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A unifying hypothesis of schizophrenia: Abnormal immune system development may help explain roles of prenatal hazards, post-pubertal onset, stress, genes, climate, infections, and brain dysfunction

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SUMMARY

We propose a unifying hypothesis of schizophrenia to help reconcile findings from many different disciplines. This hypothesis proposes that schizophrenia often involves pre- or perinatal exposure to adverse factors that produce a latent immune vulnerability. When this vulnerability is manifested, beginning around puberty with changes in immune function and involution of the thymus, individuals become more susceptible to infections and immune dysfunctions that contribute to schizophrenia. Our hypothesis suggests theoretical bridges between different lines of evidence on schizophrenia and offers explanations for many puzzling findings about schizophrenia. For example, the hypothesis helps account for why schizophrenia patients tend to have had increased exposure to neurotropic infections, but most individuals with such exposure do not develop schizophrenia, and why prenatal hardships increase risk for schizophrenia, but the onset of symptoms typically does not occur until after puberty. The hypothesis also explains another paradox: lower socioeconomic status and poor prenatal care increase risk for schizophrenia at the same geographic site, but international comparisons indicate that countries with higher per capita incomes and better prenatal care actually tend to have *higher* schizophrenia prevalences. As the hypothesis predicts, (1) prenatal adversity, which increases risk for schizophrenia, also impairs post-pubertal immune competence, (2) schizophrenia patients experience elevated morbidity from infectious and auto-immune diseases, (3) genetic and environmental risk factors for schizophrenia increase vulnerability to these diseases, (4) factors that exacerbate schizophrenic symptoms also tend to impair immune function, (5) many anti-psychotic medications combat infection, (6) effects of early infections may not appear until after puberty, when they can produce neurologic and psychiatric symptoms, and (7) immune dysfunctions, such as imbalances of pro- and anti-inflammatory cytokines, may contribute to the onset of psychotic symptoms and the progressive loss of brain tissue in schizophrenia. The disruptive effects of prenatal adversity on the development of the immune system may often combine with adverse effects on prenatal brain development to produce schizophrenia. This paper focuses on the adverse immune system effects, because effects on the brain have been extensively discussed in neurodevelopmental theories of schizophrenia. We propose new tests of scientific predictions. We also point out potential clinical implications of the hypothesis; for example, individuals with schizophrenia may often have underlying infections or immune dysfunctions, such as imbalances in inflammatory cytokines, that contribute to the illness. This possibility could be tested experimentally – e.g., by clinical trials in which patients' exposure to infection is reduced or immune function is normalized.

Introduction

We propose a unifying hypothesis to help account for many puzzling and seemingly unrelated, sometimes even contradictory, sets of findings about schizophrenia. We describe how the hypothesis may help explain these findings and why they may complement, rather than contradict, one another. We describe several predictions of the hypothesis and consider empirical evidence pertinent to respective predictions. The hypothesis proposes that

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schizophrenia often involves abnormalities in development and function of the immune system, which result from exposure to adverse factors during vulnerable periods of pre- or perinatal development.

One of the most widely reported research findings on schizophrenia is that risk for the disorder is significantly increased by pre- and perinatal exposure to a number of adverse environmental factors. These adverse factors include certain infections [1,2], maternal stress [3–5], malnutrition [6,7], and maternal medical complications [8,9]. A second finding is that the onset of schizophrenia typically does not occur until long after birth, following puberty, usually in late adolescence or early adulthood [10]. Third, increased risk for schizophrenia is significantly associated with being a male [11], and with certain environmental variables such as living in an urban setting [12] or at a higher latitude [12,13]. Fourth, many lines of evidence, including twin, family, and adoption studies, indicate that familial and genetic factors are etiologically significant in schizophrenia [14–16]. Fifth, a number of studies indicate that individuals with schizophrenia are more likely than control populations to have had exposure to a number of neurotropic infectious agents [17], but most people with this exposure do not develop schizophrenia. Finally, several lines of research suggest that certain immunologic abnormalities are more common in schizophrenia and contribute to psychotic symptoms in schizophrenia (e.g. [18].

It has been unclear how to explain and reconcile these several sets of findings in schizophrenia. The evidence that prenatal exposure to various environmental hazards increases risk for schizophrenia makes the disorder's typical post-pubertal onset puzzling, because it raises the question of why there is such a long delay between the time of prenatal insults and the first episode of the illness. This evidence for prenatal risk factors is also puzzling in view of epidemiologic data on geographic variation in the prevalence of schizophrenia [12,13,19]. Because prenatal hazards are usually associated with increased risk for schizophrenia within the same country, one might expect the prevalence of schizophrenia to be highest in developing countries, where the levels of prenatal nutrition and care tend to be the worst. In fact, schizophrenia prevalence tends to be *lowest* in developing countries, and highest in industrialized countries, including some Scandinavian countries that have low infant mortality rates and unusually good pre- and perinatal health care. Finally, it has been unclear how evidence for increased exposure to certain infections in schizophrenia patients is related to the other findings, or why such exposure might lead to schizophrenia in some individuals but not in others.

A hypothesis to reconcile different findings on schizophrenia

A unifying hypothesis to reconcile these different findings is suggested by the results of a prospective longitudinal study by Moore et al. [20,21] in the African nation of The Republic of Gambia, which has long suffered from seasonal periods of widespread food shortage and malnutrition. Moore and her colleagues found that individuals from an index cohort born during the rainy season (known there as the "hungry" season, because it is when food becomes scarce) were more than 10 times as likely to die prematurely as were individuals born during the dry season. However, the respective mortality rates for cohorts born during the rainy vs. dry seasons did not begin to diverge until after individuals were aged roughly 15 years. The excess mortality among those who have been born during the rainy season was mainly due to infectious diseases.

To explain these findings, Moore et al. [20,21] invoked the concept of prenatal programming of developing tissues, including the immune system. This concept was originally proposed by Barker [22,23] in his Fetal Origins Hypothesis. Barker's hypothesis states that undernourishment during critical periods of gestation permanently alters the function and structure of organs, but that the effects of this may not be apparent for years, or even decades, after birth [24]. Moore et al. noted that many components of the immune system begin to develop early in fetal life and continue to develop during gestation.

Moore et al. proposed that the delayed effect of prenatal malnutrition on mortality might be the result of the thymus gland protecting the index cohort from the effects of a latent vulnerability in the immune system, a vulnerability that only became manifest after the involution of the thymus gland that begins around the time of puberty. As Moore et al. pointed out, beginning at puberty parts of the thymus gland undergo a major reduction in volume. Investigations by Steinmann et al. [25] found that the volumes of the various thymic tissue components begin to decrease significantly after age 15 and continue to decrease over the next two decades. This is consistent with the idea that a latent defect in the immune system is masked until thymic involution begins, after which there is increased vulnerability to infections and immune dysfunction.

In this paper, we examine the hypothesis that an analogous mechanism plays a role in schizophrenia. The hypothesis proposes that exposure to adverse environments during vulnerable periods of gestation can disrupt the normal prenatal programming of the immune system. This creates a latent vulnerability in the individual's immune system that renders the individual more vulnerable to infectious diseases and/or dysregulation of immune processes that affect the central nervous system. The latent vulnerability in the immune system does not typically become manifest, however, until puberty, when major changes in the immune system begin to occur, and parts of the thymus gland begin to undergo a major reduction in volume. When this immune vulnerability is manifested, individuals become more susceptible to infectious and/or immune diseases that can contribute to the onset of schizophrenia.

This phenomenon would help explain why the onset of schizophrenia typically does not begin until after puberty, and why the onset of most cases occurs between puberty and age 35 – the period during which the volume of key thymic structures declines to about 20% of pre-pubescent volume [25]. This increased vulnerability to infectious or immune diseases may also help explain other findings on schizophrenia. For example, as we will discuss later, several important genetic and environmental factors that increase risk for schizophrenia are also associated with increased vulnerability to infections and/or auto-immune disorders.

Adverse pre- and perinatal environmental and genetic factors that disrupt programming of the immune system are often likely to disrupt the programming of the brain as well. We hypothesize that schizophrenia often results from the confluence of these adverse effects on both nervous and immune systems. However, the disruptive effects of prenatal hazards on central nervous system development in schizophrenia have been extensively discussed in previous research and in neurodevelopmental hypotheses of the disorder [26–29]. We therefore focus in this paper on how abnormal development and function of the immune system may help explain diverse and puzzling findings on schizophrenia, particularly ones not addressed by previous neurodevelopmental theories.

Predictions of the hypothesis and pertinent evidence

The hypothesis makes a number of testable predictions for which pertinent evidence is available.

Prediction #1: Prenatal adversity can adversely affect post-pubertal immunocompetence and thymic structure

Complementary lines of research indicate that prenatal exposure to maternal psychosocial stress and malnutrition can have

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significant effects on adolescent and adult immunocompetence, as well as the structure of the thymus. For example, Coe et al. [30] found that administering adrenocorticotrophic hormone (ACTH) to pregnant monkeys – thereby mimicking the effect of external stressors on the expectant mother – led to multiple alterations in the physiology and immunology of the offspring. Stressing pregnant sows and rats with restraint or loud noise reduced immunocompetence in their offspring – an effect also reported in studies of prenatal exposure to other environmental hazards such as poor maternal diet, lead, and methylmercury [31–35]. Interestingly, two studies have suggested that prenatal exposure to maternal social stress alters immune function in male rats when they experience stressful life events as adults [36,37]. Complementary research has found that in humans, prenatal exposure to psychosocial maternal stress also has significant effects on adult immune function. Thus, Entringer et al. [38] found that if women had experienced prenatal exposure to severe maternal stress, then as adults they had cytokine production levels that differed significantly from a control group and resembled those of chronically stressed individuals.

In monkeys, prenatal exposure to synthetic corticosteroids produced marked alterations in the structure of the thymus [39]. Maternal undernutrition has been shown to have a strong effect on *human* thymic and lymphoid tissue [40,41]. Thus, Collinson et al. [40] found that thymus gland volume was significantly smaller in infants born in the hungry rather than the harvest season. Prenatal undernutrition was also significantly associated with reduced thymopoietin production in adolescents from the Philippines, even after controlling for a range of postnatal exposures [42]. Reduced antibody response to typhoid vaccination in Pakistani adults was associated with low birth weight, suggesting that there is a prolonged postnatal compromise of immune response as a result of fetal growth retardation [43].

Thus, several lines of evidence suggest that thymic dysfunction due to adverse factors such as psychosocial stress, toxins, or undernutrition during gestation can have significant deleterious effects on the immune system, resulting in an increased vulnerability to infections and auto-immune disease after birth that can extend into adulthood. The diminution in the volume of the thymus gland that normally occurs after puberty could thus be especially problematic – and more likely to lead to schizophrenia – in cases where key elements of the immune system, such as the thymus, are already diminished in size or function as a result of the adverse prenatal environmental factors to which schizophrenia patients are more likely to have been exposed.

Prediction #2: Schizophrenia patients have increased exposure – and vulnerability – to certain infections and immune disorders

A number of studies have reported that schizophrenia patients have increased rates of *exposure* to certain infections. For example, a meta-analysis of the 19 most careful studies [17] found a significantly higher prevalence of exposure to *Toxoplasma gondii* in schizophrenia patients vs. controls. A number of studies have also reported higher rates of exposure to other infectious agents, such as cytomegalovirus and human herpes virus type 6, in schizophrenia patients than in controls [44,45]. Some research indicates that this exposure occurs prior to the onset of illness, and that some increased exposure may even have occurred prenatally.

However, exposure to these infections is hardly unique to patients with schizophrenia, and most individuals with a history of exposure do not develop schizophrenia. This may be explained by several lines of evidence which suggest that individuals with schizophrenia also tend to be more *vulnerable* to infections when they are exposed. For example, several studies have found mortality from infectious disease to be significantly higher in patients with schizophrenia than in the general population. This suggests that schizophrenia patients may have increased vulnerability to infection. A meta-analysis of six studies, including investigations from the US, Israel, and Sweden that encompassed 16,522 cases, found that, after adjusting for age and gender, the risk of death from infectious disease was 9.4 times higher in patients with schizophrenia than in the general population [46]. It is noteworthy that in these studies the largest and most significant increase in relative risk for mortality in patients with schizophrenia was for infectious disease – an increase greater than for any other class of medical condition, such as circulatory disease or cancer.

A number of studies have also reported significant alterations of immune function in schizophrenia [47,48]. This evidence includes, for example, elevated serum levels of the cytokine IL-6 [49], and depressed NK cell activity in schizophrenia [50]. The latter finding is notable because NK cells play a key role in the first line of immune defense against viral infections.

Because of extensive evidence for familial and genetic factors in schizophrenia, it is notable that genetic factors have been estimated to account for 30–35% of the risk for *auto-immune diseases* [51,52], and that the prevalence of auto-immune disorders is significantly elevated in both schizophrenia patients and their biological relatives. In a study using the personal and familial data on 7704 patients with schizophrenia admitted to Danish psychiatric facilities [53], a personal history of auto-immune disease was associated with a 45% increase in risk for developing schizophrenia. Moreover, nine auto-immune disorders and 12 auto-immune diseases were significantly more prevalent among the relatives of patients with schizophrenia than among family members of controls. Wright et al. [54] also found that an auto-immune disorder, insulin-dependent diabetes, was significantly more prevalent in the first-degree relatives of patients with schizophrenia than in controls.

Consistent with the prediction that schizophrenic patients have increased exposure to infections, it is notable that many auto-immune disorders – including multiple sclerosis (MS), rheumatoid arthritis, lupus erythematosis, and myocarditis – are often associated with infections [55,56]. Infections can trigger a number of auto-immune diseases, such as type I diabetes, nephritis, and rheumatic fever; this may involve molecular mimicry in which antigens expressed by infectious agents closely resemble those on the surface of the host's own cells [57].

Multiple sclerosis (MS) is a particularly relevant precedent in this regard, for several reasons. First, there is evidence suggesting that exposure to infectious agents, such as Epstein-Barr virus, helps trigger auto-immune attacks on the patients' nervous tissue [58]. Second, there are notable epidemiologic parallels between MS and schizophrenia. For example, in both illnesses, there is a strong tendency for prevalence to increase with latitude [12,13,59] and with vitamin D deficiency [60]. This and other lines of evidence suggest that vitamin D deficiency may play a contributing role in both MS and schizophrenia [61], as individuals residing in areas at high latitudes experience months-long periods where sunlight is too indirect for cutaneous vitamin D synthesis [60]. Third, consistent with this, patients with both MS and schizophrenia have been reported to have unusually low mean serum levels of vitamin D [62,63].

In summary, complementary lines of evidence suggest that individuals with schizophrenia not only are more likely to have been exposed to neurotropic infections, but also tend to be more vulnerable to the harmful effects of such infections, including possible auto-immune reactions. This increased vulnerability could thus help explain why schizophrenia patients have increased rates of exposure to neurotropic microbes, but most people, being less vulnerable to infections and auto-immune reactions, do not develop schizophrenia after they have been exposed.

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Prediction #3: Genetic and environmental factors that increase risk for schizophrenia will also tend to be associated with increased vulnerability to infectious diseases or immune dysfunction

Epidemiologic studies have identified several *environmental* factors that significantly increased risk for schizophrenia. Thus reviews and meta-analytic studies have concluded that a higher prevalence of schizophrenia is associated with urban residence [12,64–66], just as higher rates of many infectious diseases are found in urban areas [67,68]. As population density increases, the prevalence of psychosis also increases [69,70], an association that persists even after controlling for patients' own lifetime psychiatric histories and the histories of psychosis in their parents [71].

Moreover, there is wide (>10-fold) geographic variation in the prevalence of schizophrenia around the world, with a strong tendency for the prevalence to be higher in developed countries with particularly good and comprehensive prenatal health care and nutrition [12,13,72]. It is notable in this regard that vitamin D deficiency may help explain the striking tendency for schizophrenia prevalence to increase with latitude [12,13,61], because exposure of skin to sunlight is the major natural source of vitamin D. Moreover, even after controlling for an index of healthcare resources – infant mortality rates – Kinney et al. [19] found significant associations of lower fish consumption and darker skin with greater schizophrenia prevalence at higher latitudes. These patterns were also consistent with effects of vitamin D deficiency on schizophrenia risk, because fish are the major dietary source of vitamin D, and darker skin reduces production of vitamin D from sunlight.

It is therefore significant for our hypothesis that vitamin D deficiency is associated with increased vulnerability to infections [60,73], as well as increased risk for schizophrenia. Vitamin D is important for several aspects of brain development, so that the negative effects of vitamin D deficiency could contribute to schizophrenia by disrupting early development of the nervous system [61]. Vitamin D is also critically important for immune function [74,75], as it plays a key role in several processes that defend against infection, and it is also involved in the prevention of auto-immune disorders [73,76]. Thus there is evidence that vitamin D deficiency could contribute to schizophrenia in several ways. Vitamin D deficiency significantly weakens resistance to influenza [73], and both pre- and postnatal influenza exposure has in turn been linked to increased risk for schizophrenia [2]. Prenatal exposure to maternal vitamin D deficiency may increase vulnerability to prenatal infections that have been implicated in schizophrenia, while post-pubertal vitamin D deficiency is likely to increase vulnerability to infections and immune processes in adolescence and adulthood that may contribute to the onset of schizophrenia. These considerations would predict that risk for schizophrenia is highest in populations living at high latitudes, where vitamin D deficiency is most prevalent.

These patterns may explain why risk for schizophrenia at the same region is increased by prenatal exposure to environmental hazards, yet prevalence is especially high in a number of industrialized countries with better prenatal care – several times higher in some Scandinavian countries with particularly good universal prenatal care – than in developing countries. Latitude and levels of income of countries are confounded in cross-national comparisons, because industrialized countries tend to be located at higher latitudes where vitamin D deficiency is common [60], whereas developing countries tend to be located nearer the equator. The higher schizophrenia prevalence in most industrialized countries would be explained if the effects of reduced exposure to sunlight and increased vitamin D deficiency in industrialized countries are so strong that they outweigh the protective effects of advantages such as generally better prenatal medical care and nutrition. Consistent with this possibility, meta-analyses of international schizophrenia prevalence studies find that prevalence rates increase rather markedly across different geographic sites as latitude increases, but at the same geographic site, economically disadvantaged groups with high infant mortality rates tend to have a significantly higher schizophrenia prevalence than advantaged groups [19].

Meta-analyses also indicate that schizophrenia tends to have a higher incidence and a more severe course *in males* than in females [11]. It is therefore notable that males tend to be more susceptible than females to many infections [77], including meningitis, pneumonia, rabies, syphilis, and tetanus [78,79]. Males are also more susceptible to protozoan, fungal, bacterial, and viral infections that are linked to circulating steroid hormone concentrations by several field and laboratory studies [77,80]. Mean antibody production tends to be higher in females than in males [81–83], a sex difference that becomes apparent only after sexual maturity [84], consistent with the typical post-pubertal onset in schizophrenia. It is of interest in this regard that research suggests that, in women, there is a second peak in the onset of schizophrenia after menopause, when there is a decrease in estrogen production [85]. This would be consistent with a possible role for infections in schizophrenia, because estrogen appears to facilitate defense against infection [77,80].

Several lines of research indicate that *genetic* factors are important etiologic factors in schizophrenia. This research includes twin, adoption, and family studies, as well as genetic linkage and association studies [14,16,86]. Two recent studies have provided some of the strongest evidence for association of specific alleles with increased risk for schizophrenia. Stefansson et al. [87] examined data on single nucleotide polymorphisms from several large genome-wide association studies. In analyses of data on more than 12,000 schizophrenia cases and over 34,000 controls, they found significant associations between increased risk for schizophrenia and alleles at several loci on the major histocompatibility complex (MHC) region of chromosome 6. Stefansson et al. note that this association between schizophrenia and markers on the MHC region is consistent with evidence from other studies that have also found that alleles in the MHC increase risk for schizophrenia, and that a number of auto-immune and infectious diseases are associated with alleles at some of these loci. They conclude that the results are consistent with previous research suggesting that the immune system is involved in schizophrenia.

Complementary evidence for an association of schizophrenia with genetic factors that influence immune function is provided by a case-control whole-genome association study. In that study, Lencz et al. [88] found that alleles in the pseudo-autosomal region of the X and Y chromosomes were strongly associated with schizophrenia. Lencz et al. found that several complementary lines of evidence, from two different samples, indicated that risk for schizophrenia is increased several-fold by alleles of two genes located on the pseudo-autosomal region. These genes influence variation in the structure of receptors of pro-inflammatory cytokines, and the expression of these cytokines. Lencz et al. note that these effects on cytokines may contribute to the variable and episodic course of schizophrenia. They further note that these cytokines, interleukin 3 and granulocyte–macrophage colony stimulating factor, play roles in central nervous system repair and modulation of the neurotransmitters acetylcholine and GABA. Lencz et al. call for research to investigate whether the association of schizophrenia with alleles at these cytokine receptor loci reflects a role in schizophrenia of immune responses to infectious pathogens, or abnormal inflammatory or auto-immune processes.

In summary, several genetic and environmental factors that are associated with increased risk for schizophrenia are also associated with increased exposure and/or vulnerability to infectious and auto-immune diseases, particularly ones that have been linked to schizophrenia.

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Prediction #4: Psychosocial stress, which tends to exacerbate symptoms in schizophrenia, will also tend to disrupt immune function and increase vulnerability to infection

Several lines of research suggest that psychosocial stress may act as a trigger of the onset or exacerbation of psychotic symptoms in schizophrenia patients [89–91]. For example, prospective longitudinal studies have reported an increased frequency of major independent stressful life events – those whose occurrence is unlikely to have been influenced by the individual – during the period immediately preceding psychotic exacerbations [92–94]. Minor life events or daily hassles have also been reported to prospectively predict symptom exacerbation and subjective distress in individuals at risk for psychosis [95,96]. Multilevel regression analyses revealed significant increases in psychosis intensity with increases in event-related stress in individuals in remission from psychosis [97]. Finally, a randomized trial of a stress management program for individuals with schizophrenia [98] found that patients who received the stress management program had fewer hospitalizations over the course of one year.

Anti-psychotic medications affect activation of the hypothalamic–pituitary-adrenal axis, which helps mediate neuroendocrine responses to stressors [99]. Anxiety and psychosocial stressors in turn affect production of pro-inflammatory cytokines, including levels of IL-6 [47,100], which, as noted earlier, have been found to be elevated in schizophrenia patients. Recurrent or chronic activation of the acute stress response can suppress the immune system, leading to increased susceptibility to infectious agents [101,102]. Lack of social support and chronic stress, as in individuals caring for a spouse with dementia, greatly increases levels of IL-6 [103].

Prediction #5: Medications that ameliorate symptoms in patients with schizophrenia will also tend to decrease vulnerability to infection and modulate immune function

Given the evidence noted earlier for increased *T. gondii* exposure in schizophrenia, it is notable that the replication of *T. gondii* is inhibited *in vitro* by various anti-psychotic drugs, including valproic acid, haloperidol, fluenazine, clozapine, olanzapine, risperidone, and carbamazepine [104,105]. In laboratory mice, both haloperidol and valproic acid normalized the behavior of mice infected with *T. gondii*, so that they no longer showed the parasite-induced suicidal attraction to the odor of cats [106].

Phenothiazine drugs also have significant anti-microbial activity against a wide variety of other pathogens [107]. For example, chlorpromazine has been shown *in vitro* to have bacteriostatic and bactericidal activity against several microorganisms, including *Mycobacterium tuberculosis* [108,109]; thioridazine may be particularly useful against methicillin-resistant *Staphylococcus aureus* [110]; and the anti-psychotic drug thioxanthene flupenthixol exhibited antibacterial property against 352 strains of bacteria [111].

Several studies have reported that a number of anti-psychotic medications can also have significant effects on the immune system. For example, various neuroleptics normalized levels of $CD3^+$ T- and $CD19^+$ B-lymphocytes in drug-naïve schizophrenia patients suffering from acute psychosis [112], and olanzapine and quetiapine have been used to moderate levels of the cytokine IL-6 in treating anemia of chronic disease [113]. Leweke et al. [44] found that a number of immune abnormalities were present in untreated patients with schizophrenia, but were absent in patients who were receiving treatment.

Prediction #6: Effects of pre- or perinatal infections may not appear until after puberty, when they can produce neurologic and psychiatric symptoms

As noted earlier, prenatal exposure to certain infectious agents such as toxoplasmosis and cytomegalovirus is much more common in schizophrenia patients than in controls [17,45], yet the onset of schizophrenia tends not to occur until after puberty. One explanation for this could be that the effects of CNS infections acquired during gestation or childhood can lie dormant for long periods and then become active again when immune surveillance is weakened. There is some evidence that this could occur in schizophrenia, as a number of infectious agents that have been linked to schizophrenia can indeed lie dormant for long periods in the brain tissue of individuals who carry them.

Toxoplasmosis, for example, can remain in a person's body for an entire lifetime [17]. Sen and Barton [114] note that most humans become infected with multiple herpes viruses during childhood. After clearance of acute infection, the herpes virus enters a latency stage, which is presumed to be parasitic, and lasts for the lifetime of the host, but can flare up later in life. Most healthy individuals also have been exposed to human cytomegalovirus and harbor a dormant form of the virus, which can become active again in situations of immune compromise [115]. Thus, several lines of evidence indicate that the infectious agents to which schizophrenia patients tend to have had increased exposure can lie dormant for very long periods, but flare up again when the immune system is compromised.

Another precedent for a long-delayed effect of early brain infection on adult brain function is provided by animal models and human studies of multiple sclerosis (MS), which suggest that early infections can lead to a delayed auto-immune disorder of the nervous system. For example, Rodriguez et al. [116] found that genetically susceptible mice showed no immediate or short-term neurologic effects of infection with Theiler's virus, and developed significant spinal cord demyelination only after a relatively long incubation period. A similar delayed effect has also been noted in complementary research in humans; DeLorenze et al. [117] found that serum collected up to 30 years prior to onset of MS showed significantly higher levels of antibodies to Epstein-Barr virus in individuals who developed MS than in controls.

Our hypothesis suggests that analogous processes might occur in schizophrenia, when there may be a confluence of factors that conspire to weaken immune surveillance after puberty, including normal developmental changes in the thymus, abetted by immune-compromising factors, such as psychosocial stress and vitamin D deficiency, that research suggests are risk factors for schizophrenia. This post-pubertal immune vulnerability could help explain why (a) schizophrenia patients have increased exposure to certain neurotropic pathogens, such as *T. gondii*, yet most individuals with this exposure do not develop the illness, and (b) exposed individuals who *do* develop schizophrenia typically *don't* do so until after puberty.

It is notable in this regard that converging lines of evidence indicate that vitamin D deficiency will increase vulnerability to such neurotropic pathogens, and that Schneider et al. [62] found that the mean blood serum level of vitamin D was significantly lower in schizophrenia patients than in controls. Both *in vitro* studies and experiments with lab animals have shown that administration of vitamin D can inhibit the growth of *T. gondii* [118]. It is also of interest that Hinze-Selch et al. [119] found that schizophrenia patients differ significantly from demographically matched controls in their immune response to *T. gondii*, displaying more severe inflammatory responses, particularly if they were experiencing a first episode of illness. Hinze-Selch et al. note that this kind of severe immune response may help to explain the symptoms of schizophrenia, because an important side effect of host defense against *T. gondii* can be excessive dopaminergic activity, which in turn may tend to contribute to psychotic symptoms.

Multiple sclerosis (MS) often has a variable course with episodes in which the severity of auto-immune processes and neurological symptoms flare up, followed by periods of remission of

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syndrome but often results in increasing levels of disability over time. Similar processes in schizophrenia might help explain a course that can involve analogous periods of varying levels of symptom severity, and progressive loss of cognitive function and brain tissue, especially around the time of the first episode of psychosis [120,121].

Prediction #7: Immune dysfunction can contribute to schizophrenia symptoms and loss of brain tissue

Finally, several lines of evidence point to mechanisms by which immune dysfunction may produce symptoms in schizophrenia. Müller and Schwarz [18] review evidence that neuroinflammatory processes in schizophrenia can cause dysregulation of glutamatergic and dopaminergic neurotransmission, which in turn contributes to positive and negative symptoms of the illness. For example, evidence for an inflammatory process in schizophrenia is provided by the presence of elevated serum levels of C-reactive protein – an indicator of inflammation – in schizophrenia patients with more severe psychopathology [122]. Müller and Schwarz [18] note that there is evidence from many studies for an imbalance between type-1 and type-2 immune responses in schizophrenia, with type-1 response being inhibited and type-2 response being overactivated. Müller and Schwartz note that this immune imbalance can result from early sensitization of the immune system or the presence of long-standing infection that the immune system has been unable to clear. This imbalanced pattern of immune activity, in turn, leads to elevated levels of kynurenic acid (KYNA), which is an antagonist of the *N*-methyl-D-aspartate (NMDA) receptor and produces glutamatergic dysfunction. Elevated levels of KYNA have been found in the cerebrospinal fluid of patients with schizophrenia, including drug-naïve, first-episode patients [123]. It is therefore noteworthy that anti-psychotic drugs significantly reduce brain levels of KYNA [124].

Increased expression of cyclo-oxygenase-2 (COX-2) was reported in schizophrenia patients [125], and COX-2 inhibitors work to decrease levels of KYNA and to correct the imbalance of type-1 and type-2 immune responses reported in schizophrenia. Experiments with laboratory rats yielded complementary evidence for the hypothesis that neuroinflammatory processes contribute to psychopathology in schizophrenia: experimentally elevated levels of COX-2 in the rat striatum were associated with behavioral impairments in sensory gating and latent learning similar to those seen in schizophrenia, and treatment with the COX-2 inhibitor celecoxib ameliorated these impairments [126].

In randomized, double-blind studies, Müller et al. [127,128] administered celecoxib as an adjunct to risperidone in treating patients with acute schizophrenia. Both significantly greater improvement in symptoms and an augmentation of type-1 immune responses were observed in the group receiving adjunctive treatment with the anti-inflammatory drug celecoxib; the efficacy was most marked in the first few years after onset. Further research investigating the clinical efficacy of anti-inflammatory agents in schizophrenia is needed, with examination of whether particular immune or infectious processes may distinguish subgroups of schizophrenia patients with different genotypes or treatment responses. For example, Garver et al. [129] reported that significantly higher levels of the cytokine IL-6 distinguished schizophrenia patients who subsequently showed better treatment response.

Moreover, a number of lines of evidence reviewed by Monji et al. [130] indicate that neuroinflammation and the pro-inflammatory cytokines such as TNF-α inhibit neurogenesis, induce apoptosis in cortical neurons and oligodendrocytes, and affect synapse formation and connectivity. Monji et al. note that release of pro-inflammatory cytokines by microglia may be responsible for the progressive loss of brain tissue observed in patients with schizophrenia in longitudinal MRI studies of brain structure [120]. Complementing this, as Monji et al. note, is evidence that atypical anti-psychotics inhibit release of pro-inflammatory cytokines by microglia.

Discussion

The hypothesis complements neurodevelopmental hypotheses

Our hypothesis complements *neurodevelopmental hypotheses* of schizophrenia [27–29]. These influential hypotheses have been advanced to explain a phenomenon concerning schizophrenia that was discussed earlier, namely evidence that pre- and perinatal adversity – such as exposure to maternal infections, diabetes, or obstetric complications – increases risk for schizophrenia, but the illness itself typically does not manifest until after puberty. Neurodevelopmental hypotheses have proposed that genetic and/or environmental factors operating during pre- or perinatal periods produce a CNS abnormality that does not produce symptoms of schizophrenia until it interacts with maturational changes in the CNS, such as synaptic pruning and myelination of certain circuits, that occur around the time of adolescence [26,131].

However, while these neurodevelopmental hypotheses offer explanations for some phenomena, they do not offer an explanation for the many associations between immune disorders or infections and schizophrenia that we have discussed in this paper, for example, (a) that prenatal stressors that increase risk for schizophrenia also have adverse effects on post-pubertal immunocompetence, (b) that schizophrenia patients have increased exposure and vulnerability to certain infections and immune disorders, (c) that many genetic and environmental factors that increase risk for schizophrenia also increase immune vulnerability and/or dysfunction, (d) that psychosocial stress contributes both to schizophrenic symptoms and immune compromise, and (e) that many medications that ameliorate schizophrenia symptoms also improve immune function.

Many lines of evidence suggest that schizophrenia may involve the confluence of abnormalities of both the immune and the nervous systems. Extensive research has documented bidirectional influences between the immune and neuroendocrine systems [132]. Moreover, as discussed earlier, research indicates that prenatal hardships that increase risk for schizophrenia also can have disruptive effects on the development of both the nervous and the immune systems. Thus, for example, adverse prenatal factors such as maternal malnutrition or psychosocial stress – which increase risk for schizophrenia – are also associated with disturbances in prenatal brain development and adult immune function [6,38]. Moreover, as Meyer et al. [133] note, cytokines are not just key mediators of immune systems responses, but also influence prenatal brain development, and cytokines and their receptors are expressed during fetal brain development as well as in neurons and glial cells of the adult brain.

Evidence implicating inflammatory cytokines in schizophrenia

Several complementary lines of research suggest that one type of immune abnormality that plays a key role in schizophrenia involves dysregulation of pro-inflammatory cytokines. For example, animal experiments indicate that elevated levels of maternal pro-inflammatory cytokines mediate the adverse effects on fetal brain development of prenatal exposure to a number of adverse factors – such as maternal infection and diabetes – that epidemiologic studies indicate are significant risk factors for schizophrenia [1,134]. In experiments with mice, Meyer et al. [133,135] have shown that

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prenatal exposure to pro- and anti-inflammatory cytokines during critical windows of gestation can produce many of the cognitive abnormalities associated with schizophrenia, such as specific impairments in sensory gating, associative learning, and working memory. Moreover, Buka et al. [136] found that increased risk of schizophrenia was significantly associated with higher levels of a pro-inflammatory cytokine, tumor necrosis factor-α, in maternal serum samples taken in late pregnancy.

Complementary evidence for a role of these cytokines comes from genetic studies; alleles recently found to produce particularly marked increases in risk for schizophrenia also affect the structure of receptors for pro-inflammatory cytokines and the expression of those cytokines [88]. Moreover, as we noted earlier, prenatal exposure to maternal stress – a major risk factor for schizophrenia reported in several studies – increases pro-inflammatory cytokine production in adult women to the level shown by chronically stressed individuals [38]. Psychosocial stressors that precipitate symptoms in schizophrenia also tend to increase release of pro-inflammatory cytokines. Finally, as noted earlier, Müller and Schwarz [18] and Monji et al. [130] have described mechanisms by which an excessive inflammatory response can respectively produce (a) an imbalance of glutamatergic and dopaminergic neurotransmission that leads to psychotic symptoms in schizophrenia, and (b) a progressive loss of brain tissue that contributes to cognitive deficits.

New research to test scientific predictions of the hypothesis

Further research is thus warranted to investigate our hypothesis more extensively. One interesting line of investigation, for example, would involve prospective longitudinal studies of individuals at high risk for schizophrenia, to observe how immune, clinical, and neurological factors, and signs of infection, may co-vary over time. A related issue is whether the combination of these factors may distinguish different subtypes of schizophrenia that differ in their genotypes or type of prenatal adversity. Another potentially informative approach would be clinical trials on the effects of anti-microbial and anti-inflammatory medications or other substances, such as vitamin D supplements, to bolster immune defense against both infection and auto-immune dysfunction in pregnant women or in individuals who are at high risk for schizophrenia. The hypothesis would predict that pregnant women who receive supplements will have lower levels of pro-inflammatory cytokines, and their children should have fewer of the cognitive and neurologic abnormalities found in individuals who later develop schizophrenia. These supplements should also reduce pro-inflammatory cytokine levels and improve clinical outcomes when administered to adolescents and adults who are at high risk for schizophrenia.

Clinical implications and strategies for testing them

Our hypothesis has clinical implications as well, and these should also be amenable to empirical tests. For example, the hypothesis suggests that schizophrenia patients may often have undiagnosed infections or immune disorders that contribute to their symptoms, and that addressing such underlying conditions may aid treatment. If this is so, then steps to address established immune-compromising factors – such as sleep disorders, chronic pain, dietary deficiencies, and insufficient exercise or exposure to sunlight – warrant more investigation as possible complements to traditional therapies.

It would be important to investigate whether administration of anti-inflammatory or anti-microbial agents to individuals with either prodromal or first-episode psychotic symptoms of schizophrenia can not only reduce psychotic symptoms, but also protect against the progressive losses in cognition and regional brain volume observed in schizophrenia [120,121]. Because these losses appear to be concentrated in the few years around the time of the first onset of psychosis, this kind of research would be particularly interesting, since Müller et al. [127] found that treatment of schizophrenia patients with the anti-inflammatory agent celecoxib had the greatest therapeutic effect on patients if it was given within a few years of the onset of illness.

Another possibility suggested by the hypothesis is that, if patients are immunologically vulnerable and carry infectious diseases that contribute to their illness, then the infectious agents might be exchanged with fellow patients who also are immunologically compromised. In that case, conditions that promote close contact among patients – such as shared waiting rooms, half-way houses, or hospital wards – might unwittingly contribute to the exacerbation and transmission of the illness. This possibility may also be amenable to empirical testing, e.g., by steps to dramatically improve hygiene on randomly selected wards or to house randomly selected schizophrenia patients in quarters with minimal contact with other patients.

In summary, we hypothesize that abnormalities in immune system development and function contribute to schizophrenia. Our hypothesis helps to explain a number of puzzling findings on schizophrenia, and many predictions of the hypothesis are supported by available evidence. The hypothesis also makes a number of additional scientific and clinical predictions, and we suggest ways of experimentally testing those.

Conflict of interest statement

All of the authors declare that they have no conflict of interest. The sponsors of the research had no involvement in either writing the paper or deciding to submit it.

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