Inflammatory Cytokines and Neurological and Neurocognitive Alterations in the Course of Schizophrenia

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A growing body of evidence suggests that immune alterations, especially those related to inflammation, are associated with increased risk of schizophrenia and schizophrenia-related brain alterations. Much of this work has focused on the prenatal period, because infections during pregnancy have been repeatedly (albeit inconsistently) linked to risk of schizophrenia. Given that most infections do not cross the placenta, cytokines associated with inflammation (proinflammatory cytokines) have been targeted as potential mediators of the damaging effects of infection on the fetal brain in prenatal studies. Moreover, additional evidence from both human and animal studies suggests links between increased levels of proinflammatory cytokines, immune-related genes, and schizophrenia as well as brain alterations associated with the disorder. Additional support for the role of altered immune factors in the etiology of schizophrenia comes from neuroimaging studies, which have linked proinflammatory cytokine gene polymorphisms with some of the structural and functional abnormalities repeatedly found in schizophrenia. These findings are reviewed and discussed with a life course perspective, examining the contribution of inflammation from the fetal period to disorder presentation. Unexplored areas and future directions, such as the interplay between inflammation, genes, and individual-level environmental factors (e.g., stress, sleep, and nutrition), are also discussed.

Key Words: Cytokines, infection, inflammation, neuroimaging, pregnancy, schizophrenia

Schizophrenia is a severe neurodevelopmental disorder resulting from genetic and environmental factors (1). Although genetic factors contribute to the etiology of schizophrenia, an examination of environmental factors is needed to explain the 40%–55% discordance rate in monozygotic twins who do not share schizophrenia diagnoses (2). Among the environmental contributors, infection and immune responses to infection have gained increasing attention as being integrally involved in the etiopathogenesis of the disorder (3). A growing body of evidence links prenatal infection and maternal immune alterations during pregnancy to risk of schizophrenia and brain alterations found in the disorder (3–5). Similarly, immune-related genes and immune alterations have been found in patients diagnosed with schizophrenia (6,7). This review will discuss the primary findings linking immune alterations, namely inflammation, to brain changes in schizophrenia. Because many of these findings stemmed from infection research, we will briefly summarize the role of infection in schizophrenia, focusing on the prenatal period. We will then discuss evidence linking immune alterations to risk of schizophrenia and to neurological alterations in the course of the disorder, with an emphasis on unexplored areas and future directions.

Overview of Link Between Schizophrenia and Infection

The first associations between schizophrenia and infection were found in ecologic studies (8). Although findings have been mixed, winter to spring births (a period of heightened infections) and pregnancy during influenza epidemics have been associated with risk for schizophrenia among offspring (3). However, ecologic studies are limited by their presumption of infection based on events that occur for an entire population without direct confirmation of exposure (3).

Nevertheless, the association between schizophrenia and maternal infection was further supported by longitudinal cohort studies that prospectively collected obstetric information, including medical records and maternal sera from pregnancy, and identified offspring who developed schizophrenia spectrum disorders (3). Although findings have not been completely consistent, a number of maternal infections during pregnancy—including influenza (5,9), rubella (10), measles (11), polio (12), maternal upper respiratory infections (13), genital and/or reproductive infections (14), herpes simplex virus-type 2 (15), and exposure to the protozoan parasite *Toxoplasma gondii* (16,17)—have been associated with risk of schizophrenia in offspring. Furthermore, maternal infections during pregnancy have been associated with schizophrenia-related neurocognitive/neuroanatomical abnormalities, including decreases in premorbid cognitive functioning (5,10), executive functioning problems after schizophrenia onset (18), and increases in cavum septum pallucidum, a reliable marker of cerebral dysgenesis (19).

One explanation for the associations between schizophrenia and many different infections that have not been consistently replicated is that these infections might impact the developing fetal brain through a common mechanism, such as the maternal immune response to infection (further discussed in Immune Response and the Fetal Brain section) (20). In this regard, we would expect damage to the fetal brain to be linked to individual differences in maternal immune responses to infection and not necessarily to the infection itself. Some support for this idea comes from evidence suggesting that exposure to different strains of influenza during pregnancy differentially impacts the risk of schizophrenia in offspring, indicating that virulence of the infection might be key in conferring risk to the fetus (5). Moreover, prenatal infection during pregnancy could interact with genetic liability for schizophrenia to increase risk among offspring. This hypothesis is supported by evidence that the

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influence of prenatal infection on increased risk of schizophrenia is increased when offspring have a family history of psychosis, although replication of this finding is needed (21). Lastly, a number of individual factors that influence the immune system and susceptibility to infection could potentially contribute to these findings, such as maternal stress (22), sleep (23), exercise (24), and other obstetric insults (25), none of which have been explored in models examining maternal infection during pregnancy and risk of schizophrenia; therefore a number of questions remain for future research.

Immune Response and the Fetal Brain

Cytokines

With the exception of parasitic infections, like toxoplasmosis gondii, most infections do not seem to cross the placenta; thus, damaging effects to the fetus are likely operating through maternal, fetal, and/or placental responses to infection (26,27). Among these responses to infections, prime candidates have been cytokines associated with inflammation (termed proinflammatory cytokines), some of which seem to cross the placenta (28,29). Cytokines are soluble polypeptide signaling proteins that are involved in initiation and maintenance of immune responses (30) and serve as critical mediators of the cross-talk between the brain and the immune system (31). Infections activate proinflammatory cytokines (as well as other immune factors), such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6 (32), which play crucial roles in the early defense against infection and the initiation and/or progression of inflammation (33).

Relevant to prenatal studies in schizophrenia, pregnancy is characterized by a shift in immune functioning, favoring humoral immunity or T_H2 immune responses, with preferential production of T_H2 cytokines, such as IL-4, IL-5, and IL-10 (34). The relative increase in T_H2 cytokines during pregnancy has been associated with a downregulation of T_H1 proinflammatory cytokines, leading to a suppression of cell-mediated immunity and potentially decreasing the ability of the mother to respond to infections (35,36). In fact, disruption of the T_H1/T_H2 balance during pregnancy can lead to pregnancy failure (37,38), and influenza infection has been associated with increased rates of stillbirth and miscarriage, which might be consequences of elevations in proinflammatory cytokines (39). These findings support the idea that pregnancy represents a period in which the mother is more vulnerable to infection and that elevations in proinflammatory cytokines represent an aberration from normal immune processes during pregnancy.

In humans, a number of pre- and perinatal conditions, many of which have been linked to increased risk of schizophrenia, such as infection, fetal hypoxia, maternal stress, and prepregnancy body mass index (BMI), have also been associated with increases in proinflammatory cytokines (4,40). Furthermore, fetal exposure to proinflammatory cytokines has been associated with white matter lesions in infant offspring (41) as well as neurodevelopmental abnormalities, such as periventricular leukomalacia, cerebral palsy, and mental retardation (42,43). Given that white matter abnormalities and premorbid motor and cognitive disturbances are frequently found in the course of schizophrenia, these results suggest that fetal exposure to inflammation can lead to neurodevelopmental sequelae related to schizophrenia even in the absence of a genetic vulnerability for schizophrenia (44). Similarly, proinflammatory cytokines are implicated in neuronal death and dysfunction after injury or neurodegenerative disease in the adult brain, indicating that inflammation can alter neuronal processes at various stages of development even in individuals at presumed low genetic liability for schizophrenia (45).

Schizophrenia and Proinflammatory Cytokines during Pregnancy

Given the aforementioned findings, it is not surprising that investigations have begun to examine maternal proinflammatory cytokines during pregnancy and schizophrenia risk in offspring. Specifically, studies have linked elevations in TNF-α levels at birth and elevations in IL-8 levels during the second and third trimesters with increased risk for schizophrenia in offspring (46,47). Despite these findings, it remains unclear whether there are specific cytokines and/or specific periods of gestation in which the fetal brain is particularly vulnerable to inflammation exposure.

Nevertheless, there is now evidence that increases in one maternal inflammatory cytokine during pregnancy are related to structural brain changes in schizophrenia. Ellman *et al.* (4) found a significant association between higher maternal IL-8 levels in the second/third trimesters of pregnancy and increases in ventricular cerebrospinal fluid (CSF) volume as well as volume reductions in the left entorhinal cortex, right posterior cingulate, and multiple basal ganglia structures in adults with schizophrenia, the latter of which approached significance (4). These findings are especially relevant to schizophrenia, because increases in ventricular volumes are the most well-replicated brain anomaly found in schizophrenia research (48) and the other neuroanatomical alterations have been found in schizophrenia and prodromal populations, suggesting that these brain abnormalities might have neurodevelopmental origins (48–50). Interestingly, no brain alterations were observed among control participants after fetal exposure to increases in maternal IL-8, which is consistent with previous findings that liability for schizophrenia might be necessary for inflammation to damage the fetal brain (4). However, the control group was particularly small in the aforementioned study ($n = 8$); therefore future studies are needed to determine whether brain alterations occur among those at presumed low liability for schizophrenia after fetal exposure to increases in maternal proinflammatory cytokines.

Animal Models of Immune Activation During Pregnancy

There has been a virtual explosion of studies examining maternal immune activation during pregnancy in animal models [for example, see (51–55)], which is beyond the scope of this review. Consistent with the Ellman *et al.* study (4), evidence suggests that fetal exposure to proinflammatory cytokines is associated with behavioral, cognitive, and neuroanatomical alterations consistent with schizophrenia, such as increases in ventricular volume and impairments in hippocampal-dependent tasks (26).

An intriguing piece of these findings is evidence suggesting that prenatal exposure to infection or inflammation can lead to long-lasting immune abnormalities across development. Specifically, rodent models of prenatal influenza exposure (56,57), chronic gestational lipopolysaccharide (LPS) exposure (58–60), prenatal IL-6 treatment in mid-to-late gestation (61), and acute polyinosinic-polycytidylic acid treatment in early/middle gestation (62,63) have identified immune abnormalities such as inflammatory changes in the peripheral and central nervous systems, enhanced microglia and/or astrocyte activation, and sustained increases in peripheral levels of proinflammatory cytokines among offspring. Similarly, exposure to prenatal infection

can increase vulnerability for late-life alterations in cytokine production by inducing latent neuroinflammatory abnormalities that surface after exposure to environmental stressors throughout postnatal life (64). Prenatal immune priming theories suggest that early inflammatory exposure during the pre- or perinatal period can lead to atypical and potentially more vigorous responses to subsequent environmental and/or immunological challenges (64). These results suggest that fetal exposure to infection and maternal immune responses to infection might lead to alterations in immune functioning that continue to exert damaging effects on the brain well past the fetal period. This possibility has been virtually ignored in human samples but is supported by animal models that implicate cytokines like IL-6 as mediators of the long-term behavioral deficits found in offspring after maternal immune activation (65) and warrants considerable attention when attempting to understand the role of inflammation in the neurodevelopmental course of schizophrenia.

Immunological and Inflammatory Cytokine Alterations in Schizophrenia

Research on the influence of early life exposure to infection and inflammation on immune functioning across the lifespan is highly relevant, given repeated studies that have found immunological abnormalities in schizophrenia populations (66). Furthermore, schizophrenia has been associated with inflammation and increased levels of cytokines, IL-2 receptors, IL-1 receptor agonists (IL-1RA), and acute phase reactants such as IL-1β and IL-6 in plasma (67,68). Potvin *et al.* (31) published a recent meta-analysis on inflammatory cytokine alterations in schizophrenia and found increased levels of in vivo peripheral IL-1RA, soluble IL-2R, and IL-6 in schizophrenia patients, suggesting evidence of immune activation in schizophrenia (31). Importantly, increases in IL-6 and IL-1RA did not seem to be related to antipsychotic medication (31). Findings on IL-1β levels in the CSF of patients with schizophrenia have been mixed, with this meta-analysis finding no significant effect sizes for IL-1β (31), whereas a recent study of drug-naïve schizophrenia patients found significant elevations in IL-1β levels (69). One plausible explanation for this discrepancy is that only 3 of the 62 studies included in the review by Potvin *et al.* (31) comprised drug-naïve patients. There is also some emerging evidence of increases in T_H2 cells (e.g., IL-4 producing lymphocytes) and T_H17 cells (presumed to be involved in inflammation and autoimmune disorders) among these cases (70), although these types of cells have been studied significantly less than T_H1 responses.

Despite evidence of an inflammatory state persisting after disorder onset, it is unclear whether increases in inflammatory cytokines in schizophrenia populations represent alterations in immune functioning related to the causes of schizophrenia or inflammation in response to a variety of factors associated with the disorder, such as stress (71), malnutrition (72), and other disorder-related factors that are known to influence immune functioning (further discussed in the Interactions Between Immune and Individual Factors section). In fact, there is some evidence that individuals with schizophrenia have increases in prevalence of a variety of infections (e.g., HIV, hepatitis B and C) (73,74), which are known to lead to increases in inflammation. Furthermore, schizophrenia populations are less likely than nonpsychiatric populations to perform self-care or health promotion activities, which could put these patients at greater risk for a multitude of infections (75). No studies have prospectively collected immune markers from the prenatal period until symptom onset; therefore the causal directionality of immune activation in schizophrenia populations remains unclear and presents a promising direction for future research.

Cytokines and Neuroanatomical Alterations: Neuroimaging Studies

A number of immune-related genetic polymorphisms have been associated with brain changes found in schizophrenia (Table 1). Although findings have not always been consistent, genetic association studies (76) and neuroimaging studies (77) have linked genetic variability in the IL-1 gene complex to increased risk of schizophrenia and to some of the neuroanatomical alterations observed in schizophrenia patients (77). The IL-1β and interleukin 1 receptor antagonist (IL-1RN) genes encode for IL-1β and IL-1RN, respectively, and are part of the IL-1 gene cluster on chromosome 2q13, which has been linked to schizophrenia (78). The IL-1β and IL-1RN also are involved in neurodevelopmental processes (79) and acute and chronic neurodegeneration (80), making them prime candidates for studies of their effect on brain morphology in schizophrenia.

Some of the most consistent magnetic resonance imaging (MRI) structural findings in schizophrenia, such as ventricular enlargement and temporal and frontal lobe volume reductions (81), have been associated with polymorphisms of the IL-1 complex. Variability at the IL-1RN gene has been associated with ventricular enlargement in schizophrenia. Patients carrying allele*2 of the IL-1RN gene—a genotype associated with enhanced IL-1β production and a more prolonged and severe pro-inflammatory immune response compared with other IL-1RN genotypes (82)—have been found to show significant enlargements of both left and right ventricles in MRI scans (77). Similarly, among schizophrenia patients, allele*2 carriers (genotype T/T or C/T) displayed bifrontal-temporal gray matter and generalized white matter tissue volume reductions (83). Although these results suggest that the IL-1RN gene might contribute to the ventricular and gray matter volumetric changes observed in schizophrenia patients, an MRI study of first-episode nonaffective psychosis patients was unable to replicate these findings but found a nonsignificant trend toward larger ventricles at early phases of the disorder among carriers of allele*2 (84). Taken together, these findings suggest that IL-1RN gene variations might be involved in susceptibility to brain changes that occur over the course of the disorder in some individuals such that, compared with first-onset patients, chronic patients might show greater structural changes associated with IL-1RN*2 (84).

Polymorphisms of the IL-1 gene complex also have been associated with patterns of brain activity that are common in schizophrenia populations. Although there is inconsistency between studies, hypofrontality, or reduced activity of the dorsolateral prefrontal cortex, during a variety of cognitive tasks has been found in schizophrenia neuroimaging studies (85–87). One positron emission tomography (PET) study found that a functional polymorphism (-511 C/T functional polymorphism) of the IL-1β gene was associated with decreased metabolic activity in the left dorsolateral prefrontal cortex of schizophrenia patients during an attention task, such that patients who were carriers of allele 2 (-511 T) (promotes greater expression of the gene that regulates IL-1β expression) showed lower metabolic activity relative to patients who were homozygous for allele 1 (88). These findings provide some preliminary evidence that genetic polymorphisms in immune-related genes might contribute to both structural and functional brain abnormalities associated

Table 1. Immune-Related Genetic Polymorphisms Associated with Schizophrenia-Related Brain Change

Reference	Technique	Population	Major Finding	Strength of Association
Fatjó-Vilas *et al.* (133)	Genomic DNA extraction and genotyping of a biallelic base-exchange polymorphism at the promoter region (-511 C/T; rs16944) of IL-1β gene; fMRI imaging during the n-back working memory task	48 patients with chronic schizophrenia and 46 control subjects	-511 C/T polymorphism of the IL-1β gene had differential effects in schizophrenia patients and control subjects such that schizophrenia patients carrying at least one copy of the T allele showed higher task-related prefrontal activation than CC homozygotes, whereas the IL-1β polymorphism did not modulate brain activation during task performance in control subjects	In patients, T-carriers showed higher activations than CC homozygotes, who in some cases showed deactivation rather than activation ($t = -4.33$, $p < .001$)[a]
Roiz-Santianez *et al.* (84)	MRI volumetric analysis and analysis of IL-1RN gene polymorphisms	73 first-episode psychosis patients with the following diagnoses: schizophrenia ($n = 42$), schizophreniform disorder ($n = 20$), psychosis not otherwise specified ($n = 5$), and brief reactive psychosis ($n = 3$)	Carriers of allele*2 had reduced occipital gray matter volume. After correcting for multiple comparisons, the relationship did not remain significant; no significant differences found for other brain regions	Effect size of occipital gray matter volume reduction in carriers of allele 2 (relationship was not significant after correcting for multiple comparisons): $d = .296$[b]
Papiol *et al.* (88)	Analysis of IL-1β gene functional polymorphism (-511 C/T; rs16944) influence on DLPFC activity with MRI/PET image fusion to assess brain metabolic activity during a Continuous Performance Test	19 schizophrenia patients of Spanish origin (9 first-episode, medication-naïve patients; 10 chronic patients with at least 1 month of haloperidol treatment)	Allele 2 (-511 T) carriers of polymorphism of IL-1β gene showed a significant decrease in metabolic activity in the left DLPFC with respect to patients homozygous for allele 1 (-511 C)	$U = 16$, $z = -2.32$, $p = .02$; $d = -1.204$[b]
Papiol *et al.* (77)	MRI volumetric analysis and genotyping of polymorphisms of IL-1β and IL-1RN genes	23 schizophrenia patients (10 first-episode and 13 chronic patients) of Caucasian Spanish origin and 45 healthy control subjects	Schizophrenia patients who were carriers of the VNTR allele*2 of IL-1RN gene showed significant bilateral enlargement of ventricles compared with patients with noncarrier genotypes	For patients carriers of VNTR allele*2: left ventricle enlargement [$t_{21} = 3.504$, $p = .002$]; right ventricle enlargement [$t_{21} = 2.784$, $p = .01$][a]
Meisenzahl *et al.* (83)	MRI and analysis of an IL-1β polymorphism (C→T transition at position -511)	44 male schizophrenia patients and 48 male comparison subjects	Schizophrenia patients who were IL-1β -511 allele 2 carriers (genotype T/T or C/T) showed bifrontal-temporal gray matter volume reductions and generalized white matter deficits compared with noncarrier patients	Frontal: $F_{1,42} = 6.06$, $p < .02$; temporal: $F_{1,42} = 11.62$, $p = .001$; white matter deficits $F_{1,42} = 5.54$, $p < .03$[a]

DLPFC, dorsolateral prefrontal cortex; fMRI, functional magnetic resonance imaging; IL, interleukin; IL-1RN, interleukin-1 receptor antagonist; PET, positron emission tomography; VNTR, variable nucleotide tandem repeat.

[a]No effect size or odds ratio reported.

[b]Effect size or odds ratio not reported in review. Calculated by authors on the basis of available data reported in manuscripts.

with schizophrenia. Nevertheless, it is unlikely that one polymorphism contributes to brain alterations in the preponderance of schizophrenia cases; therefore archiving immune-related genes associated with schizophrenia and using approaches examining multiple functionally related immune genes might reveal important future findings. Moreover, an unexamined possibility is that environmental (e.g., stress) and individual-level factors (e.g., medication-induced increases in BMI) that might be associated with both schizophrenia (89,90) and increases in inflammatory cytokines (91,92) might additively or interactively influence the aforementioned findings. In this case, IL-1RN–associated increases in proinflammatory cytokines might not be evident until the disorder onset when disorder-related factors emerge.

Schizophrenia and Neuroinflammation

Neuroinflammation is characterized by activation of microglia cells, which are the resident macrophages of the brain and primary reservoirs of proinflammatory cytokines (93,94). Findings on neuroinflammation in schizophrenia have been mixed, with some postmortem studies finding increases in activated microglia cells in the brains of schizophrenia patients (95–97), whereas others fail to find differences (98–101). Active neuroinflammation can be assessed with a PET tracer, *(R)*-*N*-^{11}C-methyl-*N*-(1-methylpropyl)-1-(2-chlorophenyl) isoquinoline-3-carboxamide (^{11}C-(*R*)-PK11195), which has been used to identify neuroinflammation in neurodegenerative diseases like Parkinson's disease, Alzheimer's disease, and multiple sclerosis (93). Doorduin *et al.* (93) found significantly higher binding potential of ^{11}C-(*R*)-PK11195 in the hippocampus of schizophrenia patients compared with healthy control subjects, indicating neuroinflammation in a focal area after the onset of psychosis. However, these studies are plagued by similar interpretation difficulties as previously noted, given that evidence of neuroinflammation after symptom onset could be the result of disorder-related factors. Evidence of neuroinflammation in the premorbid period of schizophrenia would ameliorate some of these potential confounds; however, such investigations have yet to be undertaken, would require large samples of individuals at risk for schizophrenia, and would be methodologically challenging (e.g., PET studies with younger populations).

Interactions Between Immune and Individual Factors

A number of genetic polymorphisms linked to immune functioning have been associated with risk for schizophrenia (Table 2). Specifically, among the available genome-wide association studies in schizophrenia research, polymorphisms associated with dysregulation in immune functioning—such as markers in the major histocompatibility complex region, a cluster of genes on human chromosome 6 that encode proteins involved in antigen processing (102)—have been consistently associated with schizophrenia (6,103–105). Polymorphisms in and around the IL-3 and IL-3 receptor α genes (106–108) and in the promoter region of the IL-10 gene (109), which code for the T_H2-produced anti-inflammatory cytokines IL-3 and IL-10, respectively, have also been linked to schizophrenia. Polymorphisms of the IL-10 gene have been associated with higher IL-10 production (110), and polymorphisms of the IL-3 gene have been associated with changes in IL-3 expression; however, it is unclear how the expression is altered, because there is a paucity of studies on the mechanisms of these polymorphisms. Similarly, polymorphisms in TNF-α (promoter region A2) and IL-1 gene complex [IL-1α (-889) allele 2, IL-1β (-511) allele 1, and IL-1RA allele 1] have been associated with schizophrenia outcome in association studies (111–114). These polymorphisms typically lead to production of proinflammatory cytokines without any known infection (i.e., basal levels) as well as overproduction of proinflammatory cytokines in response to infection and might contribute to the observed elevations in proinflammatory cytokines found in schizophrenia populations (115). Given these findings, it is possible that in prenatal studies of infection, if the fetus and/or the mother is a carrier of genetic polymorphisms associated with inflammation or dysregulation in immune functioning, then the fetus could be more vulnerable to the damaging influences of exposure to maternal infection (44). Despite this possibility, no human study has directly examined the additive and/or interactive influences of specific risk alleles with maternal infection during pregnancy and/or other immune-related conditions during pregnancy, which is a promising area for future research with cohorts with archived prenatal sera. It also is possible that carriers of immune-related polymorphisms have lifelong exposure to increased levels of proinflammatory cytokines, thereby leading to potential damage to the brain across development. Again, this possibility has yet to be tested but seems promising given evidence from postmortem brain studies of increased expression of immune-related genes (e.g., *IFITM2*, *IFITM3*, *SERPINA3*) in the prefrontal cortex of schizophrenia patients (116,117) and represents an intriguing area for future studies.

As mentioned previously, individual characteristics could contribute to alterations in immune functioning in pregnant and nonpregnant populations. For instance, factors such as increases in BMI (118), race (particularly African-American) (119), exercise (24), stress (22), depression (120), sleep (23), nutrition (121), and health-risk behaviors (e.g., substance use and abuse) (122) have been linked to altered immune functioning, susceptibility to infection, and schizophrenia. There is some support for these individual-level factors influencing cytokine levels among schizophrenia patients. One study found that increases in proinflammatory cytokines and chemokines were related to individual characteristics commonly found in schizophrenia populations (123). Specifically, gender, increased BMI, hyperglycemia, diabetes, reduced high-density lipoprotein cholesterol or increased levels of triglycerides or the metabolic syndrome were associated with increases in a number of proinflammatory cytokines (e.g., TNF-α, IL-1B, IL-6) and chemokines, whereas only IL-1β and IL-6 were increased in the serum of patients not affected by any of the aforementioned characteristics (123). Given these findings, a necessary step in determining how inflammation operates within the etiology of schizophrenia is to examine the interactions between inflammation and other individual-level factors, including lifestyle and environmental variables as well as variations in related genetic factors.

Remarks

Most studies on inflammation and schizophrenia have examined proinflammatory cytokines in the prenatal period and after schizophrenia onset, leaving the premorbid period unexamined. Understanding inflammation and immune abnormalities during the premorbid and prodromal periods of schizophrenia will play a crucial role in determining whether inflammation contributes to the neurodevelopmental course of schizophrenia. Currently, there are two primary theories with regard to how early immune insults might influence long-term immune functioning.

Table 2. Immune-Related Genetic Polymorphisms Associated with Schizophrenia

Reference	Technique	Population	Major Finding	Strength of Association
Jia *et al.* (6)	GWAS (369,808 SNPs mapped to 19,896 protein-coding genes, which were involved in 511 biological pathways) with two statistical methods, GSEA and hypergeometric test	1158 schizophrenia cases and 1378 control subjects from unrelated European ancestry samples	Two pathways related to apoptosis, inflammation, and the immune system showed a significant association with schizophrenia with both GSEA and hypergeometric methods: the TGF-β signaling pathway and the TNFR1 pathway	NES: TGF-β signaling pathway: 1.845; TNFR1 pathway: 1.649;
Purcell *et al.* (105)	GWAS of case-control sample for approximately 1 million SNPs, augmented by imputed common HapMap SNPs	3322 European individuals with schizophrenia and 3587 control subjects; combined sample (after exchanging GWAS summary results with the MGS and SGENE consortia for genotyped SNPs) included 8008 schizophrenia cases and 19,077 control subjects of European decent	Significant association of schizophrenia with more than 450 SNPs on chromosome 6 spanning the MHC	ORs for classical HLA alleles associated with schizophrenia: HLA-A0101: .785; HLA-C0701: .778; HLA-B0801: .757; HLA-DRB0301: .768; HLA-DQB0201: .857; HLA-DQA0501: .798 (the six HLA alleles were significant at $p < 10^{-3}$, although the association could not be ascribed to any specific HLA allele, haplotype, or region) (CIs not reported)
Shi *et al.* (104)	GWAS of common SNPs (671,424 SNPs passed QC filters in European ancestry samples; 811,340 SNPs passed QC filters in African-American samples) in the MGS case-control sample; meta-analysis of European-ancestry data from MGS, ISC, and SGENE datasets	MGS case-control samples of European ancestry (2681 cases, 2653 control subjects) and African-American (1286 cases, 973 control subjects); cases were included with diagnoses of schizophrenia or (in 10% of cases) schizoaffective disorder; meta-analysis of European-ancestry subjects (8008 cases, 19,077 control subjects)	Schizophrenia was significantly associated with SNPs in the extended MHC region on chromosome 6. No MGS finding achieved genome-wide statistical significance. In meta-analysis of European-ancestry subjects, significant association with schizophrenia observed in region of linkage disequilibrium on chromosome 6p22.1, a region that includes a histone gene cluster and several immunity-related genes	No MGS findings reached genome-wide significance. From meta-analysis of European ancestry subjects, ORs for seven SNPs on chromosome 6p22.1 showed genome-wide significant associations with schizophrenia—ORs listed as follows (MGS-OR, ISC-OR, SGENE-OR): rs6904071 (.879, .819, .799); rs926300 (.879, .819, .791); rs6913660 (.884, .819, .798); rs13219181 (.881, .819, .791); rs13194053 (.880, .819, .783); rs3800307 (.886, .880, .787); rs3800316 (.856, .886, .834) (CIs not reported)
Stefansson *et al.* (103)	GWAS of 314,868 SNPs to search for sequence variants associated with schizophrenia	2663 schizophrenia cases and 13,498 control subjects from 8 European locations (SGENE-plus GWAS dataset); the top 1500 markers were combined with results from the nonoverlapping 2602 cases and 2885 control subjects in the ISC and the 2681 cases and 2653 control subjects from the European-American portion of the MGS study; 25 of the top 1500 markers were followed up in four additional samples from Europe for an additional 4,999 cases and 15,555 control subjects	Significant association of several markers spanning the MHC region on chromosome 6p21.3–22.1, a marker located upstream of the neurogranin gene (*NRGN*) on 11q24.2 and a marker in intron four of transcription factor 4 (*TCF4*) on 18q21.2; findings implicating the MHC region are consistent with an immune component to schizophrenia risk, whereas the association with *NRGN* and *TCF4* points to perturbation of pathways involved in brain development, memory and cognition	ORs and 95% CIs for the 7 markers associated with schizophrenia: rs6913660[C]: 1.15 (1.10–1.21) rs13219354[T]: 1.20 (1.14–1.27) rs6932590[T]: 1.16 (1.11–1.21) rs13211507[T]: 1.24 (1.16–1.32) rs3131296[G]: 1.19 (1.13–1.25) rs12807809[T]: 1.15 (1.10–1.20) rs9960767[C]: 1.23 (1.15–1.32)

Table 2. (*Continued*)

Reference	Technique	Population	Major Finding	Strength of Association
Sun *et al.* (106)	Family-based association study genotyping 2 SNPs (rs6603272 and rs6645249) at the IL3RA gene with PCR-based RFLP	101 Chinese parent-offspring trios (parent, affected offspring, and unaffected offspring) of Han descent	Single marker analysis showed a significant association for rs6603272 with schizophrenia but not for rs6645249. There was significant genotypic association of both SNPs with schizophrenia. Haplotype TDT was statistically significant, with the rs6603272(T)-rs6645249(G) haplotype significantly associated with schizophrenia	Single marker analysis of rs6603272 [$\chi^2_1 = 5.15$, $p = .023$][a] Genotypic associations: rs6603272 [$\chi^2_2 = 6.15$, $p = .046$][a] rs6645249 [$\chi^2_2 = 21.79$, $p = 1.85e^{-005}$][a] OR and 95% CI for association of rs6603272(T)-rs6645249(G) haplotype with schizophrenia: 1.66 (1.08–2.55)
Chen *et al.* (107)	12 SNPs on chromosome 5q21–33, in and around the IL-3 gene, were genotyped in two family samples and one case-control sample with either TaqMan assay or the FP-TDI protocol	Study included 3 samples: 1. ISHDSF sample collected in Northern Ireland, the United Kingdom, and the Republic of Ireland. Cases were split into three overlapping diagnostic classes: narrow ($n = 515$), intermediate, ($n = 634$), and broad ($n = 686$) definitions of schizophrenia ranging from schizophrenia and poor-outcome schizoaffective disorder (narrow) to the entire schizophrenia spectrum (broad). Sample included 273 unaffected relatives with significant family history. 2. A subset of the ICCSS sample comprising 657 affected subjects with diagnosis of schizophrenia or poor-outcome schizoaffective disorder and 411 control subjects. 3. ITRIO comprising 187 families, including 87 probands with positive family history	5 SNPs in the promoter and enhancer of the IL-3 gene (rs3914025, rs3846726, rs3916441, rs31400, and rs2069803) were associated with schizophrenia in the ISHDSF; two- and three-marker haplotypes involving rs31400, rs31480 (single marker not significant), and rs2069803 were significant in all diagnostic classes. The associations were largely driven by females. Results showed similar female-specific patterns in the ICCSS and ITRIO but only in those subjects with a family history of schizophrenia (all subjects in ISHSF had a family history of schizophrenia). Risk haplotypes identified in the family studies were found to be protective in the case-control study	Significant ORs and p values disequilibrium tests for two- and three-marker haplotypes (statistics are for females only unless otherwise specified; ISHDSF refers to narrow definition only; ICCSS and ITRIO refer to probands with family history of schizophrenia only): rs3914025-rs3846726- rs3916441 haplotype 1-1-1: ISHDSF, OR = .63, $p = .0087$ (in males, OR = 1.25, $p = .0066$); ICCSS, OR = 1.27, $p = .0142$ haplotype: 2-2-2: ISHDSF, OR = 2.00, $p = .0087$ (in males, OR = .74, $p = .0073$); ICCSS, OR = .75, $p = .0445$ rs31400-rs31480 haplotype 1-1: ISHDSF, OR = .43, $p = .0002$; ITRIO, OR = .54, $p = .0134$ haplotype 2-1: ISHDSF, OR = 1.91, $p = .0064$ rs31400-rs31480-rs2069803 haplotype 1-1-2: ISHDSF, OR = .43, $p = .0005$; ITRIO, OR = .56, $p = .0216$ haplotype 2-1-1: ISHDSF, OR = 2.00, $p = .0060$; ITRIO, OR = 2.28, $p = .0344$
Hänninen *et al.* (134)	Genomic DNA isolated for genotyping from blood samples by salting-out method; screening of IL-1β -511 gene polymorphisms and NRG-1 SNP8NRG221533	113 Finnish schizophrenia patients and 393 healthy control subjects	Allele and genotype frequencies of IL-1β and NRG-1 did not differ between schizophrenia patients and control subjects, but the risk of schizophrenia was more than 10 times higher among subjects with the IL-1β 2.2, NRG-1 CC genotypes compared with subjects with the IL-1β 2.2, NRG-1 T-allele carriage	OR and 95% CI: 10.20 (2.53–41.09)

Table 2. (*Continued*)

Reference	Technique	Population	Major Finding	Strength of Association
Lencz *et al.* (108)	Case-control WGA study examining approximately 500,000 markers	178 patients with schizophrenia-spectrum disorders (schizophrenia, $n = 158$; schizoaffective, $n = 13$, schizophreniform, $n = 7$) and 144 healthy control subjects	rs4129148 locus near the *CSF2RA* (colony stimulating factor, receptor 2 α) gene in the PAR1 was significantly associated with schizophrenia; sequencing of *CSF2RA* and its neighbor, IL 3 receptor α (*IL3RA*), revealed common intronic haplotypes and several rare exonic missense variants—CSF2RA (exon 3 C/G, exon 7 G/A, exon 7 C/T, exon 8 C/T) and IL3RA (exon 5 G/A, exon 7 G/A, exon 7 C/G)—associated with schizophrenia (rare missense variants were collectively associated with schizophrenia)	Homozygosity for the C allele of SNP rs4129148 was significantly associated with schizophrenia, with 59% of cases but only 31% of control subjects being CC homozygotes (OR = 3.23; 95% CI = 2.04–5.15; population attributable risk = 23.5%) OR for rare exonic missense variants within the *CSF2RA* and *IL3RA* genes collectively associated with schizophrenia: OR = 6.703[b]
Schwarz *et al.* (7)	Genotyping of IL-2 (IL-2 -330 T/G SNP) and IL-4 (IL-4 -590 C/T SNP) gene polymorphisms performed by FRET with the Light Cycler System in a study comparing schizophrenia patients and control subjects	230 schizophrenia patients and 251 healthy control subjects	Identified a significant association of the IL-2 -330 TT genotype and of the IL-4 -590 CC genotype with schizophrenia	IL-2 polymorphism: $\varphi = .124$ (small effect); IL-4 polymorphism: $\varphi = .123$ (small effect)[b]
Yu *et al.* (109)	Analyzed the -1082G/A, -819T/C, and -592A/C polymorphisms of the IL-10 gene promoter; polymorphisms amplified with PCR	341 schizophrenia patients and 334 control subjects of Han Chinese descent	Statistically significant differences observed in allelic and genotypic frequencies of the -592A/C polymorphism in the promoter region of the IL-10 gene between schizophrenia patients and control subjects	ORs and 95% CI for: Allelic frequencies of -592A allele: 1.26 (1.02–1.5) Genotypic frequencies for the distribution of -592A/C genotypes: 1.55 (1.09–2.19)
Tan *et al.* (111)	Investigation of 4 biallelic polymorphisms (-1031T/C, -863C/A, -857C/T, and -308G/A) in the TNFα gene promoter with PCR	302 schizophrenia patients and 152 control subjects subjects	Statistically significant differences in genotype distribution and allele frequencies for the -308G/A polymorphism in TNFα gene promoter between schizophrenia patients and control subjects	ORs and 95% CIs for: -308 G/A allele frequencies between control and patients: 2.16 (1.49–3.12) G allele (when G allele was considered as recessive) between cases and control subjects: 2.48 (1.61–3.76) (difference in distribution of G allele was not significant when it was considered as dominant) TNFα gene promoter haplotypes -1031T, -863C, -857C, -308A: .51 (.34–.77) TNFα gene promoter haplotypes -1031C, -863T, -857C, -308A: .33 (.13–.81)
Chiavetto *et al.* (110)	Analyzed allele, genotype, and haplotype distributions of IL-10 in a case-control study with PCR-SSCP and PCR RFLP methods	106 schizophrenia patients (schizophrenia: $n = 91$; schizoaffective disorders: $n = 15$) and 143 unrelated healthy volunteers	Significant increase of GCC homozygotes (the high IL-10-producing haplotype) in schizophrenia patients compared with control subjects	OR and 95% CI: 3.30 (1.274–7.355)

Table 2. (*Continued*)

Reference	Technique	Population	Major Finding	Strength of Association
Boin *et al.* (112)	Analyzed allelic and genotype distributions of TNF-α -308 gene polymorphism in schizophrenia patients and control subjects	84 schizophrenia patients recruited from an inpatient facility and 138 unrelated healthy control subjects	Significant increase in frequency of TNF -308A (TNF2) allele in schizophrenia patients as compared with healthy control subjects; genotype distribution was also significantly different, with TNF2 homozygotes represented only in the patient group	For allele frequency: $\varphi = .192$ (small effect); for genotype: $\varphi = .233$ (small effect)[b]
Katila *et al.* (113)	DNA isolation and screening of polymorphisms of the IL-1 gene complex (IL-1α (-889), IL-1β (-511), IL-1RA VNTR, located on chromosome 2q13-q21	50 schizophrenia patients and 400 control subjects	Frequencies of IL-1α (-889) allele 2, IL1-β (-511) allele 1, and IL-1RA allele 1 were higher in schizophrenia patients. Number of carriers of this IL-1 complex haplotype was significantly higher in the schizophrenia patients than in control subjects, and the number of homozygotes of this haplotype was significantly high in schizophrenia patients	ORs for association with schizophrenia: Number of carriers of the IL-1α (-889) allele 2 positive/IL1-β (-511) allele 2 negative/IL1RA allele 2 negative: OR = 2.0 Number of IL-1α (-889) allele 2/IL-1β (-511) allele 1/IL-2RA allele 1 homozygotes: OR = 4.3 (CIs not reported)
Laurent *et al.* (114)	Association study of *TaqI* and *IB-175/IB-173* polymorphisms (within the 3′UTR) of the IL-1β gene with PCR-SSCP	75 schizophrenia patients and 75 control subjects	There was no significant difference in allelic or genotypic distribution of the *IL-1β* gene polymorphisms (*TaqI* and *1B-175/1B-173)* between schizophrenia patients and healthy control subjects	Allelic and genotypic distributions of *TaqI* polymorphism in patients and control subjects were not significantly different [$\chi^2_1 = .073$, $p =$ NS; $\chi^2_2 = .128$, $p =$ NS][a] Similarly, no differences in allelic/genotypic distribution of *IB-175/IB-173* [$\chi^2_1 = .444$, $p =$ NS; $X^2_2 = .447$, $p =$ NS][a]

CI, confidence interval; FRET, fluorescence resonance energy transfer method; GSEA, Gene Set Enrichment Analysis; GWAS, genome-wide association study; HLA, human leukocyte antigen; ICCSS, Irish Case-Control Study of Schizophrenia; ISHDSF, Irish Study of High Density Schizophrenia Families; ITRIO, Irish Trio Study of Schizophrenia; MGS, Molecular Genetics of Schizophrenia; MHC, major histocompatibility complex; NES, normalized enrichments scores; NRG, neuregulin; OR, odds ratio; PAR, pseudoautosomal region; PCR, polymerase chain reaction; QC, quality control; RFLP, restriction fragment length polymorphism; SNP, single nucleotide polymorphism; SSCP, Single Strand Conformation Polymorphism; TDT, transmission disequilibrium test; TGF-β, transforming growth factor β; TNFR1, tumor necrosis factor receptor 1; WGA, whole-genome association; other abbreviations as in Table 1.

[a]No effect size or odds ratio reported.

[b]Effect size or odds ratio not reported in review. Calculated by authors on the basis of available data reported in manuscripts.

Table 3. Anti-Inflammatory Treatments for Individuals with Psychotic Symptoms

Reference	Technique	Drug (dosage)	Reported Side Effects	Population	Major Finding	Strength of Association
Prasad *et al.* (135)	18 weeks of double-blind placebo-controlled drug add-on trial comparing antipsychotics and valacyclovir with antipsychotics and placebo	Valacyclovir (1.5 g twice daily orally) – antiherpes virus-specific medication for treatment of HSV1	Six subjects on placebo reported drooling, muscle tightness, mild tremors, akathisia, bloating, feeling tired, elbow pain, increased sex drive, insomnia, and leg cramps. Five subjects on valacyclovir reported constipation, stomach pain, motion sickness, occasional muscle twitch, tremor, and upset stomach. All side effects were mild; none of the subjects required discontinuation of treatment.	24 HSV1 seropositive schizophrenia subjects (age 18–50) who were on stable doses of antipsychotics for at least 1 month and scored ≥4 on a least one item of the PANSS	Valacyclovir group improved in verbal memory, working memory, and visual object learning compared with placebo group, but psychotic symptom severity did not improve	Cohen's *d* effect sizes: Immediate verbal memory: $d = 1.14$ Working memory: $d = .79$; Visual object learning: $d = .97$
Amminger *et al.* (132)	Randomized, double-blind, placebo-controlled 12-week trial comparing ω-3 PUFAs with placebo	Long-chain ω-3 PUFAs (1.2 g/day)	No statistically significant group differences in adverse events were observed between ω-3 PUFAs and placebo on the Udvalg for Kliniske Undersøgelser (side effect rating scale for psychotropic drugs)	81 individuals (age 13–25) at ultra-high risk of psychotic disorder	Long-chain ω-3 PUFAs significantly reduced cumulative risk of progression to full-threshold psychosis over a 12 month period as well as total, positive, negative symptoms, and general symptoms, and improved functioning as assessed by the PANSS compared with placebo	12-month conversion rates to psychotic disorder: 4.9% in the ω-3 group and 27.5% in the placebo group Effect sizes for secondary outcomes: PANSS total, $d = .70$; PANSS positive, $d = .69$; PANSS negative, $d = .52$; PANSS general, $d = .68$; GAF, $d = -.72$; MADRS, $d = .32$ (MADRS change not significant) Difference between groups in cumulative risk of progression to full-threshold psychosis: 22.6% (95% CI: 4.8–40.4)
Laan *et al.* (129)	Randomized, double-blind placebo-controlled drug augmentation trial comparing antipsychotics and aspirin with antipsychotics and placebo	Aspirin (acetylsalicylic acid) (1000 mg/day) – a selective COX inhibitor, NSAID (proton pump inhibitors, such as omeprazole, were additionally prescribed	No substantial side effects were recorded—no serious gastric or bleeding events requiring medical attention were observed during the trial	70 antipsychotic-treated schizophrenia spectrum disorder inpatients and outpatients (age 18–55) from 10 psychiatric hospitals	Addition of aspirin to regular antipsychotic treatment substantially reduced total and positive symptoms as assessed with the PANSS	Significant results: PANSS total: $d = .47$; PANSS positive: $d = .39$ Nonsignificant results: PANSS negative: $d = .26$; PANSS general: $d = .39$

Table 3. (*Continued*)

Reference	Technique	Drug (dosage)	Reported Side Effects	Population	Major Finding	Strength of Association
		to reduce risk of mucosal gastric injury)				
Levkovitz *et al*. (136)	Longitudinal double-blind, randomized, placebo-controlled drug add-on trial comparing atypical antipsychotics and minocycline with atypical antipsychotics and placebo	Minocycline (200 mg/day) –second-generation tetracycline antibiotic	In minocycline group, 2 patients had indigestion, 2 had pigmentation, and 1 attempted suicide (in 4 of these 5 cases, minocycline treatment was discontinued, and patients were excluded from the study; in 1 case, in which the subject experienced mild pigmentation, treatment was continued as planned). No adverse events occurred in the placebo group.	54 early-phase schizophrenia patients (age 18–35)	Minocycline add-on therapy was associated with improvements in negative symptoms and executive functioning	Reduction in SANS score: $r = .46$ Change in executive functioning (composite score) of the CANTAB: $r = .47$[a]
Müller *et al*. (137)	Double-blind, placebo-controlled, randomized trial of celecoxib augmentation to amisulpride treatment in patients with first-episode schizophrenia	Celecoxib (400 mg/day) - selective COX-2 inhibitor, NSAID	No patient needed to be excluded from the trial due to side effects; bradycardia was seen in one patient in the placebo group, a well-known side effect of amisulpride. No important effect on cardiovascular function could be determined in this short-term trial from celecoxib	49 patients (age 19–49) with a first episode of schizophrenia ($n = 42$) or schizophreniform disorder ($n = 7$)	Significant improvements in PANSS negative, PANSS global, and PANSS total scores observed in the patient group treated with amisulpride plus celecoxib compared with the amisulpride plus placebo group	PANSS total: $d = .631$; PANSS negative: $d = .910$; PANSS general: $d = .503$; PANSS positive (nonsignificant finding): $d = .312$[b]
Akhondzadeh *et al*. (131)	Prospective, double-blind, placebo-controlled trial of celecoxib drug augmentation to risperidone treatment	Celecoxib (400 mg/day) – selective COX-2 inhibitor, NSAID	No clinically important side effects were observed	60 inpatients (age 19–44) with chronic schizophrenia who were in the active phase of the disorder	After 8 weeks the risperidone plus celecoxib group showed significantly greater improvement in positive, general, and total PANSS scores compared with the risperidone plus placebo group	PANSS positive: $d = .066$; PANSS general: $d = .073$; PANSS total: $d = .082$

Table 3. (*Continued*)

Reference	Technique	Drug (dosage)	Reported Side Effects	Population	Major Finding	Strength of Association
Rapaport *et al.* (138)	8-week prospective, double-blind, placebo-controlled drug augmentation trial comparing atypical antipsychotics and celecoxib with atypical antipsychotics and placebo	Celecoxib (400 mg/day) – selective COX-2 inhibitor, NSAID	Celecoxib augmentation did not impact measures of extrapyramidal side effects, functioning, or any safety parameters	38 symptomatic outpatient schizophrenia subjects (age 19–67) who were on a stable dose of atypical antipsychotic medication for at least 3 months	Treatment cohorts did not differ on any of the clinical outcome measures, and celecoxib augmentation did not improve clinical symptoms or measures of disability among continuously ill outpatient schizophrenia subjects	Effect sizes for nonsignificant results: PANSS total: $d = -.340$; SANS: $d = -.115$; CGI-S: $d = -.196$; Calgary Depression Scale: $d = -.038$; HAM-A: $d = -.225$; Scale of Functioning: $d = .513$[b]
Müller *et al.* (139)	Double-blind, placebo-controlled, randomized trial comparing risperidone and celecoxib with risperidone and placebo	Celecoxib (400 mg/day) – selective COX-2 inhibitor, NSAID	No clinically important side effects were observed	50 schizophrenia patients (age 18–65)	In the celecoxib but not in the placebo group, decreases in $CD19^+$ lymphocytes (markers of the immune-response type-2 related B-lymphocytes in the blood) were significantly associated with decreases on the PANSS negative scale; celecoxib group also displayed significantly higher levels of sIL-2R (markers of the type-1 immune response)	Decreases in $CD19^+$ lymphocytes and PANSS negative scale score ($r = .48$ $p < .03$) Increases in sIL-2R in celecoxib group compared with placebo: ($z = 2.28$, $p < .01$)[a]
Müller *et al.* (130)	Prospective, double-blind, placebo-controlled, randomized trial comparing risperidone and celecoxib with risperidone and placebo	Celecoxib (400 mg/day) – selective COX-2 inhibitor, NSAID	No clinically important side effects were observed (side effects that have previously been attributed to the administration of celecoxib, especially gastrointestinal problems, were not observed)	50 patients (age 18–65) with schizophrenia who had been hospitalized after acute exacerbation of their psychosis; all subjects received risperidone	After 5 weeks the risperidone plus celecoxib group showed significantly greater improvement in the PANSS total score compared with the risperidone plus placebo group	[$F_{1,47} = 3.80$, $p = .05$][a]

CANTAB, Cambridge Neuropsychological Test Automated Battery; CGI-S, Clinical Global Impression – Severity; COX, cyclooxygenase; GAF, Global Assessment of Functioning; HAM-A, Hamilton Anxiety Scale; HSV1, herpes-simplex virus, type 1; MADRS, Montgomery Asberg Depression Rating Scale; NSAID, nonsteroidal anti-inflammatory drug; PANSS, Positive and Negative Syndrome Scale; PUFA, polyunsaturated fatty acid; SANS, Scale for Assessment of Negative Symptoms; sIL-2R, soluble interleukin-2 receptors.

[a]No effect size or odds ratio reported.

[b]Effect size or odds ratio not reported in review. Calculated by authors on the basis of available data reported in manuscripts.

One possibility is that fetal exposure to maternal infection and/or immune responses to infection create a focal lesion or brain pathology that is then reactivated in adolescence when normal developmental processes (e.g., synaptic pruning) occur (124). Another possibility presumes greater developmental continuity, with fetal exposure to inflammation and/or infection leading to a cascade of neurodevelopmental sequelae that cumulatively result in long-term brain pathology and schizophrenia onset (64). Along these lines, early alterations in immune function might lead to increased inflammation over time, which in turn can lead to brain abnormalities, such as those associated with schizophrenia.

It is also possible that individuals exposed to maternal infection during pregnancy and/or inflammation might have subtle developmental difficulties that alter subsequent interactions with the environment across development. As mentioned in the preceding text, there is support for maternal infection during pregnancy leading to developmental problems in the premorbid period among children who later develop schizophrenia, such as cognitive and social problems (5,26). Similarly, maternal infection during pregnancy has been linked to developmental disorders, like autism, characterized by severe social and cognitive impairments (125). However, what has not been tested is the possibility that premorbid difficulties interact with contextual factors (e.g., interactions with peers, family, teachers), which could subsequently create additional contextual stressors for the child (e.g., bullying from peers), which in turn could result in a cascade of difficulties for the child ultimately increasing risk for schizophrenia via numerous processes (e.g., increases in stress hormones). Contextual factors (e.g., peer influences and familial context) have largely been overlooked in studies of immune processes in schizophrenia, possibly due to difficulties measuring theses constructs nonetheless, contextual factors are important for future investigations to consider.

Finally, although genes associated with abnormal immune functioning have been linked to schizophrenia, it remains unclear whether genes and other individual-level factors (e.g., stress, diet, substance use) interact with pre- and postnatal immune insults such as infection and increased levels of proinflammatory cytokines to increase risk of schizophrenia and brain alterations associated with the disorder. Questions also remain with regard to the role of timing of immune insults. For example, the preponderance of ecologic data supports the association between second trimester infection and offspring schizophrenia, whereas more recent, methodologically rigorous studies have made it less clear which trimester or life period, if any, might be key in conferring risk for schizophrenia after infection/inflammation exposure (126). With the exception of a few previously mentioned studies that have examined polymorphisms of the IL-3 and IL-10 genes, previous work on immune functioning in schizophrenia has predominantly examined T_H1-mediated immune responses, leaving the association between schizophrenia and T_H2 responses (127) in need of further examination, perhaps with dynamic measures of immune response—such as exposure to viruses (128)—to determine how T_H1 and T_H2 responses might work in tandem in schizophrenia.

Accumulating evidence has found relations between inflammation and immune function and risk of schizophrenia and schizophrenia-related brain alterations. In fact, there is preliminary evidence that treatments for infections and inflammation have promising results in schizophrenia populations. Specifically, herpes treatment in schizophrenia can improve cognition (19) and anti-inflammatory treatments can improve positive and negative symptoms in patients with schizophrenia (129–132) (Table 3). Although some of these anti-inflammatory treatments have more severe side-effect profiles than others, anti-inflammatory agents like omega-3 fatty acids have promising effects on the symptoms of schizophrenia and have very few known side effects (132). Understanding how immune alterations operate within the course of the disorder is critical, especially given that inflammation and infection are fairly common in the population and represent potentially easy targets for early intervention and treatment.

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