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Involvement of virus infections and antiviral agents in schizophrenia

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Review Article

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Abstract

Background. Schizophrenia is a chronic and complex mental disorder resulting from interactions between cumulative and synergistic genetic and environmental factors. Viral infection during the prenatal stage constitutes one of the most relevant risk factors for the development of schizophrenia later in adulthood.

Methods. A narrative review was conducted to explore the link between viral infections and schizophrenia, as well as the neuropsychiatric effects of antiviral drugs, particularly in the context of this specific mental condition. Literature searches were performed using the PubMed, Scopus, and Web of Science databases.

Results. Several viral infections, such as herpesviruses, influenza virus, Borna disease virus, and coronaviruses, can directly or indirectly disrupt normal fetal brain development by modifying gene expression in the maternal immune system, thereby contributing to the pathophysiological symptoms of schizophrenia. In addition, neuropsychiatric effects caused by antiviral drugs are frequent and represent significant adverse outcomes for viral treatment.

Conclusions. Epidemiological evidence suggests a potential relationship between viruses and schizophrenia. Increases in inflammatory cytokine levels and changes in the expression of key genes observed in several viral infections may constitute potential links between these viral infections and schizophrenia. Furthermore, antivirals may affect the central nervous system, although for most drugs, their mechanisms of action are still unclear, and a strong relationship between antivirals and schizophrenia has not yet been established.

Highlights

- Epidemiological evidence suggests a potential relationship between viruses and schizophrenia.
- Several viral infections can disrupt fetal brain development by activating the maternal immune system.
- Increases in inflammatory cytokine levels and changes in the expression of key genes may be possible links between viral infections and schizophrenia.
- Both immune and non-immune genes associated with schizophrenia are likely to be targets of viral proteins.
- Neuropsychiatric effects of antiviral drugs are common side effects that complicate viral treatment.

Introduction

The suggestion that microorganisms might provoke psychotic disorders in humans was established a long time ago. In the late nineteenth century, the Germ Theory of Disease was postulated, establishing that bacteria could be the etiologic agents related to several psychiatric disorders, including *dementia praecox*. At the time, the impossibility of a direct bacterial infection of the brain was verified, but it could occur indirectly through the secretion of microbial toxins in a process known as autointoxication (Yolken & Torrey, 2008). However, the Theory of Autointoxication fell into disrepute after several researchers attempted to surgically remove the infection sites in various organs, often with tragic results (Noll, 2006). After the influenza pandemic in 1918–1919, it was found that viral infection caused psychosis in many affected individuals (Menninger, 1994; Kępińska et al., 2020). In the 1980s, this virus hypothesis gained renewed attention due to the occurrence of herpesvirus infections in the cerebrospinal fluid (CSF) of schizophrenic subjects (Morozov, 1983).

Despite controversial findings, an extensive corpus of evidence links microbial infections to neuropsychiatric disorders, with host genes influencing microbial virulence and pathogens affecting host genes, including those related to schizophrenia (Krause et al., 2010; Pouget et al., 2019; Yolken, 2023). Furthermore, research on the gut-brain axis shows that bacteria can influence brain function and behavior without directly replicating in the central nervous

system (CNS) (Borrego-Ruiz & Borrego, 2024a; Hashimoto, 2023). In this regard, the gut microbiome and schizophrenia exhibit a bidirectional relationship, as translocated gut microbial metabolites can negatively impact brain connectivity, inducing neuroinflammation, a critical factor in schizophrenia (Kannan et al., 2017). In fact, this mental condition can alter the function of endothelial cells and disrupt the permeability of the blood–brain barrier (BBB), causing inflammation and the translocation of inflammatory cells into the brain (Khandaker & Dantzer, 2016; Severance & Yolken, 2020).

Diverse pathogenic microorganisms have been associated with psychotic symptoms, including those characteristic of schizophrenia. These pathogens encompass (i) bacteria, such as *Treponema pallidum, Mycoplasma pneumoniae, Chlamydia trachomatis*, and *Borrelia burgdorferi*; (ii) viruses, such as herpesviruses, orthomyxoviruses, rubiviruses, paramyxoviruses, picornaviruses, poxviruses, enteroviruses, arboviruses, retroviruses, and Borna disease virus; and (iii) protozoa, such as *Toxoplasma gondii* (Caroff, Mann, Gliatto, Sullivan, & Campbell, 2001; Yolken & Torrey, 2008). Although various of these pathogenic microorganisms have been extensively studied, interest has converged on a few viruses (Prasad, Watson, Dickerson, Yolken, & Nimgaonkar, 2012; Watson et al., 2013). In addition, a better understanding of neurodevelopment and neuroinflammation has provided insights into how viruses, either alone or in combination with other microorganisms or host variables, may impact the etiopathogenesis of schizophrenia (Meyer, 2013; Tran, Lee, & Cho, 2022).

Congenital infections are a major cause of childhood neurodevelopmental disabilities, contributing to structural brain abnormalities that can lead to severe impairments such as cerebral palsy, epilepsy, and neurosensory deficits (Fortin & Mulkey, 2023). Meyer, Yee, & Feldon (2007) previously suggested that infection-associated immune events during early fetal life may have a greater neurodevelopmental impact than infections occurring later in pregnancy. This is because infections in early gestation can disrupt key neurodevelopmental processes, such as cell proliferation and differentiation, and may predispose the developing nervous system to subsequent disruptions in cell migration, target selection, and synapse maturation, ultimately leading to a range of brain and behavioral abnormalities in adult offspring. In this regard, evidence suggests that exposure to infectious agents, autoimmune diseases, and other stressors during fetal and postnatal life may contribute to the development of schizophrenia and other non-affective psychoses (Benros, Nielsen, Nordentoft, Eaton, Dalton, & Mortensen, 2011; Brown & Patterson, 2011; Dickerson, Severance, & Yolken, 2017; Eaton et al., 2006; Megli & Coyne, 2022; Severance & Yolken, 2020; Yolken & Torrey, 2008). Proposed mechanisms include (i) excessive inflammatory cytokine production, contributing to immune dysregulation (Di Nicola et al., 2013); (ii) early-life disruptions in brain development (Ahmed, Ramadan, Elbeh, & Haridy, 2024); and (iii) neurotransmitter dysfunction, including glutamate, epinephrine, dopamine, serotonin, and γ-aminobutyric acid (GABA), driven by cytokine imbalance (Murray et al., 2004; Potvin et al., 2008). Within this context, epidemiological studies on maternal infections during pregnancy have provided contradictory results regarding microbial exposure, but have reported consistent associations with *T. gondii* maternal transmission (Blomström, Gardner, Dalman, Yolken, & Karslsson, 2015; Cheslack-Postava & Brown, 2022). Interestingly, other studies indicate that the association between early-life infection and later schizophrenia development is not completely explained by shared familial factors or by genetic liability (Karlsson & Dalman, 2020; Wahbeh & Avramopoulos, 2021).

Taking into consideration the growing evidence linking viral infections to neuropsychiatric disorders, and recognizing that both viral infections and their treatments may influence brain function, this narrative review synthesizes the current understanding of how viral infections may contribute to the development of schizophrenia, addressing the underlying mechanisms. Additionally, it explores the potential therapeutic impact of antiviral drugs in neuropsychiatric conditions, emphasizing schizophrenia as the primary focus of the review.

Methods

The present work consists of a narrative review aimed at gathering and analyzing existing literature to offer a comprehensive and thorough overview of the central topic under investigation (Agarwal, Charlesworth, & Elrakhawy, 2023), which contemplates the link between viral infections and schizophrenia, and also the neuropsychiatric effects of the antiviral drugs, especially on schizophrenia. The authors individually conducted an exhaustive literature search within the field pertinent to the subject of study. With this aim, PubMed, Scopus, and Web of Science databases were searched between February and March 2024, using various combinations of keywords related to the research topic, such as "viral infection," "viruses," "schizophrenia," "antivirals," or "psychiatric disorders." The search strategy involved an iterative process and also included an examination of the reference list of previous reviews and research papers. Both authors screened all eligible records separately, and each article found was individually assessed for relevance by first screening the title and abstract. Duplicates were removed, as well as articles excluded due to their subject being out of scope for this review. The full texts of the remaining articles were carefully retrieved, and relevant data were extracted for further analysis.

Section 1: Psychopathology and pathophysiology of schizophrenia

Psychological and psychiatric aspects of schizophrenia

Schizophrenia is defined as a severe mental disorder that impacts more than 21 million individuals globally, which is related to chronic disability and to impaired cognitive, emotional, and social abilities (WHO, 2018). Symptoms of schizophrenia typically appear during adolescence or early adulthood (Orsolini, Pompili, & Volpe, 2022; Riedmüller & Müller, 2017) and include positive symptoms (delusional beliefs, hallucinations, and formal thought disorder), negative symptoms (alogia, anhedonia, avolition, and social isolation), and cognitive impairments, including deficits in areas such as attention, working memory, information processing rate, verbal and visuospatial acquisition, analytical reasoning, and cognitive adaptability (Marder & Cannon, 2019; McCutcheon, Reis Marques, & Howes, 2020; Moritz, Silverstein, Dietrichkeit, & Gallinat, 2020; Moura et al., 2022). In addition, dysfunctions in social cognition (comprising social reasoning, emotional intelligence, emotion detection from facial cues, and general emotion assessment) can markedly hinder the functional recovery of individuals with schizophrenia, due to the adverse effects on interpersonal interactions, community integration, and vocational performance (Green, Lee, & Wynn, 2020; McCutcheon et al., 2020). Concomitant occurrence with other mental disorders contributes to elevated

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incidence of symptom relapse, medical confinement, propensity for suicide, and family and social problems, as well as to a higher risk of negative short-term outcomes, including higher mortality rates (Correll et al., 2022; Drake, Xie, & McHugo, 2020; Plana-Ripoll et al., 2020).

Schizophrenia constitutes a syndrome that encompasses a compilation of clinical features stemming from diverse etiologies, etiopathogenesis, and psychopathological processes that may be involved (Barch, Karcher, & Moran, 2022; Insel, 2010; van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009). Nevertheless, numerous emerging neurobiological approaches have been recently proposed regarding the pathogenesis of schizophrenia (Chekroud et al., 2021; DeLisi, 2022; Nasrallah, 2022), such as the following: (i) genetic factors implicated in developmental disturbances at different periods of the fetal phase that influence brain programming, leading to the manifestation of prepsychotic features during prepubertal or pubertal stages (Ahmed et al., 2024; Boog, 2004); (ii) the neurodevelopmental model of schizophrenia, which integrates various non-genetic determinants, including perinatal challenges, immigration status, and traumatic experiences of maltreatment and neglect during the childhood stage, potentially mediating epigenetic modifications and determining structural and functional neurodevelopmental deviations (Powell, 2010); (iii) pathological changes in several brain areas, encompassing the frontal, parietal, temporal, and cingulate regions, as well as glial components, alongside heightened synaptic pruning and/or perturbed neuroplasticity capability (Chung & Cannon, 2015); (iv) immune dysfunction and neuroinflammation (Di Nicola et al., 2013; Kannan et al., 2017); and (v) various abnormalities in neurotransmitter pathways (Murray et al., 2004; Nyffeler, Meyer, Yee, Feldon, & Knuesel, 2006).

Recent findings corroborate the notion that schizophrenia is a multifactorial disorder resulting from inextricable interactions between cumulative and synergistic genetic and environmental factors (van Os, Kenis, & Rutten, 2010), with a highly variable and heterogeneous clinical presentation (Gur, 2022). Hence, owing to the absence of distinct demarcations and the large amount of involved etiological determinants, pathophysiological processes, and conjectures (Cannon, 2022; Taghia et al., 2018; Tandon et al., 2013), the perspective on schizophrenia has currently been expanded to a spectrum concept in the DSM-5-TR (APA, 2022), or as a principal psychotic disorder in the ICD-11 (Gaebel & Salveridou-Hof, 2022; WHO, 2019).

Pathophysiology of schizophrenia

Schizophrenia affects temporal brain regions, such as the hippocampus, which undergo development during prenatal periods and over an extended time frame before the initiation of psychosis (Zaidel, Esiri, & Harrison, 1997), impeding the multiplication of neurons and the establishment of axial linkages, and thereby resulting in limited CNS development (Kotsiri et al., 2023; Sanfilipo et al., 2000). The brain of schizophrenic subjects has shown expansions in the lateral ventricles and a diminished dimension in the frontal and the temporal lobes of the cortex, along with reduced hippocampal size (Sanfilipo et al., 2000; Thaker & Carpenter, 2001).

Schizophrenia is not considered a neuroinflammatory disease because there is no proof of astrogliosis and microglial activation (De Picker et al., 2021; Najjar, Pearlman, Alper, Najjar, & Devinsky, 2013; van Kesteren et al., 2017), or of lymphocytic infiltration (Bogerts et al., 2017; Schlaaff et al., 2020). However, several astrocytic and microglial indicators exhibit dysregulation in schizophrenia (Najjar & Pearlman, 2015; Najjar et al., 2013; Ramaker et al., 2017; Toker, Mancarci, Tripathy, & Pavlidis, 2018; Trépanier, Hopperton, Mizrahi, Mechawar, & Bazinet, 2016; van Kesteren et al., 2017). Microarray and RNA sequencing studies of the different brain regions have consistently shown upregulated or dysregulated expression of genes in pathways related to immune response and to inflammation within schizophrenia (Bergon et al., 2015; Chang et al., 2017; Fillman et al., 2013; Gamazon, Zwinderman, Cox, Denys, & Derks, 2019; Gandal, Zhang, et al., 2018; Hess et al., 2016; Hwang et al., 2013; Kim, Hwang, Lee, & Webster, 2016; Lanz et al., 2019; Lindholm Carlström et al., 2021; Mistry, Gillis, & Pavlidis, 2013). Neuropathologic studies have shown a downregulation of microglia-related transcripts in schizophrenia, which coincides with the upregulation of sequences associated with inflammation (Gandal, Haney et al., 2018; Snijders et al., 2021). It appears that in patients with schizophrenia, microglia could remain in a dormant state, inactive with respect to preserving cerebral homeostasis (Murphy & Weickert, 2021).

The consistent upregulation of immune indicators observed in schizophrenia suggests a potential involvement of viral infection and the BBB in both the etiology and neuropathology of this disorder (Webster, 2023). These dysregulated immune-related markers varied from study to study, although the following subset of genes is frequently upregulated. SERPINA3, a serpin peptidase inhibitor, is triggered by cytokines and possesses anti-inflammatory and antioxidant properties (Sánchez-Navarro, González-Soria, Caldiño-Bohn, & Bobadilla, 2021). Its upregulation in astrocytes at the BBB suggests that the astrocytes may be mounted against the infectious agent as a counteracting defensive mechanism, leading to an increase in interferon-induced transmembrane (IFITM) proteins within the endothelial cells (Murphy et al., 2020). IFITM proteins are recognized for their role in defending various viruses, inhibiting viral cytosolic access, and thereby impeding an initial stage of viral replication (Ren et al., 2020). GBP2 protects against viral infection in the innate immune system (Braun et al., 2019). CD163, a cysteine-rich scavenger receptor of macrophages, has multiple functions as an innate immune sensor and as an inducer of local inflammation (Etzerodt & Moestrup, 2013). Interestingly, after intracerebral hemorrhage, CD163 mediates the internalization into macrophages of haptoglobin-hemoglobin complexes, which is essential for the clearance of hemoglobin from erythrocytes lysis (Garton, Keep, Hua, & Xi, 2017). Table 1 shows the major immune-related dysregulated markers in schizophrenia.

Cytokines released by innate and adaptive immune cells act as signaling molecules and exert influence on the CNS and also on the peripheral immune system. In schizophrenia, changes in peripheral cytokine may affect the brain through multiple mechanisms (Khandaker & Dantzer, 2016). Certain cytokines, such as IL-6, IL-1β, IL-8, IL-18, and TNF-α, are humoral host defense factors produced in response to infection or to tissue injury and stimulate the acute phase response, hematopoiesis, and immune processes (e.g., inflammation and interferon-γ production) (Bernhard et al., 2021; Ren & Torres, 2009; Tanaka, Narazaki, & Kishimoto, 2014; Zhang & An, 2007). The genes responsible for these factors manifest expression in astrocytes, perivascular macrophages, and vascular endothelial cells, suggesting BBB involvement and a possible aberrant interplay with the peripheral immune system in schizophrenia (Cai et al., 2020; Hwang et al., 2013; Kim, Hwang, Lee, et al., 2016; Murphy et al., 2020; Purves-Tyson et al., 2021; Siegel, Sengupta, Edelson, Lewis, & Volk, 2014; Volk et al., 2015). Murphy &

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Table 1. Immune-related dysregulated markers in schizophrenia

Markers	DEGs	Biological function	References
Serpin Family A Members 3	SERPINA3	Anti-inflammatory. Antioxidant.	Kim, Hwang, Lee, et al. (2016) Trépanier et al. (2016) Zhang et al. (2016) Purves-Tyson et al. (2020) Purves-Tyson et al. (2021)
Guanylate-binding protein 2	GBP2	Viral infective defense.	Merikangas et al. (2022)
Interferon-induced transmembrane proteins	IFITM1,2,3	Viral infective defense.	Siegel et al. (2014) Volk et al. (2015) Trépanier et al. (2016) Merikangas et al. (2022)
Scavenger receptor of macrophages	CD163	Innate immune sensor. Local inflammation.	Kim, Hwang, Lee, et al. (2016) Cai et al. (2020) Purves-Tyson et al. (2020)
Soluble intercellular adhesion molecule–1	ICAM–1	Leukocyte adhesion. Leukocyte migration.	Cai et al. (2020) Purves-Tyson et al. (2020)
Complement components	C4,C3,C1qA	Microbial defense. Inflammation. Chemoattraction.	Purves-Tyson et al. (2020)
C-reactive protein	CRP	Recognizing pathogens. Opsonization. Complement activation.	Dickerson et al. (2007) Dickerson et al. (2013) Khandeker et al. (2014a) Miller et al. (2014) Baumeister et al. (2016) Fernandes et al. (2016) Johnsen et al. (2016)

Note: DEGs: differentially expressed genes.

Weickert (2021) postulated that the microglia do not mount a typical inflammatory response, suggesting that the immune response may be persistent and even due to previous exposure so that microglia would be depleted. Table 2 shows cytokine alterations observed in schizophrenia.

Without any doubt, one of the most revealing neuropathologic findings within the pathophysiology of schizophrenia is the deficit of GABAergic interneurons (Dienel & Lewis, 2019). Inverse correlations between elevated cytokine levels and higher IFITM mRNA levels, as well as GABAergic neuron markers in the frontal cortex, have been reported by several authors (Fillman et al., 2013; Siegel et al., 2014). Moreover, in the hippocampal region, the gene expression modules associated with immunity and inflammation also exhibit an inverse correlation with GABAergic indicators (Hwang et al., 2013; Kim, Hwang, Webster, & Lee, 2016). Several upregulated genes are linked to the response to viral infection, which suggests that the immune response induced by these pathogenic microorganisms is not exclusively related to schizophrenia, but also to a decrease in GABAergic interneurons (Kim, Hwang, Webster, et al., 2016). In animal models, the maternal immune activation in utero by poly(I:C) or LPS inoculation results in increased cytokine concentrations inside the fetal cerebrum (Meyer et al., 2006), which could persist postnatally (Garay, Hsiao, Patterson, & McAllister, 2013; Purves-Tyson et al., 2021), affecting the neural circuit development process (Meyer, Nyffeler, Yee, Knuesel, & Feldon, 2008; Richetto, Calabrese, Riva, & Meyer, 2014; Warm, Schroer, & Sinning, 2022). Other upregulated genes in schizophrenia include midbrain immune-related transcripts that may contribute to the dopaminergic abnormalities observed in the disease (Purves-Tyson et al., 2021). The top genome-wide association studies implicating gene complement components, such as C4, C3, and C1qA, are also frequently identified as being upregulated in the brains of individuals with schizophrenia (Gamazon et al., 2019; Gandal, Zhang, et al., 2018; Lindholm Carlström et al., 2021; Wang, Liu, et al., 2018). The correlation between the HLA area and schizophrenia is reinforced by the complement component C4 gene, which actively participates in synaptic trimming throughout postnatal growth (Sekar et al., 2016).

In summary, according to Webster (2023), the pleiotropic effects of dysregulated immune molecules, which also contribute to various crucial processes such as cerebral development, neural plasticity, and homeostasis, may play an important role in the pathophysiology of schizophrenia compared to immune activation by microbial infection. Nevertheless, infection occurring during vulnerable periods of development in genetically predisposed subjects could indefinitely disrupt the typical expression of these pleiotropic immune molecules, thus increasing susceptibility to successive stress on brain development and function (Borrego-Ruiz & Borrego, 2024b).

Section 2: Virus infection and schizophrenia

Schizophrenia and other psychiatric conditions may eventually be activated by different viral infections, but the precise mechanisms are yet unknown. Maternal viral infections occurring in the first stages of gestation may potentially contribute to the onset of psychiatric conditions in the progeny during later developmental stages (Kotsiri et al., 2023). We comprehensively review the literature addressing the role of several neurotropic viruses, such as herpesviruses, influenza virus, Borna disease virus, and coronaviruses, on the onset of schizophrenia.

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Table 2. Cytokine alterations in schizophrenia

Cytokines	Findings	References
IL–6	Increased in first episode of schizophrenia. Associated with schizophrenia symptoms and cognitive impairment.	Miller et al. (2011); Khandaker, Pearson, et al. (2014a) Volk et al. (2015) Goldsmith et al. (2016) Kim, Hwang, Lee, et al. (2016) Zhang et al. (2016) Misiak et al. (2021) Purves-Tyson et al. (2021) Herniman et al. (2023)
IL–1β	Decreased in first episode of schizophrenia. Increased during acute episode.	Miller et al. (2011) Noto et al. (2015) Zhang et al. (2016) Purves-Tyson et al. (2021)
sIL–2R	Increased in schizophrenia.	Goldsmith et al. (2016) Wang, Lin, et al. (2018)
IL–12	Increased in chronic schizophrenia.	Wang, Lin, et al. (2018)
IL–1RA	Increased in acute schizophrenia. Role in the pathophysiology of schizophrenia.	Goldsmith et al. (2016) Lin et al. (2018) Zhou et al. (2019)
IL–8	Increased in CSF of schizophrenia patients. Associated with schizophrenia prognosis and treatment response.	Wang, Lin, et al. (2018) Ben Afia et al. (2020) Tsai (2021)
IL–2	Related to the pathogenesis of schizophrenia.	Huang et al. (2022) Shangguan et al. (2023) Ozdilli et al. (2024)
IL–18	Elevated in first episode and chronic schizophrenia. Associated with schizophrenia symptoms. Activation of the inflammasome.	Syed et al. (2021) Szabo et al. (2022) Guan et al. (2023)
IL–10/IL–4	Related to symptoms of schizophrenia.	Şimşek et al. (2016)
IL–17/IL–23	Related to activation of Th17 cells pathway.	Debnath & Berk (2017)
TGF-β1	Elevated in psychotic episode. Linked to impairments in brain structure and function in schizophrenia.	Miller et al. (2011) Pan et al. (2022)
IFN-γ	Increased in chronic schizophrenia.	Wang, Lin, et al. (2018) Herniman et al. (2023)
TNF-α	Increased in schizophrenia. Central mediator of neuroinflammation.	Baumeister et al. (2016) Goldsmith et al. (2016) Kim, Hwang, Lee, et al. (2016) Wang, Lin, et al. (2018) Purves-Tyson et al. (2021) Herniman et al. (2023)

Note: sIL-2R: soluble IL-2 receptor; IL-1RA: IL-1 receptor antagonist; CSF: cerebrospinal fluid; TGF-β1: transforming growth factor beta 1. IFN-γ: Interferon-gamma; TNF-α: tumor necrosis factor-alpha.

Herpesviruses

Herpesviruses consist of double-stranded DNA viruses (family *Herpesviridae*) that cause persistent latent infections, which can periodically reactivate and lead to disease in susceptible populations (Croen, 1991). The herpesviruses that are able to infect humans are divided into three groups on the basis of their genetic and antigenic characteristics: the alpha group includes herpes simplex virus 1 (HSV-1, or human herpesvirus 1, HHV-1), herpes simplex virus 2 (HSV-2, or HHV-2), and varicella-zoster virus (VZV, or HHV-3); the beta group comprises cytomegalovirus (CMV or HHV-5), human herpesvirus 6 (HHV-6), and human herpesvirus 7 (HHV-7); and the gamma group consists of Epstein–Barr virus (EBV or HHV-4), and Kaposi's sarcoma-associated herpesvirus (HHV-8) (Gatherer et al., 2021). Among them, HSV-1, CMV, and EBV have been recognized for inducing moderate symptoms in adults, but for provoking more severe disease manifestations in neonates or immunosuppressed subjects. In such vulnerable people, immune deficiency leads to a loss of viral replication regulation, resulting in tissue harm and, in more extreme instances, terminal organ pathology and mortality (Griffiths & Reeves, 2021; Griffiths, Baraniak, & Reeves, 2015).

Herpes simplex virus

Herpes simplex virus (HSV) is a common infection that is spread primarily through skin-to-skin contact and can cause painful blisters or ulcers (Kriebs, 2008). Its prevalence remains within populations, escalating with age, reaching 90% or higher in certain geographic areas (Prasad et al., 2012). There are two types of HSV: HSV-1 spreads primarily through oral contact and causes infections inside or around the mouth (oral herpes), but it can also cause genital herpes. Type 2 (HSV-2) is spread through sexual contact and provokes genital herpes.

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HSV-1 often induces primary infections in human mucosal epithelial cells (Ryder, Jin, McNulty, Grulich, & Donovan, 2009), while severe corneal keratitis and encephalitis are less common (Harkness, Kader, & DeLuca, 2014; James & Kimberlin, 2015; Marcocci et al., 2020; Steiner, Kennedy, & Pachner, 2007). After initial mucosal infections, which may be asymptomatic, viral particles enter sensory neurons through nerve terminals and travel retrogradely along axons, establishing a latent state in neuronal cell bodies that can persist for the entire lifetime of the host (Harkness et al., 2014; Nicoll, Proença, & Efstathiou, 2012; Steiner et al., 2007). The viral DNA may endure within the neuronal cell body in an episomal state, indicating its independence from integration into the host cell chromosome, instead remaining suspended within the cytoplasm (St Leger, Koelle, Kinchington, & Verjans, 2021). The state of latency is maintained through a complex interplay of host and viral factors, with the virus potentially reactivating later in life via sensory nerves, returning to its initial entry site (Shimomura & Higaki, 2011). Triggers recognized to initiate reactivation comprise aging, stress, immunosuppression, and co-infection with other viruses (Yan et al., 2020). HSV-1 reactivation rarely causes encephalitis, but mutations in toll-like receptors and neuronal immunity increase the risk (Lafaille et al., 2019). Newborns of mothers with HSV-1 genital infections may develop encephalitis or multi-organ infections (James & Kimberlin, 2015). In the cerebrum, however, HSV-1 typically results in a persistent infection regulated by the CNS immune system (Marcocci et al., 2020).

Initial analyses indicated an increased prevalence of seropositivity for antibodies directed against HSV-2, cytomegalovirus, and *T. gondii* in subjects with diagnosed cognitive decline (Nimgaonkar et al., 2016). There is a long history of research linking HSV-1 to mental disorders (Dickerson et al., 2003; Kotsiri et al., 2023; Prasad et al., 2012; Yolken, 2004), but several studies have not found heightened HSV-1 serum antibodies from subjects with schizophrenia (Aiello et al., 2006; Katan et al., 2013), and a current meta-analysis suggested a divergence between cases and controls, showing a small to medium effect size (Dickerson, Schroeder, Nimgaonkar, Gold, & Yolken, 2020). Additional supportive evidence includes brain imaging studies showing diminished gray matter volume in HSV-1 seropositive subjects (Prasad et al., 2011; Schretlen et al., 2010), and enhancement in the cognitive function of HSV-1 seropositive individuals with schizophrenia who underwent extended courses of high-dose antiviral treatment (Bhatia et al., 2018; Prasad et al., 2013). More recently, HSV-1 seropositivity was associated with suicidal behavior in a cohort of Danish blood donors (Nissen et al., 2019).

While the evidence for HSV-1 infection in schizophrenia versus control populations is inconclusive (de Witte et al., 2015), there is compelling data suggesting that HSV-1 infection may play a role in cognitive decline in the context of schizophrenia. Two recent systematic reviews and a meta-analysis have indicated that HSV-1 negatively impacts the neurocognitive function of schizophrenic subjects, with small to moderate effect sizes (Tucker & Bertke, 2019; Dickerson et al., 2020).

Cytomegalovirus

Human cytomegalovirus (CMV) belongs to the family *Orthoherpesviridae* (*Betaherpesvirinae* subfamily). Failure to achieve complete viral clearance after primary infection results in long-lasting infection marked by intervals of latency and reactivation in approximately 80% of the general population worldwide, with significant differences by age, sex, and geographic area (Goodrum, 2016; Zuhair et al., 2019). Primary infection with CMV frequently takes place during childhood via exposure to oral or genital secretions (Petersen, Patel, Abraham, Quinn, & Tobian, 2021).

Primary infections in immunocompetent subjects may be subclinic or generate nonspecific symptoms like a slight fever or a mononucleosis syndrome, because CMV harbors a large number of genes that encode for evasion of the host's innate and adaptive immune mechanisms, such as attenuation of type I interferon (IFN-I) production, downregulation of the activity of natural killer cell, inhibition of MHC class I and II antigen presentation, and interference with the proliferation of T cells (Griffiths & Reeves, 2021; Mishra, Kumar, Ingle, & Kumar, 2020; Patro, 2019; Ye et al., 2020). This virus-host interaction can modify host immunity gradually, as a significant proportion of the immune system is directed against CMV antigens (Picarda & Benedict, 2018), and frequent viral reactivation may detrimentally affect the immunity of the host to infections by other microorganisms (Furman et al., 2015; Martinez et al., 2021; Nicoli et al., 2022; Wall et al., 2021). Additional evidence suggests that CMV may protect against heterologous infections and enhance vaccine efficacy through sustained immune activation, with minimal impact in healthy populations (Furman et al., 2015; Forte, Zhang, Thorp, & Hummel, 2020). However, repeated episodes of CMV reactivation can result in a decrease in T cells and an increase in CMV-specific T cells, especially effector memory cells (Ford et al., 2020), leading to disease or tissue damage in immunocompromised populations, and potentially in patients with psychiatric disorders (Griffiths & Reeves, 2021; Savitz & Yolken, 2023).

The conceptualization that CMV might be implicated in the development of schizophrenia began to develop in the 1970s, with the first investigations based on serological studies (Yolken & Torrey, 1995). Later, other serological studies included socioeconomic and geographical variables, and also individuals experiencing the initial onset or the first episode of schizophrenia (Torrey et al., 2006). Furthermore, a cohort study revealed that symptomatic CMV infection of the CNS in early life conferred a higher risk of developing schizophrenia (Dalman et al., 2008). Besides, in patients with schizophrenia, higher CMV IgG titers correlated with reduced right hippocampal volume and diminished episodic verbal memory (Houenou et al., 2014). In contrast, several studies have reported lower cognitive function in CMV-seropositive schizophrenia patients (Dickerson et al., 2014; Shirts et al., 2008). More recently, Moya Lacasa et al. (2021) did not find a significant difference in the prevalence of CMV seropositivity and scores in schizophrenia and other nonaffective psychotic disorders compared to healthy controls. Clinical heterogeneity and several confounding factors, including age, medication, as well as socioeconomic and habitat status, may potentially contribute to the conflicting results between studies (Bolu et al., 2016; Zheng & Savitz, 2023). The detection of CMV nucleic acid in patients with schizophrenia using hybridization or polymerase chain reaction techniques has improved the sensitivity of viral detection in postmortem brain studies and strengthened the association between viral infection and schizophrenia (Cassedy, Parle-McDermott, & O'Kennedy, 2021). Nevertheless, it is noteworthy that the likelihood of detecting CMV transcripts a priori is constrained due to the typically low levels of RNA/DNA associated with latent CMV infection (Shnayder et al., 2018), particularly considering that postmortem investigations frequently utilize aged and fixed brain tissue. Furthermore, the nondetection of genetic material of the virus in postmortem samples does not conclusively dismiss the potential for CMV to contribute to the pathology only in the initial phases of psychiatric disorders, or for CMV to exert pathological effects through immune activation without direct cerebral infection.

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Brain-derived cells, such as BBB endothelial cells, vascular pericytes, myeloid lineage cells, astrocytes, glia, and neurons, have been shown to be completely permissive to CMV infection and replication (Alcendor, Charest, Zhu, Vigil, & Knobel, 2012; Luo, Schwartz, & Fortunato, 2008; Tsutsui, Kosugi, & Kawasaki, 2005). Hence, it is plausible that CMV itself or the inflammation linked to repeated CMV reactivation can result in irregularities within cerebral morphology and function. A primary question is whether CMV can infect brain cells *in vivo* and induce the symptoms of psychosis, including schizophrenia. The BBB constitutes a protective barrier that plays a pivotal role in restricting the unconstrained movement of large molecules, like viral particles, from the blood stream into the CSF and the cells of the CNS. In this regard, several pathophysiological mechanisms may be involved. First, CMV particles in the circulation attain and infect brain microvascular endothelial cells, thereby gaining access to the CNS. In addition, CMV could potentially weaken the tight junctions of the BBB, predisposing the parenchyma to a pathogenesis driven by the immune system. Primary and latent CMV infections induce a systemic inflammatory response and the expression of chemokines and cytokines (e.g., MCP-1, and IFN-γ) (Hamilton, Scott, Naing, & Rawlinson, 2013; Lurain et al., 2013; van de Berg et al., 2010), which can decrease the expression of tight junction protein and increase BBB permeability (Chai, She, Huang, & Fu, 2015). Upon the entry of peripheral cytokines into the brain, the function of glial cells may be impaired, resulting in axonal demyelination and neural degeneration (Hammond, Marsh, & Stevens, 2019; Mechawar & Savitz, 2016; Wohleb, Franklin, Iwata, & Duman, 2016). Furthermore, CMV could potentially compromise the host immune response and trigger host immunosuppression, thereby potentially facilitating the cellular senescence and the neuropathological changes that resemble the aging process (Naniche & Oldstone, 2000; Salminen, 2021). Additionally, CMV can induce autoimmunity, and thus neuroinflammation, mediated by the autoimmune process (Halenius & Hengel, 2014; Vanheusden et al., 2017).

Although a significant and strong relationship between CMV and schizophrenia may not be fully established, CMV infection may implicate a greater risk of negatively impacting cognitive function in the context of schizophrenia.

Epstein–Barr virus

The gamma herpesvirus EBV is usually transmitted orally during childhood or adolescence, and the primary infection occurs in epithelial cells and is followed by infection of B lymphocytes (Vetsika & Callan, 2004). Primary infection in infants and children is associated with nonspecific respiratory symptoms, whereas infection in adolescents and young adults manifests the symptoms of infectious mononucleosis, such as fever, adenopathy, and pharyngitis (Leung, Lam, & Barankin, 2024). It seems that different age-dependent symptomatology may be related to hormonal changes that occur during puberty (Rostgaard et al., 2019). After the resolution of the acute infection, the virus can establish lifelong latency in B lymphocytes and epithelial cells, with subsequent reactivation episodes during life (Kempkes & Robertson, 2015). Long-term EBV infection has been associated with neoplastic diseases, including B-cell lymphoma, nasopharyngeal carcinoma, and gastric cancer (Dugan, Coleman, & Haverkos, 2019). In addition, this infection leads to alterations in the host immune system and is also related to several autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, and systemic sclerosis (Bjornevik et al., 2022; Houen & Trier, 2021). Acute infection is characterized by the production of early antigen (EA), antibodies (IgM and IgG) to viral capsid antigen (VCA), antibodies to EBV nuclear antigen (EBNA), and heterophilic antibodies (De Paschale & Clerici, 2012).

An increased incidence of psychotic experiences in adolescents who were infected with EBV during childhood supports the potential relationship between EBV infection and schizophrenia (Khandaker, Stochl, Zammit, Lewis, & Jones, 2014b). Individuals with schizophrenia had an aberrant response to EBV infection, characterized by increased levels of reactivity to EBV-VCA, but not to EBNA and total viral antigens. When combined with genetic risks for schizophrenia, individuals with the aberrant response to EBV were more likely to be diagnosed with schizophrenia than individuals without these risk factors (Dickerson et al., 2019). Moreover, schizophrenic patients with elevated levels of EBV antibodies presented lower levels of social cognition (Dickerson et al., 2021).

In essence, EBV has been linked to schizophrenia on the basis of psychotic experiences in adolescence among individuals with a history of EBV infection in childhood, as well as the higher likelihood of schizophrenia diagnosis in those with an aberrant response to EBV.

Influenza virus

The influenza virus, belonging to the family *Orthomyxoviridae*, represents an enveloped virus with segmented negative-sense single-stranded RNA segments and includes three genera: influenza A, B, and C (Payne, 2023), of which influenza A is responsible for pandemics (Kępińska et al., 2020) and has been historically associated with schizophrenia and psychotic symptoms. Influenza A viruses are categorized into subtypes on the basis of the antigenic properties of hemagglutinin (H) and neuraminidase (N). Specifically, the avian-derived strains and H5N1 virus are neurotropic, whereas H1N1 is non-neurotropic (Jang et al., 2009; Sadasivan, Zanin, O'Brien, Schultz-Cherry, & Smeyne, 2015). While maternal infection with microorganisms has been reported as a risk for schizophrenia (Brown & Patterson, 2011), there is no clear evidence for transplacental transmission of influenza virus into the offspring brain (Egorova, Egorov, & Zabrodskaya, 2024; Lieberman, Bagdasarian, Thomas, & Van De Ven, 2011; Shi, Tu, & Patterson, 2005), so more relevant are the effects of infection-induced maternal immune activation on the developing brain (Egorova et al., 2024; Brown & Meyer, 2018).

In animal models, maternal H1N1 infection provokes abnormalities in offspring at several levels: (i) gene expression; (ii) protein expression; (iii) brain structure; (iv) behavior; (v) neurotransmitter levels; and (vi) placental development. In humans, there is evidence that early maternal immune activation during pregnancy affects neonatal brain development and behavior (Lieberman et al., 2011). High maternal IL-6 and cortisol levels predicted larger neonatal amygdala volume and connectivity, as well as higher internalizing behavior, which in turn predicted poorer impulse control in the early years of life (Graham et al., 2018; 2019).

Fatemi et al. (2012) reported that brain gene expression was altered in offspring infected at multiple embryonic times. In the first week, prenatal infection-induced gene expression changes associated with hypoxia, inflammation, and schizophrenia in the frontal cortex and hippocampus of exposed offspring. At 16 days, prenatal H1N1 infection was associated with gene changes related to myelination in the cerebellum and hippocampus, such as *mag, plp1, mal, mbp, mobp, mog, ncam1*, and *rgs4.* Several of these genes are known to be involved in schizophrenia (Fatemi et al., 2009; Van Campen et al., 2020). At 3 weeks, microarray data showed a high number of

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dysregulated genes in the frontal cortex, hippocampus, and cerebellum of virus-exposed offspring, such as *Sema3a*, *Trfr2*, and *Vldlr*, which have also been implicated in schizophrenia (Fatemi et al., 2008). Further studies have shown that mice infected with influenza virus during pregnancy have lower hemagglutination inhibition and neutralizing antibody titers, because of a downregulation of B cell metabolism and post-translational modification systems (Swieboda et al., 2020).

Neuronal nitric oxide synthase (nNOS) produces nitric oxide (NO), a harmful molecule involved in fetal brain injury under hypoxia-ischemia conditions (Kneeland & Fatemi, 2013). In the offspring of mice infected with H1N1 on day 9, nNOS was shown to increase by 147% on postnatal day 35, with a final decrease of 29% on postnatal day 56 in rostral brain areas. In addition, nNOS levels in the midbrain zones decreased by 27% at postnatal day 56 (Fatemi, Cuadra, El-Fakahany, Sidwell, & Thuras, 2000). Upregulation of NO production has been suggested as a trigger for several human neurological disorders, including Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, and schizophrenia (Iova et al., 2023). The suggested mechanisms for its neurotoxicity are mainly centered on the increased amounts of NO produced in the brain, which may lead to decoding of neuronal dysfunction associated with neuronal death. Moreover, the extracellular secretory glycoprotein reelin plays an important role during development and also in adulthood, such as maintaining synaptic function. Several neuropsychiatric disorders, including schizophrenia, share a common feature of abnormal reelin expression in the brain (Kneeland & Fatemi, 2013). In the brains of neonatal offspring of virus-exposed mice, reelin synthesis is reduced, reflecting abnormal neuronal migration and reduced synaptic plasticity. The mechanisms for abnormal reelin expression are currently unknown, although several mechanisms have been proposed, including mutations, hypermethylation of the gene promoter, miRNA silencing, FMRP underexpression, and abnormal processing (Folsom & Fatemi, 2013).

Several brain abnormalities in mice have been associated with influenza virus infection, including increases in fractional anisotropy within the right middle cerebellar peduncle, pyramidal cell density, and brain volume, as well as decreases in area measurements within the cerebral cortex, unilateral brain hemispheres, and hippocampal region (Fatemi et al., 2002; Kneeland & Fatemi, 2013). In rhesus monkeys, maternal inflammatory responses to influenza infection reduced gray matter throughout most of the cortex, and decreased white matter in the parietal cortex of the fetal brain (Short et al., 2010).

Behavioral abnormalities, such as the acoustic startle response and head twitch response, have also been observed in the offspring of virus-exposed mice (Moreno et al., 2011; Shi et al., 2003), signs typically induced by 5-HT2A agonists. In fact, the animals had increased 5-HT2A receptor expression in the frontal cortex and reduced levels of serotonin in the cerebellum (Moreno et al., 2011). In addition, several authors have reported neurotransmitter abnormalities in the offspring of virus-exposed mice, such as altered levels of taurine, serotonin, and GABA in the cerebellar region, but not in dopamine (Fatemi et al., 2008; 2017; Winter et al., 2008). Recently, Perez-Palomar, Erdozain, Erkizia-Santamaría, Ortega, & Meana (2023) reported that prenatal viral infection in mice was mimicked by poly(I:C) administration, which resulted in decreased extracellular dopamine concentrations compared to controls, concluding that the poly(I:C)-based model reproduces catecholamine phenotypes reported in schizophrenia.

Placental giant trophoblast cells are producers of hormones and cytokines that can influence maternal physiology in response to the fetal allograft (Elgueta, Murgas, Riquelme, Yang, & Cancino, 2022). Infected placental tissue showed cytoarchitectural disorganization (Antonson et al., 2021; Van Campen et al., 2020) and an increased presence of immune cells (Fatemi et al., 2012). High levels of gene dysregulation have also been observed in the placenta of pregnant mice with influenza virus infection (Fatemi et al., 2012; Van Campen et al., 2020); these dysregulated placental genes significantly influence apoptosis, hypoxia, inflammation, immune response, and psychiatric disorders.

Both neurotropic and non-neurotropic strains of the influenza virus can induce microglial activation and contribute to inflammation (Sadasivan, Zanin, O'Brien, Schultz-Cherry, & Smeyne, 2015; Wang et al., 2008). The innate immune response to influenza infection is mediated by antiviral IFN-stimulated genes (ISGs) (Schoggins, 2019), including MXA (prevents virus nuclear import), IFITM3 (blocks host-virus cell membrane fusion), and viperin (blocks influenza virus release) (Iwasaki & Pillai, 2014). In addition, innate immune mechanisms also promote disease resistance of host tissues, and prepare the microglia to respond appropriately to a novel stimulus (Kępińska et al., 2020). Furthermore, influenza virus infection may prime microglia for increased activation, potentially increasing the risk of developing psychotic symptoms (Salam, Borsini, & Zunszain, 2018). Moreover, Littauer et al. (2017) found that influenza virus infection resulted in dysregulation of inflammatory responses and the immune responses significantly correlated with changes in hormone synthesis and regulation. Dysregulation of progesterone, COX-2, PGE2, and PGF2α expression was accompanied by remodeling of placental architecture and upregulation of matrix metalloproteinase-9, an indicator of placental spongiotrophoblast degradation, early after infection.

Thus, converging evidence suggests that influenza virus infection possesses a variety of effects on prenatal and postnatal processes that could lead to an increased risk of developing schizophrenia or acute psychosis in adulthood.

Borna disease virus

Borna disease virus (BoDV) is a negative-sense, single-stranded RNA virus of the *Bornaviridae* family whose specific hosts are horses, sheep, poultry, and cattle (Rubbenstroth et al., 2021). Several properties of BoDV make it a potential agent of human psychiatric disorders, such as: (i) it infects neurons; (ii) it has a broad host range; (iii) it presents a high tropism for the limbic circuit, which regulates behavior, memory, and emotion, and appears to play a key role in the etiopathology of several human psychiatric disorders; and (iv) experimental BoDV infection in animals can result in various symptoms related to aggression, hyperactivity, apathy, or motor symptoms that resemble core features of human psychiatric disorders, such as depression or schizophrenia (Briese, Hornig, & Lipkin, 1999). In addition, a neuronal route of BoDV transmission has been demonstrated in animals, involving the olfactory nerve in the nasal mucosa (Kupke et al., 2019).

As a neurotropic virus, BoDV infects the CNS of animals, causing neuronal degeneration and neurological disorders such as encephalitis, meningitis, various neurodevelopmental movement disorders, and behavioral disorders with schizophrenia-like manifestations (Taieb, Baleyte, Mazet, & Fillet, 2001). For example, Ovanesov et al. (2008) reported that neonatal BoDV infection of

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the rat brain was associated with microglial activation and neuronal damage. Stimulated microglia expressed MHC I, MHC II, and IL-6, showing increased secretion of TNF-α and of IL-1, which have been suggested as potential molecular biomarkers for the development of schizophrenia.

Several works have studied whether BoDV disease can directly cause schizophrenic disorders in humans (Arias et al., 2012; Azami, Jalilian, Khorshidi, Mohammadi, & Tardeh, 2018; Chen et al., 1999; Mazaheri-Tehrani et al., 2014; Sansom, 2000), or other mental conditions, such as mood-related disorders and depression (Hornig et al., 2012; Kim et al., 2003; Selten et al., 2000). In contrast, Iwata et al. (1998) measured BoDV p24 RNA in peripheral blood monocytes from psychiatric patients, and they did not find a relationship between virus infection and mood or schizophrenia. Similar results were reported in several countries, where BoDV infection and pathogenesis of schizophrenia were not found (Hornig et al., 2012; Miranda et al., 2006; Selten et al., 2000; Soltani, Mohammadzadeh, Makvandi, Pakseresht, & Samarbaf-Zadeh, 2016).

In summary, the inconsistency in the results may be due to different geographic and genetic factors such as HLA, which was included in different studies (Na, Tae, Song, & Kim, 2009), as well as to the different techniques used for virus detection (Wolff, Heins, Pauli, Burger, & Kurth, 2006).

Coronaviruses

Coronaviridae is a family of enveloped, positive-sense single-stranded RNA viruses described in the decade of the 1960s (Mahase, 2020). Human coronavirus (HCoVs) 229E, OC43, HKU1, and NL63 cause upper respiratory tract infections or the "common cold" in a typical winter season (Cui, Li, & Shi, 2019; Su et al., 2016; Woo et al., 2023). Since the turn of the 21st century, three highly virulent coronavirus strains have emerged. SARS-CoV, in 2002–2003, was identified in Guangdong (China), and subsequently spread to 17 countries, causing over 8000 cases (de Wit, van Doremalen, Falzarano, & Munster, 2016; Zhong et al., 2003). Later, Middle East Respiratory Syndrome (MERS), caused by MERS coronavirus (MERS-CoV), was reported between 2012 and 2017, primarily in Middle Eastern countries (Zaki, van Boheemen, Bestebroer, Osterhaus, & Fouchier, 2012) and later in the Republic of Korea (de Wit et al., 2016); both MERS outbreaks caused a total of approximately 2500 cases. Bats and camels were suggested to be reservoirs for SARS-CoV and MERS-CoV, respectively. The newest member of the HCoVs, known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is responsible for the COVID-19 pandemic that affected more than 130 million people worldwide. While the zoonotic aspects of SARS-CoV-2 are still under investigation, bats also appear to be its animal reservoir (Ahmad et al., 2020; Cui et al., 2019).

A key feature of these virulent HCoVs is their ability to replicate in epithelial cells and pneumocytes in the human lower respiratory tract, causing pneumonia (Cui et al., 2019; de Wit et al., 2016) and, in severe cases, acute respiratory distress syndrome. However, SARS and MERS can infect the nervous system (Netland, Meyerholz, Moore, Cassell, & Perlman, 2008), causing peripheral neuropathies, encephalopathies, motor deficits, paralysis, and coma (Arabi et al., 2015; Wu et al., 2020), as well as psychiatric manifestations such as depression, anxiety, mood alterations, mania, and psychosis (Rogers et al., 2020; Severance et al., 2011). Because the unique link between HCoVs infection and psychosis is inflammation, it is logical to think that COVID-19 infection, which induces a massive inflammatory response (Steardo, Steardo, Zorec, & Verkhratsky, 2020), could produce more psychotic symptoms (Graham et al., 2021; Mazza et al., 2021; Taquet, Geddes, Husain, Luciano, & Harrison, 2021).

SARS-CoV-2 has a similar neurotropism to SARS-CoV and enters into the CNS through the circulatory route (Baig, 2020) and via peripheral neurons, to reach the brain (Wu et al., 2020). Another pathway, the cribriform plate of the ethmoid bone near the olfactory bulb, has also been suggested (Pourfridoni & Askarpour, 2022). In addition, the isolation of SARS-CoV-2 from CSF may suggest a direct infection of the neurological system causing nerve damage (Rentero et al., 2020). The two SARS-CoV viruses share the same adsorption host cell receptor, angiotensin-converting enzyme 2 (ACE2), extensively expressed in neurons and glial cells (Steardo et al., 2020), although the binding affinity for SARS-CoV-2 is 10 to 20 times higher than that of SARS-CoV (Hoffmann et al., 2020; Wrapp et al., 2020). Binding of SARS-CoV-2 to ACE2 and subsequent viral endocytosis dysregulate the angiotensin system, leading to the loss of ACE2-mediated health protection and adverse systemic effects by releasing TNF-α, IL-6, and other cytokine mediators, which lead to the cytokine storm in COVID-19 (Davies, Adlimoghaddam, & Albensi, 2021; Gheblawi et al., 2020).

A number of pathways associated with COVID-19 overlap with those that may be involved in the pathophysiology of schizophrenia, including cellular response to dopamine, IL-1 signaling, T helper cell differentiation, and immunological synapse formation (Moni, Lin, Quinn, & Eapen, 2021). In both schizophrenia and COVID-19, as a consequence of the inflammatory process, there is an increase in levels of kynurenic acid, which acts as an anti-excitotoxic factor (Collier, Zhang, Scrutton, & Giorgini, 2021). In addition, COVID-19 may induce psychosis through the development of the anti-N-methyl-D-aspartate (NMDA) receptor encephalitis, according to the theory of molecular mimicry of the SARS-CoV-2 (Payus et al., 2022; Vasilevska et al., 2021), and increase the activity of the midbrain dopamine neurons (Erhardt, Schwieler, Nilsson, Linderholm, & Engberg, 2007). Interestingly, activation of monocytes by toll-like receptor 3 (TLR-3) and depletion of natural killer cells associated with an early antiviral response has been shown to occur in both schizophrenia and anti-NMDA receptor encephalitis (Karpiński, Samochowiec, Frydecka, Sąsiadek, & Misiak, 2018; Müller & Schwarz, 2010; Müller et al., 2012). In COVID-19, the TLR-3 pathway is linked to a tissue-destructive senescence-associated secretory phenotype that is related to short- and long-term complications (Tripathi et al., 2021).

C-reactive protein (CRP) has been studied as a potential peripheral measure of immunologic activation that may have a causal or precipitating function in schizophreniform psychosis (Fond, Lançon, Auquier, & Boyer, 2018). HCoVs possess neuroinvasive properties as a result of either autoimmune responses or viral replication, leading to the hypothesis that they cause neuroinflammation and CNS penetration in psychotic disorders (Ferrando et al., 2020). In fact, COVID-19 is involved in several inflammatory changes, including disruption of the Th1/Th2 and IL-2 balances, and alteration of Tregs (Aleebrahim-Dehkordi et al., 2022).

Although it has been suggested that an increased risk of schizophrenia in the offspring is associated with maternal infection in earlier trimesters (Brown et al., 2000), data on maternal and neonatal outcomes of COVID-19 infection are limited (Ashraf et al., 2020; Islam et al., 2020; Kulaga & Miller, 2021). Because so little time has elapsed since the beginning of the COVID-19 pandemic, it is too early to link cases of schizophrenia to SARS-CoV-2. This possibility is more likely for people who were exposed to this virus

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during the prenatal and perinatal periods, a similar dynamic that occurred in such a way after influenza epidemics when individuals developed schizophrenia due to exposure to the viral infection.

SARS and MERS lead to severe respiratory illnesses, and several studies have investigated the acute and post-illness neuropsychiatric outcomes of these diseases (Rogers et al., 2020). The mental health impact of the SARS outbreaks in 2002–2003 caused significant psychological distress and morbidities among patients, healthcare workers, and the general public in affected regions (Chau et al., 2021). The chronic psychiatric issues observed in SARS survivors underscore the potential long-term mental health complications that COVID-19 patients may face. Thus, in addition to the biological effects of COVID-19 that may increase the risk of schizophrenia, the COVID-19 pandemic may contribute to an increase in reactive psychotic disorders due to its stressful nature (Kulaga & Miller, 2021; Valdés-Florido et al., 2020). This may be explained by the diathesis-stress hypothesis. In this theory, stressful experiences have always been considered one of the most important factors in the development and exacerbation of mental disorders, independently of the effects of nervous system infections. One of the longest-standing pathoetiological hypotheses for schizophrenia is the interaction between external stimuli and internal vulnerability (Pruessner, Cullen, Aas, & Walker, 2017). According to this theory, psychosocial stress can cause the microglia to become pathologically activated, leading to excessive synaptic pruning and the loss of cortical gray matter. Therefore, damage to the stress-sensitive area may lead to immediate negative cognitive symptoms. Additionally, a loss of cortical control may prevent subcortical dopamine from acting, resulting in the positive symptoms of psychosis (Ma et al., 2021).

Section 3: Neuropsychiatric adverse effects of antiviral drugs

Within the context, neuropsychiatric adverse effects refer to brain-related symptoms developed during the treatment of pre-existing neurologic or psychiatric disorders, which range from mild symptoms, such as irritability and insomnia, to severe complications, including depression, psychosis, and painful peripheral neuropathy (Zareifopoulos, Lagadinou, Karela, Kyriakopoulou, & Velissaris, 2020). However, it is very complex to distinguish whether these symptoms are due to the viral infection, to the immune response, or to the antiviral treatment.

In the case of the influenza virus, the most commonly used antivirals are neuraminidase inhibitors (such as oseltamivir or zanamivir), which prevent the viral spread and infection in the respiratory tract. However, a causal relationship between oseltamivir treatment and abnormal behavior has not yet been established, although the risk of abnormal behavior may be due to the viral infection, not to the antiviral drug (Ueda et al., 2015). Zanamivir treatment does not appear to cause neurological effects in humans. Table 3 shows the neuropsychiatric side effects and mechanisms of neurotoxicity of the major antiviral drugs.

Acyclovir and valacyclovir are the most commonly used antivirals for herpes infections. Their neuropsychiatric adverse effects include agitation, altered state of consciousness, confusion, dysarthria, and hallucinations (Brandariz-Nuñez, Correas-Sanahuja, Maya-Gallego, & Martín Herranz, 2021). In the case of famciclovir, potential neurogenic adverse effects include ataxia, dementia, dysarthria, encephalopathy, and tremor (Fang, Zhou, Han, Chen, Guan, & Li, 2024). The prevalence of nephrotoxic side effects ranged from 13% to 21%, while the prevalence of neurotoxicity was not clearly defined (Aboelezz & Mahmoud, 2024). However, Brandariz-Nuñez et al. (2021) reported that neurotoxicity associated with acyclovir and valaciclovir was 73.9% and 29.4%, respectively. Adverse effects related to famciclovir were more common in women (59.72%) than in men (34.49%) (Fang et al., 2024).

Acute psychosis was reported in individuals with AIDS and older adults with poor renal function treated with gancyclovir (Zareifopoulos et al., 2020). Several authors have reported that valacyclovir significantly improved verbal memory, working memory, and visual object learning, as well as schizophrenia symptoms (Bhatia et al., 2018; Deshpande & Nimgaonkar, 2018; Prasad et al., 2013; Tsai et al., 2020). However, other authors did not find significant improvement with this antiviral on the psychotic symptoms and cognitive function measures (Breier et al., 2019; Jonker et al., 2023).

Antiviral drugs most used for the treatment of hepatitis B are nucleoside and nucleotide analogs (Kayaaslan & Guner, 2017). Several of these drugs produce mitochondrial DNA depletion and have been associated with myopathy and peripheral neuropathy (Kamara et al., 2016). The combination of pegylated IFN and ribavirin was the treatment of choice for hepatitis C infection until the approval of direct-acting antivirals (DAAs) that presented improved patient tolerability and lower side effects (Gutiérrez-Rojas et al., 2023; Sakamaki et al., 2019). Psychiatric disorders were a common adverse outcome during the treatment with the former drugs (Davoodi et al., 2018; Sakamaki et al., 2019). However, Cheng et al. (2021) demonstrated that the hepatitis C-associated risk of schizophrenia could be reversed by interferon-based antiviral therapy.

Nucleoside reverse transcriptase inhibitors (NRTIs) are nucleoside analogs lacking a 3-OH group, which are processed by the retroviral enzymes as unaltered nucleotides. The NRTIs incorporation into the newly synthesized viral DNA strand induces early termination of transcription, thereby inhibiting retroviral replication (Hirnschall, Harries, Easterbrook, Doherty, & Ball, 2013). Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI) also used to treat HIV infection, usually in combination with NRTIs, with its clinical use discussed due to multiple psychiatric side effects (Clifford et al., 2005; Kenedi & Goforth, 2011). Several studies establish that efavirenz is a potent psychotropic drug with a higher affinity for GABA-A, 5-HT2A, and 5-HT2C receptors, while it also acts as a monoamine oxidase inhibitor and as a dual serotonin/dopamine reuptake inhibitor (Gatch et al., 2013). Nevirapine is another NNRTI that has rarely been associated with neuropsychiatric adverse effects (Wise, Mistry, & Reid, 2002), although van Griensven et al. (2010) reported its association with hepatotoxicity and peripheral neuropathy.

Protease inhibitors can also be used as part of active antiretroviral therapy. One of these, ritonavir, is an inhibitor of cytochrome P450 3A4 (CYP3A4) and is synergistic with drugs that rely on CYP3A4 metabolism for inactivation. However, its use has been associated with a lipodystrophy syndrome characterized by insulin resistance, dyslipidemia, central obesity, and an increased risk of cerebrovascular disease (Duval et al., 2004; Gupta et al., 2012). Other HIV antivirals, such as raltegravir, elvitegravir, and dolutegravir, inhibit retroviral integrase, the enzyme that allows the integration of the viral DNA transcript into the host cell genome (Hoffmann & Llibre, 2019). Side effects similar to those of efavirenz have been reported mainly for dolutegravir, but no evidence has been reported that provides insight into the mechanisms of integrase inhibitor-induced neuropsychiatric effects (Zareifopoulos et al., 2020). The most recently approved antiretrovirals are maraviroc and enfuvirtide, two agents included in the class of entry and fusion inhibitors, which are not considered first-line agents and are therefore used in

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Table 3. Neuropsychiatric side effects and mechanisms of neurotoxicity of antivirals

Antiviral drug class	Examples	Neuropsychiatric side effects	Mechanisms of neurotoxicity	References
Neuraminidase inhibitors against influenza virus	Oseltamivir. Zanamivir.	Delusions and hallucinations; delirium-like episodes; frightening episodes; sudden anger; delirious speech; depressive episodes; mania; suicidal thoughts.	Inhibition of human MAO-A. Stimulation of D2 dopaminergic receptor.	Hama & Bennett (2017) Chen et al. (2019) Kang et al. (2019)
Antiherpetic drugs	Aciclovir. Valacyclovir. Famciclovir. Gancyclovir.	Tremor; visual and auditory hallucinations; confusion; coma; altered consciousness; ataxia; dysarthria; delusions of death; psychosis; mania.	Accumulation of neurotoxic metabolites (CMMG) commonly excreted through urine.	Helldén et al. (2006) Asahi et al. (2009) Aslam et al. (2009) Brandariz-Nuñez et al. (2021) Fang et al. (2024)
COVID–19 antivirals	Chloroquine. Hydroxychloroquine.	Psychosis; sleep disorders; anxiety; depression; cognitive dysfunction; suicide; self-harm.	Inhibitor of cytochrome P450 3A4. 3C-like proteinase. Dysregulation of the HPA axis.	Costanza et al. (2021) Garcia et al. (2020) Hamm & Rosenthal (2020)
	Ritonavir/Lopinavir. Nirmatrelvir. Remdesivir. Favipiravir.	Development of dementia; peripheral neurotoxicity; delirium; anxiety; mood symptoms; psychosis.	Depletion of neurotrophic factors secreted by macrophages at sensory ganglia.	Hashemian et al. (2023) Kumar et al. (2022) Qomara et al. (2021)
Nucleoside and nucleotide analogs against hepatitis B virus	Amivudine. Telbivudine. Entecavir. Adefovir. Tenofovir.	Peripheral neuropathy; myopathy; dystonia; delusional mania; psychotic reactions; fatigue; headache; dizziness.	Depletion of mitochondrial DNA. Dopamine D2 receptor antagonism in the striatum.	Song et al. (2005) Kayaaslan & Guner (2017)
Drugs against hepatitis C virus	Pegylated-IFN alone or with Ribavirin. DAAs: Telaprevir, Boceprevir, Ledipasvir, Sofosbuvir	Apathy; anhedonia; lack of motivation; asthenia; depressed mood; fatigue; insomnia; irritability; headache.	IFN-α treatment produces changes in central adrenergic, serotonergic, opioid, and neuroendocrine pathways.	Fontana (2000) Flamm et al. (2014) Manns et al. (2014) Yang & Choi (2017) Davoodi et al. (2018) Gallach et al. (2018) Takeda et al. (2018) Sakamaki et al. (2019) Margusino-Framiñán et al. (2020)
HIV: NRTIs	Zidovudine. Didanosine. Stavudine. Tenofovir. Emtricitabine.	Peripheral neuropathy; myopathy; myelotoxicity.	Interaction with human enzymes. Inhibition of mitochondrial DNA. DNA replication and telomere elongation.	Kakuda (2000) Walker et al. (2002) Reiss et al. (2004) Hirnschall et al. (2013) Ndakala et al. (2016)
HIV: NNRTIs	Efavirenz.	Sleep disturbances (insomnia, nightmares); psychotic symptoms (visual hallucinations, derealization, depersonalization); mood dysregulation (onset of mania at initiation, depression due to chronic use, suicidality).	Antagonism of 5-HT2A. Inhibition of MAO-A. Inhibition of serotonin and dopamine reuptake. Modulation of GABA-A receptor. Depletion of mitochondrial DNA.	Clifford et al. (2005) Kenedi & Goforth (2011) Gatch et al. (2013)
	Nevirapine.	Peripheral neuropathy; mania.	Inhibition of mitochondrial DNA polymerase γ.	Wise et al. (2002) van Griensven et al. (2010)
HIV: Protease inhibitors	Ritonavir.	Lipodystrophy syndrome; development of dementia; peripheral neurotoxicity (perioral paresyhesia, taste alteration, hearing loss).	Pathogenesis of cerebral small vessel disease. Depletion of neurotrophic factors secreted by macrophages in sensory ganglia.	Duval et al. (2004) Gupta et al. (2012)
HIV: Integrase inhibitors	Raltegravir. Elvitegravir. Dolutegravir.	Insomnia; hallucinations; abnormal dreams; mood changes (depression); fatigue; confusion.	Unknown.	Valcour et al. (2015) Hoffmann et al. (2017) Hoffmann & Llibre (2019)
HIV: Entry and fusion inhibitors	Maraviroc. Enfuvirtide.	Undetermined.	Unknown.	Llibre et al. (2015)

Note: MAO-A: monoamine oxidase-A; CMMG: carboxymethoxymethylguanine; IFN: interferon; DAAs: direct-acting antivirals; NRTIs: nucleoside reverse transcriptase inhibitors; NNRTIs: non-nucleoside reverse transcriptase inhibitors; GABA: γ-aminobutyric acid; 5HT2A: serotonin; HPA: hypothalamic–pituitary–adrenal.

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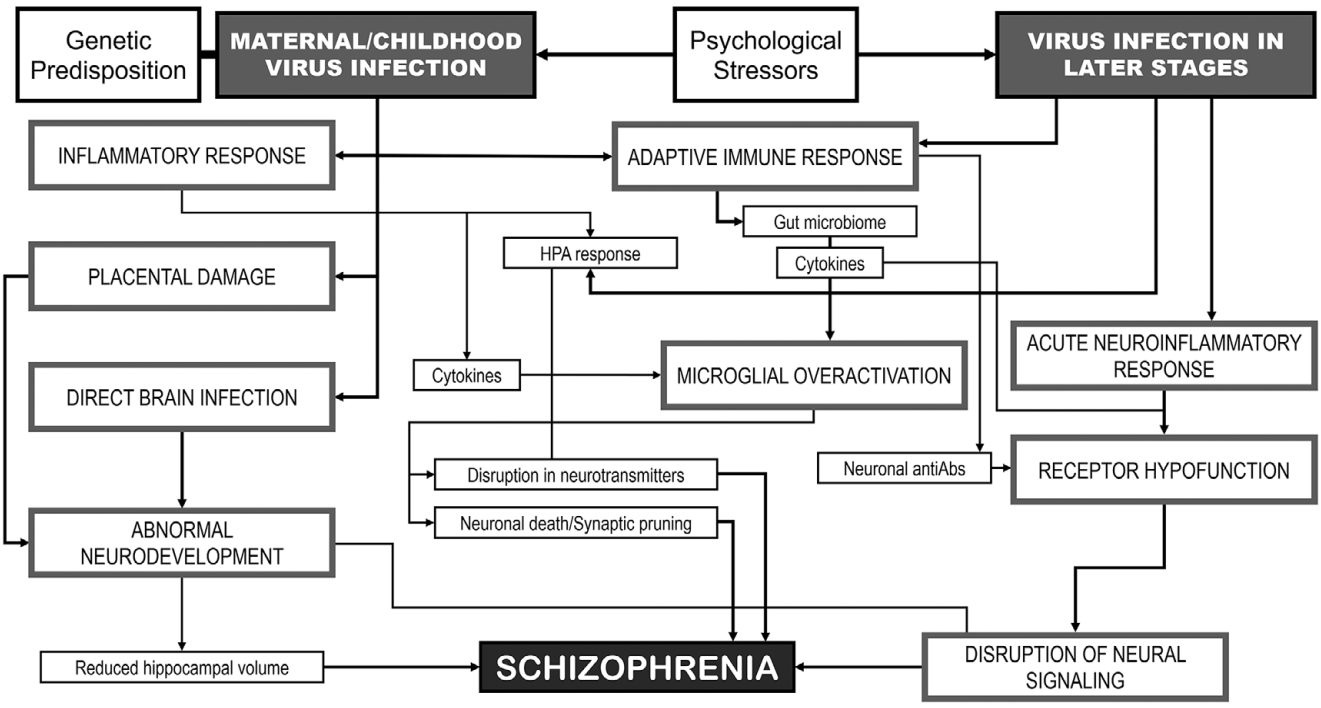

Figure 1. Hypothetical interactions between viral infection and the development of schizophrenia (according to the Inflammatory Model and to Kępińska et al., 2020).

combination with other antivirals. Clinical data indicate that maraviroc induces an increase in the $CD4^+$ count of patients (Llibre et al., 2015), but the side effects of these substances have not yet been established.

Discussion

Schizophrenia appears to be the result of the influence of hereditary and environmental factors. Some environmental contributors include birth complications, maternal nutritional deficiencies, medication use, stress during pregnancy, and viral infections. Prenatal exposure to stressors, especially early in pregnancy, is critical for fetal hippocampal development, which influences an individual's likelihood of developing a psychotic disorder (Brown & Derkits, 2010) and schizophrenia (Brown, 2011; 2012). Epidemiological research has identified viral infection as one of the environmental risk factors for schizophrenia (Khandaker, Zimbron, Lewis, & Jones, 2013). Some viral infections can disrupt normal fetal CNS development by activating the maternal immune system. Therefore, changes in the expression of key genes and increased levels of inflammatory cytokines are thought to be the connecting link between viral infection and schizophrenia (Huang, Zhang, & Zhou, 2022). Figure 1 shows hypothetical interactions between viral infection and the development of schizophrenia (according to the Inflammatory Model and to Kępińska et al., 2020).

Inflammation seems to be associated with several processes, such as microbial infections, obesity, tobacco smoking, and autoimmune diseases. Macrophages play a pivotal role as the major cellular component of the adipose tissue regulating chronic inflammation and modulating the secretion and differentiation of various pro- and anti-inflammatory cytokines (Savulescu-Fiedler et al., 2024). Elisia et al. (2020) evaluated the effects of smoking on inflammatory markers, and they found that plasma samples from heavy smokers had significantly higher CRP, fibrinogen, IL-6, and carcinoembryonic antigen levels than non-smoking controls. A possible mechanism involving many pro-inflammatory cytokines has been proposed to explain the causal relationship between the virus and schizophrenia (Figure 1). These modulators may act either directly on neurons or indirectly via neurotransmission, for example, through TNF-α (Xiu et al., 2018). Moreover, the TNF-α gene is located at a locus previously associated with genetic susceptibility to schizophrenia. Additionally, increased complement protein activity, particularly C1q, C3, and C4, was found to contribute to the accelerated synapse pruning (Presumey, Bialas, & Carroll, 2017). These authors reported that the complement system stimulates synapse loss in the early stages of neurodegenerative diseases. Similar pathways can also be activated in response to inflammation, such as in West Nile virus infection, where peripheral inflammation can promote microglia-mediated synapse loss (Stonedahl, Clarke, & Tyler, 2020).

In the present review, we have examined the influence of viral infections on schizophrenia, establishing that some of these are neurotropic and have the potential to provoke neurological disorders (Bauer et al., 2022; Capendale, Wolthers, & Pajkrt, 2023; Ludlow et al., 2016; Marcocci et al., 2020; Meyding-Lamadé, Craemer, & Schnitzler, 2019). In addition, some of these viruses induce latent infections in the host that can be reactivated by psychological stress (Cliffe et al., 2015; Griffiths & Reeves, 2021; Klopack, 2023) or by an inflammatory response to the viral infection (Cuddy et al., 2020; Savitz & Harrison, 2018), factors closely linked to the onset of several psychiatric disorders (Goldsmith & Rapaport, 2020; Kendler & Gardner, 2016; Pape, Tamouza, Leboyer, & Zipp, 2019; Savitz & Yolken, 2023). Furthermore, in this review, we have also explored the neuropsychiatric impact of antiviral drugs. Although several studies have established that antiviral therapy reduces the risk of schizophrenia (Breier et al., 2019; Jonker et al., 2023; Tsai et al., 2020), the negative effects of these antivirals have been poorly studied. On the basis of shared consequences of antivirals and schizophrenia, we can hypothesize that some antivirals provoke side effects compatible with schizophrenia symptoms, such as

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hallucinations, delusional beliefs, cognitive impairments, and psychosis, to name a few. Nevertheless, the studies reviewed present several significant limitations that must be considered when interpreting their findings. Many studies were observational or cross-sectional, which limits the capacity to establish causal relationships between viral infections, antiviral treatments, and neuropsychiatric outcomes, particularly in the context of schizophrenia. Small sample sizes were a common issue, undermining the statistical power of the studies and potentially leading to type II errors. Inconsistent reporting of variables, including variations in diagnostic criteria, medication types, and outcome measurement tools, introduced significant heterogeneity that reduced the robustness of the conclusions. Additionally, many studies did not adequately account for confounding factors such as genetic predispositions, comorbidities, or lifestyle factors like smoking, which could have influenced the results. Retrospective designs, reliance on clinical diagnoses rather than structured interviews, and incomplete or missing data (e.g., viral load, liver function tests, or genetic markers) further compromised the validity of the findings. Some studies also faced difficulties in standardizing methodologies, including the arbitrary selection of CRP cut-off values, the use of dichotomized data, and inconsistent cytokine panels. This lack of standardization, combined with publication and selection biases, limits the potential to generalize the results. Furthermore, the absence of long-term follow-up data and the failure to include diverse patient populations (e.g., regional biases) complicates the interpretation of the long-term effects of viral infections and antiviral treatments on schizophrenia. The limited focus on specific mental health diagnoses, as well as the under-recording of certain symptoms such as delirium in COVID-19 patients, may have also affected the outcomes. These methodological weaknesses point to the demand for well-designed, large-scale longitudinal studies with standardized protocols, better control of confounding factors, and more inclusive and diverse cohorts to clarify the complex relationships between viral infections, antiviral treatments, and neuropsychiatric conditions.

In addition to the key role of viral infections in the etiology of schizophrenia, it is essential to highlight the societal implications of this particular condition. Public perception often associates schizophrenia with aggressive tendencies, a belief reinforced by media coverage of violent incidents involving individuals identified as mentally ill (Wehring & Carpenter, 2011). Studies indicate that schizophrenia is among the most stigmatized mental illnesses (de Jacq, Norful, & Larson, 2016; Reisinger & Gleaves, 2023; Mannarini, Taccini, Sato, & Rossi, 2022; Valery & Prouteau, 2020), fostering prevalent beliefs about dangerousness and incompetency that contribute to a poor prognosis and increased social distance, further isolating those affected and hindering access to support and resources (Valery & Prouteau, 2020). Specifically, the perception of individuals with schizophrenia as dangerous influences the inclination for social distance, with beliefs about biogenetic causes and appropriate medical treatment also shaping these perceptions (Mannarini et al., 2022). Moreover, social exclusion is affected by the presence of negative symptoms and diagnosis awareness, where increased knowledge of the diagnosis leads to greater social distance when symptoms are absent, and decreased distance when symptoms are present (Zahid & Best, 2021). Perceived discrimination and stigma consciousness negatively impact psychological well-being, diminishing self-esteem and social functioning, while disrupting daily activities and leading to heightened mental health adverse outcomes and reduced quality of life (Magallares, Perez-Garin, & Molero, 2016; Lampropoulos, Fonte, & Apostolidis, 2019). Furthermore, higher levels of self-stigma are observed in individuals with schizophrenia spectrum disorders compared to those with depressive disorders, despite similarities in overall quality of life, suggesting that the severity of the mental disorder significantly influences self-stigmatization (Holubová et al., 2016). In addition, bullying victimization has been identified as a major risk factor for the increased incidence of schizophrenia (Jester et al., 2023), suggesting that a key prevention strategy could involve studying the psychological experiences of victims, with particular focus on the impact of negative emotions such as humiliation (Borrego-Ruiz & Fernández, 2024). Therefore, individuals with schizophrenia often face significant barriers in several aspects of life, which underscores the pressing need to enhance mental health education and assistance services, and also to dispel the uncertainty around the complex interaction of genetic and environmental factors that underlie schizophrenia, thereby clarifying its causes and raising awareness about the experiences of people suffering from it. Ultimately, understanding the diverse influencing factors of schizophrenia could lead to more targeted intervention approaches, potentially reducing some of the social and individual burdens associated with the disorder.

This review presents various potential limitations that should be appropriately acknowledged: (i) it only considers specific infections that are central to the topic under study, but the pathophysiology of schizophrenia may involve more complex and multifactorial processes in which immune dysregulation could constitute a contributing factor rather than being attributable to a single infectious agent; (ii) the potential for prevention through specific treatments is not addressed, as the primary aim of this review is to delineate underlying pathological mechanisms rather than propose direct therapeutic interventions; (iii) the samples used in some of the studies reviewed, including both experimental and control groups, exhibit heterogeneity, which may affect the comparability of findings within the broader context of neuropsychiatric disorders; (iv) the contributions of maternal infections, in utero exposures, and postnatal infections are not separately analyzed, which may limit the clarity regarding their distinct roles in the pathogenesis of schizophrenia; and (v) the impact of confounding factors, including body mass index, drug use, genetic predisposition, and socioeconomic status, may introduce bias and affect the interpretation of the results.

Conclusions

Epidemiological evidence suggests a potential relationship between viruses and schizophrenia. Some viral infections, such as the influenza virus, can disrupt fetal brain development by activating the maternal immune system. Increases in inflammatory cytokine levels and changes in the expression of key genes observed in several viral infections (e.g., coronaviruses) may constitute potential links between these viral infections and schizophrenia. In addition, immune and non-immune genes associated with schizophrenia are likely to be targets of viral proteins.

Neuropsychiatric effects caused by antiviral drugs are common and represent significant adverse outcomes for viral treatment. From the data presented in this review, it can be concluded that antivirals may affect the CNS, although for most drugs, their action mechanisms are still unclear, and a strong relationship between antivirals and schizophrenia has not yet been established. Therefore, further research is required to elucidate the mechanisms underlying the neuropsychiatric effects of antiviral drugs.

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