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Inflammatory cytokines and neurological and neurocognitive alterations in the course of schizophrenia

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Abstract

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, since 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 using 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.

Keywords

cytokines; infection; inflammation; neuroimaging; pregnancy; schizophrenia

1. INTRODUCTION

Schizophrenia is a severe neurodevelopmental disorder resulting from genetic and environmental factors (1). Although the 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

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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. As 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.

2. 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 occurring 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 (HSV-2) (15), and exposure to the protozoan parasite *Toxoplasma gondii* (16, 17) have been associated with risk of schizophrenia in offspring. Further, maternal infections during pregnancy have been associated with schizophrenia-related neurocognitive/neuroanatomical abnormalities, including decreases in premorbid cognitive functioning (5, 10), executive functioning problems following 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 section 3) (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 may 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 influence of prenatal infection on increased risk of schizophrenia is increased when offspring have a family history of psychosis, though 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.

3. IMMUNE RESPONSE AND THE FETAL BRAIN

3.1 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), many of which appear 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 down-regulation of T_H1 proinflammatory cytokines, leading to a suppression of cell-mediated immunity and potentially decreasing the mother's ability 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 may 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). Further, 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 following 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).

3.2 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 and colleagues (2010) 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, as 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 may 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 may 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 following fetal exposure to increases in maternal proinflammatory cytokines.

3.3 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 paper. Consistent with the Ellman et al. study (2010), 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 (poly I:C) 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. Similarly, exposure to prenatal infection can increase vulnerability for late-life alterations in cytokine production by inducing latent neuroinflammatory abnormalities that surface following 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 may 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 interleukin-6 (IL-6) as mediators of the long-term behavioral deficits found in offspring following maternal immune activation (65), and warrants considerable attention when attempting to understand the role of inflammation in the neurodevelopmental course of schizophrenia.

4. 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). Further, 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 and colleagues (2008) published a recent meta-analysis on inflammatory cytokine alterations in schizophrenia and found increased levels of in vivo peripheral IL-1RA, sIL-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), while 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 and colleagues (2008) 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 section 5.1). 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. Further, 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.

4.1 Cytokines & Neuroanatomical alterations: Neuroimaging studies

A number of immune-related genetic polymorphisms have been associated with brain changes found in schizophrenia (see 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-1 receptor antagonist, respectively, and are part of the IL-1 gene cluster on chromosome 2q13, which has been linked to schizophrenia (78). 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 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, as 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 to other IL-1RN genotypes (82), have been found to show significant enlargement 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 non-affective psychosis patients was unable to replicate these findings, but found a non-significant trend towards larger ventricles at early phases of the disorder among carriers of allele*2 (84). Taken together, these findings suggest that IL-1RN gene variations may be involved in susceptibility to the progressive brain changes that occur over the course of the disorder in some individuals, such that compared to first-onset patients, chronic patients may 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 (DLPFC), 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 DLPFC 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 may contribute to both structural and functional brain abnormalities associated 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 may 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 may be associated with both schizophrenia (89, 90) and increases in inflammatory cytokines (91, 92), may additively or interactively influence the aforementioned findings. In this case, IL-1RN-associated increases in proinflammatory cytokines may not be evident until the disorder onset when disorder-related factors emerge.

5. 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), while others fail to find differences (98–101). Active neuroinflammation can be assessed using 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 and colleagues (2009) found significantly higher binding potential of ^{11}C-(*R*)-PK11195 in the hippocampus of schizophrenia patients compared to healthy controls, indicating neuroinflammation in a focal area after the onset of psychosis. However, these studies are plagued by similar interpretation difficulties as noted above, given that evidence of neuroinflammation following 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).

5.1 Interactions between Immune and Individual Factors

A number of genetic polymorphisms linked to immune functioning have been associated with risk for schizophrenia (See 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 (MHC) 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 alpha 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, as 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 may 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 using 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 non-pregnant populations. For instance, factors such as increases in BMI (118), race (particularly African-Americans) (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 alterated immune functioning, susceptibility to infection, and schizophrenia. There is some support for these individual-level factors influencing cytokine levels among schizophrenia patients, as one study found that increases in proinflammatory cytokines and chemokines were related to individual characteristics commonly found in this population (123). Specifically, gender, increased BMI, hyperglycemia, diabetes, reduced HDL-cholesterol or increased levels of triglycerides or the metabolic syndrome (metS) 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.

6. 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 regarding how early immune insults might influence long-term immune functioning. One possibility is that fetal exposure to maternal infection and/or immune responses to infection create a focal lesion or brain pathology which is then reactivated in adolescence when normal developmental processes (e.g., synaptic pruning) occur (124). Another possibility presumes greater developmental continuity, with fetal exposure 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 inflammation might have subtle developmental difficulties which alter subsequent interactions with the environment across development. As mentioned above, 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 gene-environment interactions in schizophrenia as they tend to be difficult to measure; 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 regarding the role of timing of immune insults. For example, the preponderance of ecologic data supports the association between second trimester infection and offspring schizophrenia, while more recent, methodologically rigorous studies have made it less clear which trimester or life period, if any, may be key in conferring risk for schizophrenia following 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 using 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 herpes treatment in schizophrenia can improve cognition (19), and that anti-inflammatory treatments can improve positive and negative symptoms in patients with schizophrenia (129–132) (See Table 3). Although some of these anti-inflammatory treatments (e.g., celecoxib) 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, as inflammation and infection are fairly common in the population and represent potentially easy targets for early intervention and treatment.

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Table 1

Immune-related Genetic Polymorphisms Associated with Schizophrenia-Related Brain Change

Author	Year	Journal	Technique	Population	Major Finding	Strength of Association
Fatjó-Vilas et al.	2012	*Biological Psychiatry*	Genomic DNA extraction and genotyping of a biallelic base-exchange polymorphism at the promoter region (−511 C/T; rs16944) of interleukin-1β (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 controls 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 ($t = -4.33$, $p < .001$) **
Roiz-Santianez et al.	2008	*Psychiatry Research*	MRI volumetric analysis and analysis of interleukin-1 receptor antagonist (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): $d = .296$
Papiol et al.	2007	*American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*	Analysis of IL-1β gene functional polymorphism (−511 C/T; rs16944) influence on dorsolateral prefrontal cortex (DLPFC) activity using 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)	$U = 16$, $z = -2.32$, $p = .02$; *$d = -1.204$
Papiol et al.	2005	*NeuroImage*	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 controls	Schizophrenia patients who were carriers of the variable nucleotide tandem repeat (VNTR) allele *2 of IL-1RN gene showed significant bilateral enlargement of ventricles compared to patients with non-carrier genotypes	For patients carriers of VNTR allele *2: left ventricle enlargement ($t = 3.504$, $df = 21$, $p = .002$); right ventricle enlargement ($t = 2.784$, $df = 21$, $p = .01$) **
Meisenzahl et al.	2001	*American Journal of Psychiatry*	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 to non-carrier patients	Frontal: $F = 6.06$, $df = 1, 42$, $p < 0.02$; temporal: $F = 11.62$, $df = 1, 42$, $p = 0.001$; white matter deficits $F = 5.54$, $df = 1, 42$, $p < 0.03$ **

*Effect size or odds ratio not reported in paper. Calculated by authors based on available data reported in manuscripts.

** No effect size or odds ratio reported

Table 2

Immune-related Genetic Polymorphisms Associated with Schizophrenia

Author	Year	Journal	Technique	Population	Major Finding	Strength of Association
Jia et al.	2010	*Schizophrenia Research*	Genome-wide association study (GWAS) (369,808 SNPs mapped to 19,896 protein-coding genes, which were involved in 511 biological pathways) using two statistical methods, Gene Set Enrichment Analysis (GSEA) and hypergeometric test	1158 schizophrenia cases and 1378 controls from unrelated European ancestry samples	Three pathways related to apoptosis, inflammation, and the immune system showed a significant association with schizophrenia using both GSEA and hypergeometric methods: the transforming growth factor beta (TGF-beta) signaling pathway, the tumor necrosis factor receptor 1 (TNFR1) pathway, and the TOB1 pathway	Normalized enrichments scores (NES): TGF-beta signaling pathway: 1.845; TNFR1 pathway: 1.649; TOB1 pathway: 1.497 (TOB1 was not significant by GSEA: p =.070)
Purcell et al.	2009	*Nature*	GWAS of case-control sample for approximately 1 million SNPs, augmented by imputed common HapMap SNPs	3,322 European individuals with schizophrenia and 3,587 controls; combined sample (after exchanging GWAS summary results with the Molecular Genetics of Schizophrenia (MGS) and SGENE consortia for genotyped SNPs) included 8,008 schizophrenia cases and 19,077 controls of European decent	Significant association of schizophrenia with more than 450 SNPs on chromosome 6 spanning the major histocompatibility complex (MHC)	Odds ratios for classical human leukocyte antigen (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 $P < 10^{-3}$, though the association could not ascribed to any specific HLA allele, haplotype, or region) (Confidence intervals not reported)
Shi et al.	2009	*Nature*	GWAS of common SNPs (671,424 SNPs passed quality control (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 (2,681 cases, 2,653 controls) and African-American (1,286 cases, 973 controls); cases were included with diagnoses of schizophrenia or (in 10% of cases) schizoaffective disorder; meta-analysis of European-ancestry subjects (8,008 cases, 19,077 controls)	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, odds ratios for seven SNPs on chromosome 6p22.1 showed genome-wide significant associations with schizophrenia — odds ratios 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)

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						(Confidence intervals not reported)
Stefansson et al.	2009	*Nature*	GWAS of 314,868 SNPs to search for sequence variants associated with schizophrenia;	2,663 schizophrenia cases and 13,498 controls from 8 European locations (SGENE-plus GWAS dataset); the top 1500 markers were combined with results from the non-overlapping 2602 cases and 2885 controls in the ISC and the 2681 cases and 2653 controls 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 controls	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	Odds ratios and 95% confidence intervals 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)
Sun et al.	2009	*Brain Research*	Family-based association study genotyping 2 SNPs (rs6603272 and rs6645249) at the interleukin 3 receptor alpha (IL3RA) gene using polymerase chain reaction (PCR)-based restriction fragment length polymorphism (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 transmission disequilibrium test (TDT) was statistically significant, with the rs6603272(T)-rs6645249(G) haplotype significantly associated with schizophrenia	Single marker analysis of rs6603272 (X^2=5.15, *df*=1, p = 0.023) ** Genotypic associations: rs6603272 (X^2=6.15, *df*=2, p=0.046) ** rs6645249 (X^2=21.79, *df*=2, p=1.85e^{-005}) ** Odds ratio and 95% CI for association of rs6603272(T)-rs6645249(G) haplotype with schizophrenia: 1.66 (1.08, 2.55)
Chen et al.	2007	*Molecular Psychiatry*	12 SNPs on chromosome 5q21-33, in and around the interleukin 3 (IL-3) gene, were genotyped in two family samples and one case-control sample using either TaqMan assay or the FP-TDI protocol	Study included 3 samples: 1. Irish Study of High Density Schizophrenia Families (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	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 odds ratios 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

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				schizophrenia spectrum (broad). Sample included 273 unaffected relatives with significant family history. 2. A subset of the Irish Case-Control Study of Schizophrenia (ICCSS) sample comprising 657 affected subjects with diagnosis of schizophrenia or poor-outcome schizoaffective disorder and 411 controls. 3. Irish Trio Study of Schizophrenia (ITRIO) comprising 187 families, including 87 probands with positive family history		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
Hanninen et al.	2007	*European Archives of Psychiatry and Clinical Neuroscience*	Genomic DNA isolated for genotyping from blood samples by salting-out method; screening of IL-1β −511 gene polymorphisms and neuregulin-1 (NRG-1) SNP8NRG221533	113 Finnish schizophrenia patients and 393 healthy controls	Allele and genotype frequencies of IL-1β and NRG-1 did not differ between schizophrenia patients and controls, but the risk of schizophrenia was more than 10 times higher among subjects with the IL-1β 2.2, NRG-1 CC genotypes compared to subjects with the IL-1β 2.2, NRG-1 T-allele carriage	Odds ratio and 95% CI: 10.20 (2.53, 41.09)
Lencz et al.	2007	*Molecular Psychiatry*	Case-control whole-genome association (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 controls	rs4129148 locus near the *CSF2RA* (colony stimulating factor, receptor 2 alpha) gene in the pseudoautosomal region (PAR1) was significantly associated with schizophrenia; sequencing of *CSF2RA* and its neighbor, interleukin 3 receptor alpha (*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 controls being CC homozygotes (OR = 3.23; 95% CI = 2.04 – 5.15; population attributable risk = 23.5%) *Odds ratio for rare exonic missense variants within the *CSF2RA* and *IL3RA* genes collectively associated with schizophrenia: OR = 6.703
Schwarz et al.	2006	*European Archives of Psychiatry and Clinical Neuroscience*	Genotyping of interleukin 2 (IL-2) (IL-2 − 330 T/G SNP) and interleukin 4 (IL-4) (IL-4 − 590 C/T SNP) gene polymorphisms performed by fluorescence resonance energy transfer method	230 schizophrenia patients and 251 healthy controls	Identified a significant association of the IL-2 − 330 TT genotype and of the IL-4 − 590 CC genotype with schizophrenia	*IL-2 polymorphism: ϕ = .124 (small effect); IL-4 polymorphism: ϕ = .123 (small effect)

Author	Year	Journal	Technique	Population	Major Finding	Strength of Association
			(FRET) using the Light Cycler System in a study comparing schizophrenia patients and controls			
Yu et al.	2004	*Schizophrenia Research*	Analyzed the −1082G/A, −819T/C, and −592A/C polymorphisms of the IL-10 gene promoter; polymorphisms amplified using PCR	341 schizophrenia patients and 334 controls 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 controls	Odds ratios 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.	2003	*Biological Psychiatry*	Investigation of 4 biallelic polymorphisms (−1031T/C, −863C/A, −857C/T, and −308G/A) in the TNFα gene promoter using PCR	302 schizophrenia patients and 152 controls subjects	Statistically significant differences in genotype distribution and allele frequencies for the −308G/A polymorphism in TNFα gene promoter between schizophrenia patients and controls	Odds ratios 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 controls: 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.	2002	*Biological Psychiatry*	Analyzed allele, genotype, and haplotype distributions of interleukin-10 (IL-10) in a case-control study using PCR-Single Strand Conformation Polymorphism (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 to control subjects	Odds ratio and 95% CI: 3.30 (1.274, 7.355)
Boin et al.	2001	*Molecular Psychiatry*	Analyzed allelic and genotype distributions of TNF-α −308 gene polymorphism in schizophrenia patients and controls	84 schizophrenia patients recruited from an inpatient facility and 138 unrelated healthy controls	Significant increase in frequency of TNF − 308A (TNF2) allele in schizophrenia patients as compared to healthy controls; genotype distribution was also significantly different, with TNF2 homozygotes represented only in the patient group	*For allele frequency: ϕ = .192 (small effect); for genotype: ϕ = .233 (small effect)
Katila et al.	1999	*Molecular Psychiatry*	DNA isolation and screening of polymorphisms of the interleukin 1 (IL-1) gene	50 schizophrenia patients and 400 controls	Frequencies of IL-1α (−889) allele 2, IL1-β (−511) allele 1 and IL-1RA allele 1 were higher in schizophrenia	Odds ratios for association with schizophrenia:

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			complex (IL-1α (−889), IL-1β (−511), IL-1RA variable number tandem repeat (VNTR), located on chromosome 2q13–q21		patients. Number of carriers of this IL-1 complex haplotype was significantly higher in the schizophrenia patients than in controls, and the number of homozygotes of this haplotype was significantly high in schizophrenia patients	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 (Confidence intervals not reported)
Laurent et al.	1997	*Psychiatric Genetics*	Association study of *TaqI* and *IB-175/IB-173* polymorphisms (within the 3′UTR) of the IL-1β gene using PCR-SSCP	75 schizophrenia patients and 75 controls	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 controls	Allelic and genotypic distributions of *TaqI* polymorphism in patients and controls were not significantly different (χ^2= .073, df = 1, NS; χ^2 = .128, df = 2, NS) ** Similarly, no differences in allelic/genotypic distribution of *IB-175/IB-173* (χ^2= .444, df = 1, NS; χ^2 = .447, df = 2, NS) **

* Effect size or odds ratio not reported in paper. Calculated by authors based on available data reported in manuscripts.

** No effect size or odds ratio reported

Table 3

Anti-inflammatory Treatments for Individuals with Psychotic Symptoms

Author	Year	Journal	Technique	Drug (dosage)	Reported Side Effects	Population	Major Finding	Strength of Association
Prasad et al.	2012	*Schizophrenia Bulletin*	18 weeks of double-blind placebo-controlled drug add-on trial comparing antipsychotics and valacyclovir to antipsychotics and placebo	valacyclovir (1.5 g twice daily orally) – antiherpes virus-specific medication for treatment of herpes-simplex virus, type 1 (HSV1)	Six subjects on placebo reported drooling, muscle tightness, mild tremors, akithisia, 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 Positive and Negative Syndrome Scale (PANSS)	Valacyclovir group improved in verbal memory, working memory, and visual object learning compared to 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.	2010	*Archives of General Psychiatry*	Randomized, double-blind, placebo-controlled 12-week trial comparing omega-3 (ω-3) polyunsaturated fatty acids (PUFAs) to placebo	Long-chain omega-3 polyunsaturated fatty acids (1.2 g/d)	No statistically significant group differences in adverse events were observed between omega-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 omega-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* = 0.70; PANSS positive, *d* = 0.69; PANSS negative, *d* = 0.52; PANSS general, *d* = .68; Global Assessment of Functioning (GAF), *d* = −.72; Montgomery Asberg Depression Rating Scale (MADRS), *d* = 0.32 (MADRS change not significant)

Author	Year	Journal	Technique	Drug (dosage)	Reported Side Effects	Population	Major Finding	Strength of Association
								Difference between groups in cumulative risk of progression to full-threshold psychosis: 22.6% (95% CI, 4.8 – 40.4)
Laan et al.	2010	*Journal of Clinical Psychiatry*	Randomized, double-blind placebo-controlled drug augmentation trial comparing antipsychotics and aspirin to antipsychotics and placebo	aspirin (acetylsalicylic acid) (1000 mg/d) – aselective cyclooxygenase (COX) inhibitor, nonsteroidal anti-inflammatory drug (NSAID). (Proton pump inhibitors, such as omeprazole, were additionally prescribed to reduce risk of mucosal gastric injury)	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: $d = .39$ Non-significant results: PANSS negative: $d = .26$; PANSS general: $d = .39$
Levkovitz et al.	2010	*Journal of Clinical Psychiatry*	Longitudinal double-blind, randomized, placebo-controlled drug add-on trial comparing atypical antipsychotics and minocycline to atypical antipsychotics and placebo	minocycline (200 mg/d) – 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 Scale for Assessment of Negative Symptoms (SANS) score: $r = .46$ Change in executive functioning (composite score) of the Cambridge Neuropsychological Test Automated Battery (CANTAB): $r = .47^{**}$
Müller et al.	2010	*Schizophrenia Research*	Double-blind, placebo-controlled, randomized trial of celecoxib augmentation to amisulpride treatment in patients with first-episode schizophrenia	celecoxib (400 mg/d) – 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 amulsipride. No important effect on cardiovascular function could be determined in	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 to the	*PANSS total: $d = .631$; PANSS negative: $d = .910$; PANSS general: $d = .503$; PANSS positive (non-significant finding): $d = .312$

Author	Year	Journal	Technique	Drug (dosage)	Reported Side Effects	Population	Major Finding	Strength of Association
					this short-term trial from celecoxib		amisulpride plus placebo group	
Akhondzadeh et al.	2007	*Schizophrenia Research*	Prospective, double-blind, placebo-controlled trial of celecoxib drug augmentation to risperidone treatment	celecoxib (400 mg/d) – 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 to the risperidone plus placebo group	PANSS positive: $d = .066$; PANSS general: $d = .073$; PANSS total: $d = .082$
Rapaport et al.	2005	*Biological Psychiatry*	8-week prospective, double-blind, placebo-controlled drug augmentation trial comparing atypical antipsychotics and celecoxib to atypical antipsychotics and placebo	celecoxib (400 mg/d) – 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 non-significant results: PANSS total: $d = -.340$; SANS: $d = -.115$; Clinical Global Impression – Severity (CGI-S): $d = -.196$; Calgary Depression Scale: $d = -.038$; Hamilton Anxiety Scale (HAM-A): $d = -.225$; Scale of Functioning: $d = .513$
Müller et al.	2004	*European Archives of Psychiatry and Clinical Neuroscience*	Double-blind, placebo-controlled, randomized trial comparing risperidone and celecoxib to risperidone and placebo	celecoxib (400 mg/d) – 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-lymophocytes in the blood) were significantly associated with decreases on the PANSS negative scale; celecoxib group also displayed significantly higher levels of soluble	Decreases in $CD19^+$ lymphoctyes and PANSS negative scale score ($r = 0.48$ $p < 0.03$) Increases in sIL-2R in celecoxib group compared to placebo: ($z = 2.28$, $p < .01$)**

Author	Year	Journal	Technique	Drug (dosage)	Reported Side Effects	Population	Major Finding	Strength of Association
							interleukin-2 receptors (sIL-2R) (markers of the type-1 immune response)	
Müller et al.	2002	*American Journal of Psychiatry*	Prospective, double-blind, placebo-controlled, randomized trial comparing risperidone and celecoxib to risperidone and placebo	celecoxib (400 mg/d) – selective cyclooxygenase-2 (COX-2) inhibitor, NSAID	No clinically important side effects were observed (side effects that have previously been attributed to the administration of celecoxib, especially gastronintestinal problems, were not observed)	50 patients (age 18–65) with schizophrenia who had been hospitalized following 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 to the risperidone plus placebo group	($F = 3.80$, $df = 1, 47$, $p = .05$) **

* Effect size or odds ratio not reported in paper. Calculated by authors based on available data reported in manuscripts.

** No effect size or odds ratio reported