, W. I. (2012). Application of novel PCR-based methods for detection, quantitation, and phylogenetic characterization of *Sutterella* species in intestinal biopsy samples from children with autism and gastrointestinal disturbances. [Research Support, N.I.H., Extramural Research Support, U.S. Gov't, Non-P.H.S.] *mBio*, 3 (1). <http://dx.doi.org/10.1128/mBio.00261-11>.
- Xiao, J., Buka, S. L., Cannon, T. D., Suzuki, Y., Viscidi, R. P., Torrey, E. F., et al. (2009). Serological pattern consistent with infection with type I *Toxoplasma gondii* in mothers and risk of psychosis among adult offspring. *Microbes and Infection*, 11(13), 1011–1018. <http://dx.doi.org/10.1016/j.micinf.2009.07.007> pii:S1286-4579(09)00165-8.
- Yang, Y., Wan, C., Li, H., Zhu, H., La, Y., Xi, Z., et al. (2006). Altered levels of acute phase proteins in the plasma of patients with schizophrenia. [Research Support, Non-U.S. Gov't] *Analytical Chemistry*, 78(11), 3571–3576. <http://dx.doi.org/10.1021/ac051916x>.
- Ye, L., Sun, Z., Xie, L., Liu, S., Ju, G., Shi, J., et al. (2005). Further study of a genetic association between the CLDN5 locus and schizophrenia. [Letter Research Support, Non-U.S. Gov't] *Schizophrenia Research*, 75(1), 139–141. <http://dx.doi.org/10.1016/j.schres.2004.11.003>.
- Yolken, R., & Dickerson, F. (2014). The microbiome – the missing link in the pathogenesis of schizophrenia. *Schizophrenia Research*, 153(Suppl. 1), S16.

- Yolken, R.H., Bachmann, S., Ruslanova, I., Lillehoj, E., Ford, G., Torrey, E.F., et al. (2001). Antibodies to *Toxoplasma gondii* in individuals with first-episode schizophrenia. *Clinical Infectious Diseases*, 32(5), 842–844. <http://dx.doi.org/10.1086/319221> pii:CID000667.
- Yolken, R. H., & Torrey, E. F. (2008). Are some cases of psychosis caused by microbial agents? A review of the evidence. *Molecular Psychiatry*, 13(5), 470–479. <http://dx.doi.org/10.1038/mp.2008.5>.
- Zakharyan, R., Khoyetsyan, A., Arakelyan, A., Boyajyan, A., Gevorgyan, A., Stahelova, A., et al. (2011). Association of C1QB gene polymorphism with schizophrenia in Armenian population. [Research Support, Non-U.S. Gov't] *BMC Medical Genetics*, 12, 126. <http://dx.doi.org/10.1186/1471-2350-12-126>.
- Zhang, C., Xu, D., Luo, H., Lu, J., Liu, L., Ping, J., et al. (2014). Prenatal xenobiotic exposure and intrauterine hypothalamus-pituitary-adrenal axis programming alteration. [Review] *Toxicology*, 325C, 74–84. <http://dx.doi.org/10.1016/j.tox.2014.08.015>.
- Zhao, Z., Xu, J., Chen, J., Kim, S., Reimers, M., Bacanu, S. A., et al. (2014). Transcriptome sequencing and genome-wide association analyses reveal lysosomal function and actin cytoskeleton remodeling in schizophrenia and bipolar disorder. *Molecular Psychiatry*. <http://dx.doi.org/10.1038/mp.2014.82>.