

Viruses and psychiatric disorders: We have not crossed the borderline from hypothesis to proof yet (Review)

NIKOLAOS SIAFAKAS¹, CLEO ANASTASSOPOULOU², SPYRIDON POURNARAS¹,
ATHANASIOS TSAKRIS², EVANGELOS ALEVIZAKIS³, STYLIANOS KYMPOUROPOULOS³,
DEMETRIOS A. SPANDIDOS⁴ and EMMANOUIL RIZOS³

¹Clinical Microbiology Laboratory, National and Kapodistrian University of Athens, Attikon University Hospital, 12462 Athens, Greece;

²Laboratory of Microbiology, National and Kapodistrian University of Athens, Medical School, 11527 Athens, Greece;

³2nd Department of Psychiatry, National and Kapodistrian University of Athens, Attikon University Hospital, 12462 Athens, Greece;

⁴Laboratory of Clinical Virology, Medical School, University of Crete, 71003 Heraklion, Greece

Received October 6, 2023; Accepted December 10, 2024

DOI: 10.3892/mmr.2024.13426

Abstract. Most psychiatric disorders are heterogeneous and are attributed to the synergistic action of a multitude of factors. It is generally accepted that psychiatric disorders are the outcome of interactions between genetic predisposition and environmental perturbations, which involve psychosocial stress, or alterations in the physiological state of the organism. A number of hypotheses have been presented on such environmental influences that may include direct insults such as injury, malnutrition and hostile living conditions, or indirect sequelae following infection from viruses such as influenza, arboviruses, enteroviruses and several herpesviruses, or the differential expression of human endogenous retroviruses. It is known that the concept of viruses is far more extensive than their perception as mere agents of acute infections, or chronic debilitating diseases, such as AIDS or some forms of cancer. Notably, an apparent causal connection between viruses and the pathophysiology of diseases has been suggested; however, it remains unclear as to how to establish this causal connection. There are inherent difficulties in answering this question with certainty, which may be due to the multitude of genetic and environmental influences that can lead to psychopathology; the latent state of chronic infection exhibited by a number of neurotropic viruses; the late onset of psychiatric disorders with respect to the acute phase of viral infection at which detection tests would be successful; the complexity of the virome; and the existence of thousands of viral species. The present review

aims to provide an outline of the conclusions that have thus far been reached regarding a possible association between viral infection and psychiatric disease, and the obstacles confronted during the quest for the truth behind the role of viruses.

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1. Introduction

Viruses are obligate intracellular entities that exist at the border between the living and non-living world. Viruses differ from their prokaryotic and eukaryotic counterparts in that they totally rely on their host and do not have their own metabolism (1,2). Notably, they do not grow or undergo any form of division, and they are produced by the assembly of pre-formed macromolecules.

Viruses do, however, possess genetic material, either DNA or RNA exclusively. In addition, their structural and functional traits are inherited, and they are subject to the same Darwinian evolutionary forces that drive the adaptation and survival of all living organisms (1). Viruses, especially those with an RNA genome, exhibit extensive genetic variability, far greater than that of all the living world, which confers upon them the evolutionary advantage of continuous adaptation to a multitude of different organs, systems and hosts (2). Notably, all viruses have been continuously shaped in both their structure and biological life cycle by this evolutionary interaction, seeking dynamic equilibrium with their host that will sustain their

Correspondence to: Professor Emmanouil Rizos, 2nd Department of Psychiatry, National and Kapodistrian University of Athens, Attikon University Hospital, 1 Rimini Street, Haidari, 12462 Athens, Greece
E-mail: erizos@med.uoa.gr

Key words: viruses, psychiatric disease, virome, endogenous retroviruses, schizophrenia

fitness and survival, as they passively follow the stochastic driving forces of natural selection.

Until a few decades ago, conventional and cell culture-based systems were relied upon for virus detection and identification; however, the limited abilities of such systems have hindered the complete understanding of the presence and role of viruses in all domains of life. Electron microscopy has provided the means to distinguish between different viral species, genera and families purely on the basis of their morphology and size, with no information about the driving force behind viral fitness and evolutionary success in the form of adaptation to these diverse domains of life. The implementation of novel, extremely sensitive, molecular detection and sequence-based identification methods, which are applicable to all types of organisms and environmental samples, has provided an impetus to transform the concept of viruses (2). A new generation of sequencing techniques has led to the more precise classification of viruses and has identified the degree of genetic heterogeneity that drives viral evolutionary success. Furthermore, this novel methodology has set the basis for the discovery of novel viruses, and the rapid detection and characterization of re-emergent viral strains with novel virulence and epidemic potential. This may markedly improve the efficiency with which we respond to viral diseases and outbreaks. Fig. 1 provides information on what is known so far about viruses and their relationship with their hosts.

First, it is now known that humans live alongside a considerable number of viruses and continuously interact with them. Furthermore, viruses are neither confined to a single type of host, nor a certain ecological niche; they thrive in all domains of life, affecting both prokaryotic and eukaryotic organisms (1). It is estimated that there are $>10^{31}$ viruses on Earth in total (2). For example, $>200,000$ types of viruses have been identified in ocean water (3), revealing the universal evolutionary adaptation of viruses to all diverse ecosystems. A previously unsuspected multitude and variety of viruses have been discovered and remain to be discovered (4), primarily due to continuous advances in genome sequencing and bioinformatics, the two branches of the scientific discipline metagenomics.

Despite both the magnitude of virus heterogeneity and a parasitic life cycle, only a small proportion of viruses can cause disease (2). Their obligate reliance on the intracellular environment dictates that their survival and final evolutionary success depend on the establishment of a symbiotic relationship with their host, rather than a parasitic one (1). Notably, the most successful viruses are those that have reached an equilibrium with their host by evading the challenges that they face within the host, such as defensive host mechanisms and the immune system, which is generally sufficient to eliminate viruses, or to at least keep viral replication in check.

Nevertheless, there is still a significant number of viruses that cause disease, either mild or serious, when the pathogen-host equilibrium cannot be attained. Factors pertinent to both virus biology and/or human social activity may be responsible for pathogenicity, especially in the case of epidemics and pandemics. For example, the emergence of a novel viral variant due to genetic variation and natural selection in overcrowded societies with efficient transportation may lead to an epidemic and possibly to rapid pandemic spread (5,6). Past pandemics have shaped societies, or even whole human

nations and empires, such as the Spanish flu in 1918 and the recent COVID-19 pandemic (7). The genetic novelty of viral variants may not only lead to a lack of pathogen control by the immune system, but also to new virulence properties with corresponding, short-term and/or long-term effects on human physiology and disease. The recent severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic with the subsequent long coronavirus disease (COVID) sequelae is an example of this (8,9).

Following entry into the host, an acute or a chronic state of infection will be established, depending on the result of the interaction between the virus and the host defense mechanisms. Following an acute infection that is not lethal, the host will usually recover with final clearance of the virus. However, long-term sequelae may ensue, either directly by long-term damage to organs and tissues, and/or indirectly via inflammatory cascades and other pathophysiological effects irrelevant to organ damage and dysfunction; this has been demonstrated with SARS-CoV-2 infection and long COVID syndrome (10). Chronic viral infections may be the direct result of an acute infection or may develop months, or even years, after primary entry of the virus into the host organism. In contrast to acute infections, chronic infections are characterized by a dynamic and metastable equilibrium between the host immune system and the virus (11). Most chronic infections described thus far are generally benign, where the virus enters a form of symbiosis with the host; however, there is some evidence that serious diseases and syndromes can be linked to chronic viral infections with a continuous inflammatory, or other pathophysiological, component, such as cancer, immune deficiency (AIDS), neurodegenerative disorders and cardiovascular disease (11).

Human endogenous retroviruses (HERVs) provide a significant example of mutualistic symbiosis between the host and a virus. These viruses are similar in their genetic constitution to their infectious counterparts. They actually constitute fossil retroviruses in the sense that they originate from ancient, exogenous retroviruses which, during the course of 100 million years of evolutionary history, integrated cDNA sequences of their RNA into the genome of human genetic cells through reverse transcription (12). Gradual integration and vertical transmission of these sequences led to ~8% of the human genome being of HERV origin. HERVs do not produce infectious particles, but partial expression of retroviral genes has been linked to human physiology and, if aberrantly expressed, to disease (13). A significant example of that is the role of the *env* gene of certain endogenous retroviruses in human placental morphogenesis and fetomaternal tolerance (14).

The recent advances in genetic sequence detection and analysis have resulted in the realization that humans are not only colonized by diverse prokaryotic and eukaryotic microorganisms, which constitute the microbiome, but also by a marked multitude and variety of viruses, collectively termed the virome. Research has been performed on the composition and dynamics of the virome, and its role in human health and disease. The virome consists of viruses that infect human host cells and phages that infect bacteria of the microbiome (15). Viruses affect the host directly by interfering with the defense mechanisms, whereas phages may exert an indirect effect on

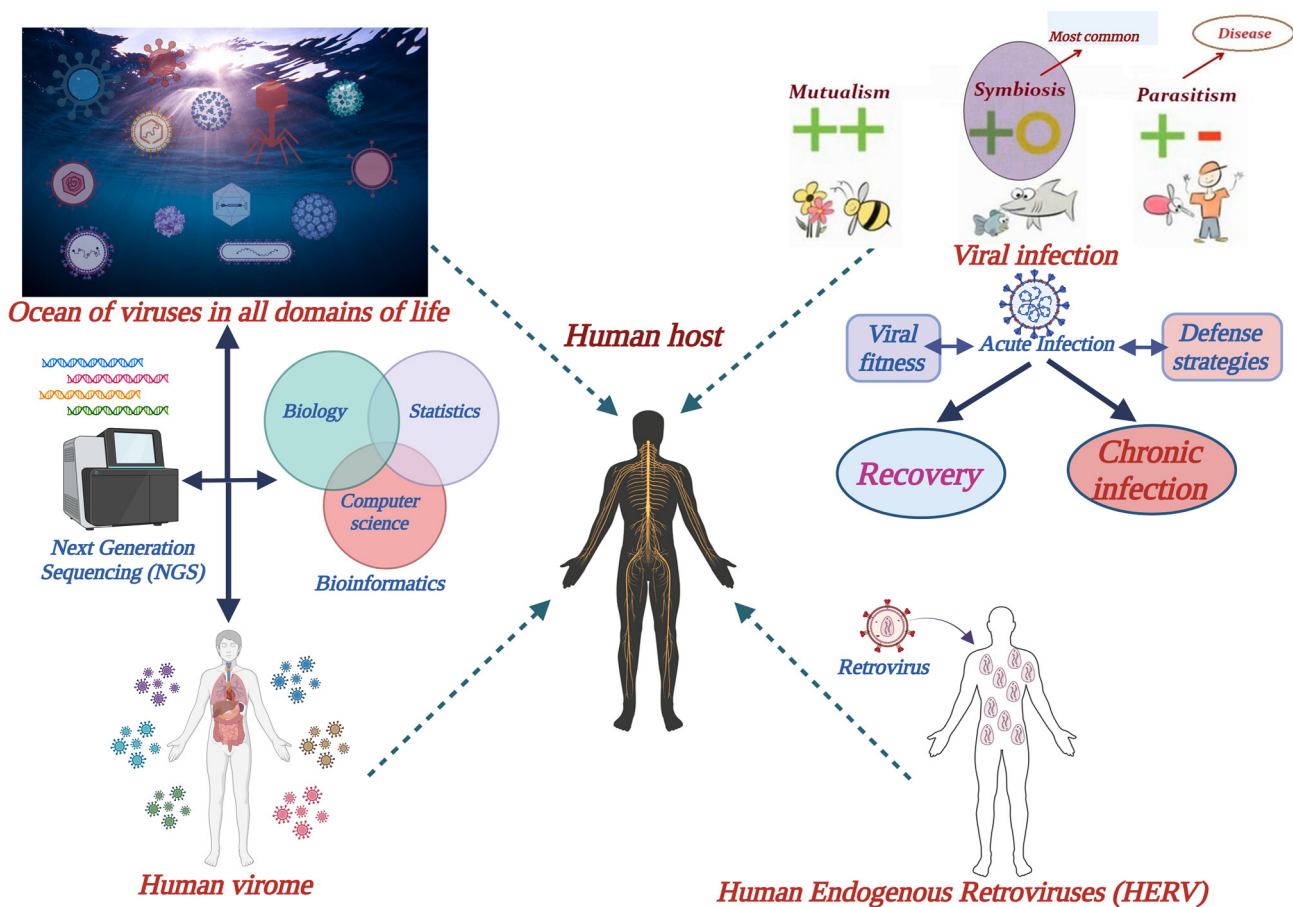


Figure 1. Diagrammatic depiction of viruses and their relationship with the human host. Novel molecular techniques and sequencing technologies have enabled the understanding that humans not only live alongside a considerable number of viruses, but also that diverse populations of viruses (collectively termed the virome) reside within the human body and may influence both physiology and disease, although substantial evidence about the association of viruses with psychiatric and numerous other diseases is still lacking. The concept of the virome constitutes fundamental proof that a small proportion of viruses cause disease. A viral infection usually leads to a symbiotic state within the host, but parasitic states that lead to disease still occur, with serious consequences for the host either during an acute, or a chronic latent phase of infection. Moreover, part of the human genome consists of integrated sequences of retroviral origin and partial expression of the endogenous retrovirus genes has been linked to human physiology and, if aberrantly expressed, to disease. Created in <https://BioRender.com>.

host physiology and disease by modulation of the composition and fitness of the bacterial microbiome (16).

The aforementioned information poses a challenge for the scientific community related to the understanding of the role of viruses in human health and disease. It is known that the concept of viruses is more extensive than their exclusive perception as mere agents of an acute infection, or some chronic debilitating diseases, such as AIDS or some forms of cancer. Notably, a causal connection between viruses and disease pathophysiology may exist; however, there are still a number of questions that need to be answered. A number of hypotheses have been put forward regarding viruses and diseases, the etiology of which was previously unknown, but it remains unclear as to how to establish a causal connection. In addition, it remains to be determined how far research has gone regarding the possible role of viruses in chronic, debilitating diseases such as psychiatric disorders; and how many, and which, viruses may contribute to the development of psychiatric disease. Considering the great diversity of the infectious properties of different viruses, research is also required regarding how a viral infection could trigger a mental disorder; whether some viruses have specific virulent properties that have not been

described so far and dictate previously unrecognized pathophysiological pathways; and whether these new associations with disease are the result of direct damage and its sequelae in the long-term, or chronic infection. Furthermore, it remains to be ascertained as to whether detection is enough, and how to detect viruses in a chronic state of infection, where viral load is frequently imperceptible and symptoms are initially obscure, developing years after viral infection. The role of the virome and endogenous retroviruses in psychiatric and other diseases also requires further assessment.

2. Suggested mechanisms and tentative data about the possible association of viral infections with psychiatric disease

Most clinical changes in an individual's cognition and mental status are heterogeneous and attributed to the synergistic action of a multitude of different factors. Genetic predisposition and environmental perturbations, by either stress from the social surroundings or alterations in the physiological state of the organism, have been proposed as significant contributing factors in the development of psychiatric disease

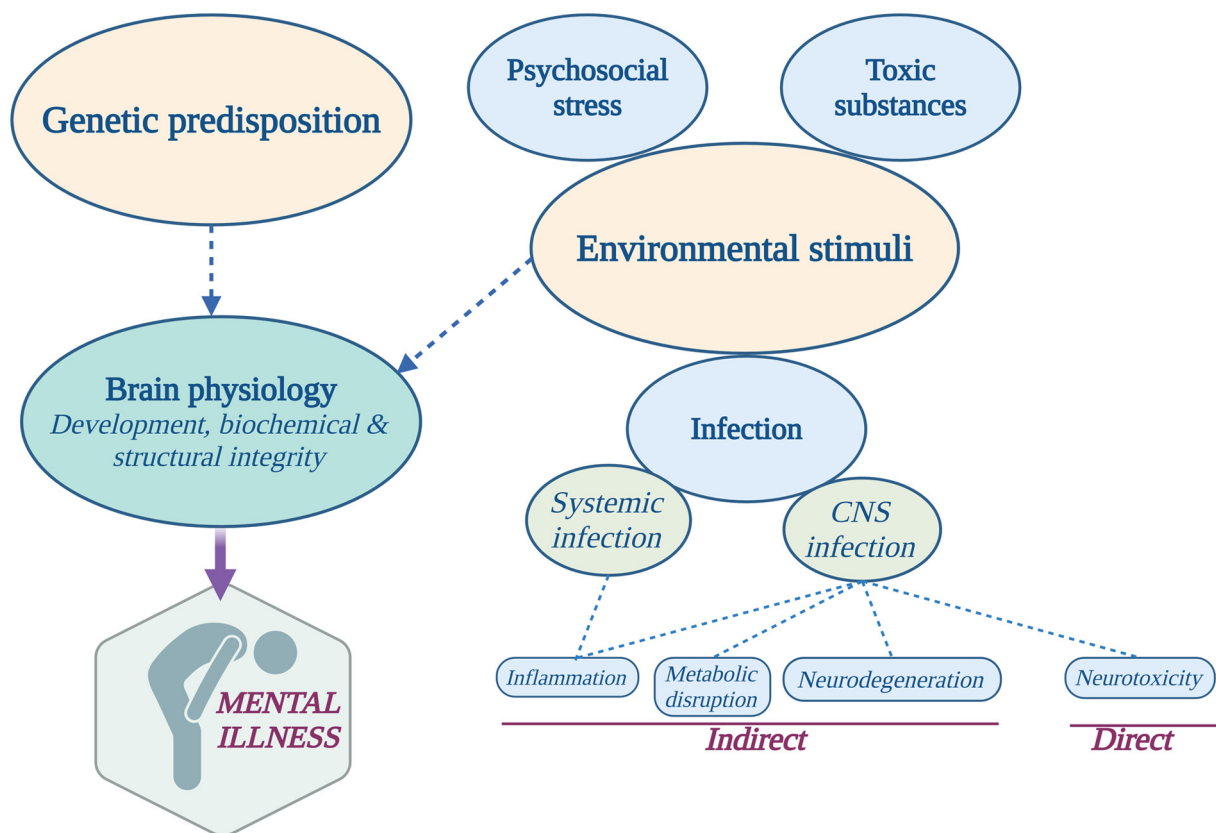


Figure 2. Outline of the different factors that may lead to the development of mental illness. Types of pathophysiological pathways in which viral infection may tentatively contribute to a psychiatric disease are also shown, despite this we still have not crossed the borderline from hypothesis to proof yet. Created in <https://BioRender.com>. CNS, central nervous system.

(Fig. 2) (17). Such environmental influences may include direct insults or indirect sequelae that follow infection from viruses such as influenza, enteroviruses, arboviruses and several herpesviruses, or the differential expression of HERVs.

Viruses may contribute to psychiatric diseases such as schizophrenia, autism, major depression, bipolar disorder and chronic fatigue syndrome through various mechanisms (18). Thus far, these tentative mechanisms generally fall into two categories (Fig. 2): Indirect immune, inflammatory, metabolic and degenerative processes in the central nervous system (CNS), and/or direct neurotoxic effects following viral invasion into the CNS (19).

Indirect effects of viral infection on the physiology of CNS

Virus-induced psychopathology linked to neurodevelopment. A number of different viruses have been implicated in a single psychiatric disease, such as schizophrenia, and this may constitute an immune-mediated disorder, rather than a pathogen-specific link between viral infection and a psychiatric disorder (20). The model of neurodevelopment disruption has been suggested as the most promising mechanism underlying the onset of schizophrenia (19). Both direct viral infection and indirect viral effects, via the activation of inflammatory pathways and the excessive release of cytokines, have been suggested as possible disrupting mechanisms in normal neurodevelopment (21). Moreover, the timing of disruption of normal neurological processes that occur at critical stages of neurodevelopmental processes has been proposed as being of

utmost importance. Specifically, effects incurred by viruses appear to be stronger when infection occurs during the late 1st and the 2nd trimesters of gestation (19), childhood and pre-adolescence (22,23). Several studies have also shown that childhood viral infection of the CNS, especially under the age of 3 years or in pre-adolescence, may be significantly associated with an increased risk for later psychosis (22,24).

However, virus-induced disruption during both pre- and postnatal neurodevelopmental processes is not solely responsible for the possible development of a psychiatric disease. Psychological trauma during adolescence or early adulthood, in conjunction with previous maternal or childhood viral infection during critical stages of neurodevelopment, has been linked with greater possibilities for the development of schizophrenia (25,26).

Activation of inflammatory pathways following infection and their link with psychiatric disease. It has been suggested that systemic or direct CNS infections may activate neuroinflammatory events mediated by activated microglia and the release of cytokines in the brain (27,28). In the case of a systemic viral infection through, for instance, the circulatory, respiratory and the gastrointestinal routes, an initial inflammatory event may ensue that leads to the release of proinflammatory cytokines and chemokines that can disrupt the integrity of the blood-brain barrier (BBB), rendering it permeable to viral particles, toxins and infected immune cells (Fig. 3) (28). Other neurotropic viruses, such as α -herpesviruses and rhabdoviruses, invade the CNS directly; therefore, a correspondingly

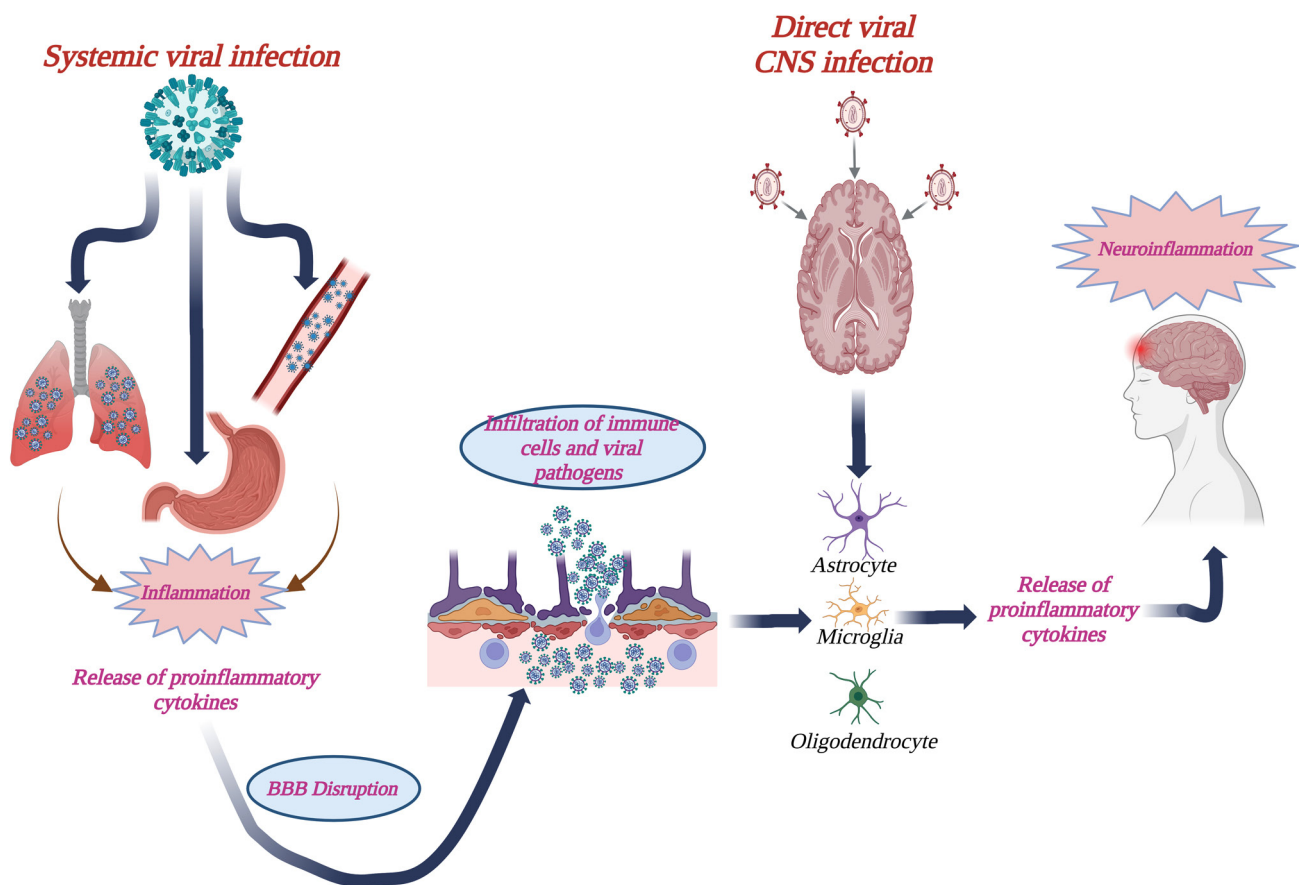


Figure 3. Diagrammatic presentation of viral-induced neuroinflammation, following either a systemic, or a direct CNS infection. Viruses that gain entry to the host through the circulatory, respiratory and the gastrointestinal routes, can still elicit neuroinflammation. Initial inflammatory events may lead to the release of proinflammatory cytokines and chemokines that can disrupt the integrity of the BBB, thus rendering it permeable to viral particles, toxins and infected immune cells. Alternatively, viruses such as α -herpesviruses and rhabdoviruses invade the CNS directly through spread within neuronal axons. In both cases, astrocytes and microglia constitute the main immune mediators within the CNS and their activation via Toll-like receptors generate further production of proinflammatory cytokines, leading to neuroinflammation in the brain. Created in <https://BioRender.com>. BBB, blood-brain barrier; CNS, central nervous system.

direct neuroinflammatory event may be elicited (Fig. 3). In both cases, oligodendrocytes, astrocytes and microglia constitute the main mediators of inflammation in the brain (28).

Extensive data from clinical and experimental models have shown the induction of proinflammatory cytokines following infection with several viruses, such as flaviviruses, including Dengue virus (DENV) and tick-borne encephalitis virus (29,30). Japanese encephalitis virus (JEV) is another flavivirus that infects microglial cells, which may serve as a reservoir for the virus (31). In addition, Zika virus (ZIKV), as well as directly damaging neuronal cells, may mediate an exaggerated neuroinflammatory response, especially in neonates; postnatal microcephaly has been linked with ZIKV-induced neuroinflammation in both animal models and fatal cases (32,33). Another example is the neuronal damage caused by the rabies lyssavirus (RABV), which has also been suggested to be the result of the high production of inflammatory cytokines in primary astrocytes and microglia (34).

Regarding the available evidence regarding the role of these neuroinflammatory events in influencing neurobiological processes, potentially contributing to the development of schizophrenia and related psychotic disorders, elevated proinflammatory cytokines have been found in both the blood and cerebrospinal fluid (CSF) of patients with

cognitive deficits (35,36). Notably, serum interleukin (IL)-6 and C-reactive protein in both childhood and adolescence have been shown to be linked to both the presence and severity of disease during adulthood (37,38). IL-6 is also considered not only as an important, diagnostic inflammatory marker but as a predictive one as well, since its increased levels during both childhood and adolescence have been associated with a high risk for adult psychotic disorders in a dose-dependent manner (39). IL-8 in the CSF has also been described as a sensitive marker of inflammation for numerous neurological and psychiatric diseases, whereas higher IL-12p70 levels have been detected in the serum of patients with schizophrenia (40).

Complement factors in the brain are also known to contribute to the process of synaptic pruning, which involves enhanced activation of proinflammatory cytokine secretion by glial cells, leading to possible neuronal cell damage and death (41). Moreover, activated complement may contribute to alterations in the BBB function, which could subsequently influence the progress of a psychiatric disease (42). Notably, elevated levels of complement have been detected in patients following first-episode psychosis (43,44).

Systemic, or CNS-specific viral infection and the inflammatory cascades that ensue may not exclusively affect brain physiology, they may also influence

hypothalamic-pituitary-adrenal (HPA) axis dysregulation, which has been linked to psychiatric diseases such as schizophrenia (45). HPA axis dysregulation, and brain neuropathology induced by proinflammatory cascades elicited by either direct or systemic infections, have a common trait; they mostly seem to render the organism more vulnerable to a possible psychiatric disorder but do not lead to the disease on their own. An environmental, psychosocial stimulus in later life may more readily affect an individual primed by such inflammatory complications (46).

Genetic predisposition in human leukocyte antigen (HLA) genes and immune response to infections that may prime a psychiatric disease. HLA genes located on chromosome 6 code for cell surface proteins that serve a fundamental role in immune responses against foreign antigens. Class I and II HLA molecules represent two major pathways that act in synergy for host protection (47). Genome-wide research on the genetic background of schizophrenia has provided evidence that genetic polymorphisms within the HLA genes located on chromosome 6 are associated with the disease (47). Specifically, polymorphisms involving HLA-DRB1 alleles of Class II antigens have been significantly linked with schizophrenia (48). There are polymorphisms, however, which are negatively associated with schizophrenia (49) or even have a protective effect (50), at least amongst certain ethnic populations.

As a consequence of the pivotal role that HLAs have in foreign antigen presentation and final elimination by the immune system, an ineffective, polymorphic version of an HLA allele may lead to more pronounced, adverse effects on the brain and the persistence of viral antigens, with poor consequences regarding inflammation and/or autoimmunity with respect to the development of psychiatric disease. For example, in a recent study, it was suggested that HLA alleles with a higher affinity for herpesviruses, leading to a more effective elimination of the consequences induced by acute infection, may confer protection against schizophrenia (51).

Viral infection could impair CNS energy metabolism, which may lead to psychiatric disease. As obligate intracellular entities, viruses rely exclusively on host cell metabolic machinery to replicate and sustain their existence. Notably, neurotropic viruses may disrupt brain physiology by altering neuron and astrocyte metabolism; they have evolved to alter host cell metabolic activities so that they can optimally be used for their own benefit, such as glycolysis, the pentose phosphate pathway, the tricarboxylic acid cycle and oxidative phosphorylation (52). For example, there is increasing evidence that ZIKV infection suppresses neuronal stem cell proliferation and induces premature differentiation by intervening with glycolysis and oxidative phosphorylation properties of the host cells, leading to microcephaly of neonates during pregnancy (53-55). Moreover, a reduction in glutamine metabolism in astrocytes following a viral infection may disrupt their cooperation with neurons to maintain the glutamate-glutamine cycle in the brain, something that may shape brain activities and lead to neuropsychiatric disorders (56,57). For instance, the release of Tat protein by infected cells in HIV-associated neurocognitive disorders (HAND) has been linked with disruption of this metabolic cooperation between astrocytes and neurons (58,59). The same has also been proposed for SARS-CoV-2, which may also be found in the brain and

mainly infects astrocytes (56,57). Finally, another means for impairment of neuronal metabolism may be elicited by a viral infection through alteration of mitophagy and mitochondrial dynamics, which has been reported for HIV-1 proteins that inhibit mitophagic flux in human primary neurons, leading to neuronal damage (60).

Direct impairment of the CNS by neurotropic virus infection. Evidence and suggestions were previously outlined above regarding the indirect effects of viral infections on inflammatory pathways and neurodevelopmental processes that may lead to severe neuropsychiatric disorders in the long-term and not immediately after infection. Moreover, these sequelae do not appear on their own; viral infections and their effects could prepare the organism to respond more readily to an appropriate environmental stimulus that would act in synergy to mount the emergence of a psychiatric disease, later on in the individual's life.

However, a number of viruses have evolved to invade the CNS directly via numerous pathways, including leukocyte-mediated transfer through the BBB, neuronal axon transport from peripheral nerves and invasion of CNS endothelial cells, or the olfactory nerve (61). Therefore, the possible role of direct damage inflicted upon the CNS by these neurotropic viruses in psychiatric disease should be assessed. So far, numerous neurotropic viruses that belong to a diverse number of families have generally been linked to psychiatric disease, and these include herpesviruses, enteroviruses, arboviruses and retroviruses, as well as respiratory viruses that also exhibit a degree of neurotropism, such as influenza and coronaviruses, (52,62-64). Clinical and *in vitro* studies have shown that these viruses can be directly neurotoxic via a number of diverse mechanisms, including manipulation of apoptosis and autophagy, production of reactive oxygen species (ROS) and disruption of the production of antioxidants, localized inflammation in the central and peripheral nervous system (neuroinflammation), and alterations in neurotransmission (52,65).

Apoptosis and autophagy during viral infection. Apoptosis and autophagy constitute two important defense mechanisms against viral spread. It has been reported that the apoptosis signaling pathway is activated in pediatric patients with HIV-1 encephalitis (66), as well as in infections caused by enterovirus A71 (EV-A71) (67), RABV (68-72), West Nile virus (WNV) (73-77) and JEV (78,79). Some viruses may evade degradation and the subsequent elimination by the immune system through inhibition of autophagy, but others modulate autophagy by exploiting autophagosomes and their secretion pathway as sites for replication, viral particle maturation and release from the host cell (80). For example, the VP1 capsid protein of EV-A71 is not only a major modulator of viral antigenic properties and interaction with the immune system, but it also contains important neurovirulence properties that induce autophagy by regulating the mammalian target of rapamycin signaling pathway to promote viral replication (81-83). Modulation of autophagy by the HIV-1 proteins Nef and Tat has also been evaluated and proposed, which may contribute to HAND (84-86).

Oxidative, mitochondrial and endoplasmic reticulum (ER) stress following viral infection. Infection by neurotropic viruses has been associated with excessive production of ROS

and deficient cellular antioxidant defenses (52). JEV is a significant example of such a neurotropic virus that increases ROS production; it has been suggested as an important contributor to psychiatric, or other neurologic sequelae, in ~50% of survivors (87,88). Other neurotropic viruses associated with excessive oxidative stress include RABV, EV-A71, which is prevalent in South East Asia, and ZKV (52). Moreover, oxidative stress is not exclusively seen in viruses causing mainly acute infections, but is also a characteristic of viruses causing latent, or persistent infections, such as herpes simplex virus (HSV) and HIV. HSV-1 infection and intracellular ROS generation have been observed in microglia (89) and neural cells (90). Glutamate-mediated excitotoxicity is also an important mechanism of neuronal injury by viral infection. The effect of HIV-1 proteins on neurotoxicity induced by glutamatergic system dysregulation has also been revealed (91).

Several *in vitro* studies have also shown that infection with certain viruses may induce mitochondrial and ER stress (52). For instance, as well as inducing neuronal damage via neuroinflammation, RABV has been reported to invoke significant alterations in different mitochondrial parameters (92). *In vitro* studies in human neural stem cells have also shown that JEV, ZIKV and WNV infection may promote the expression of ER stress-related proteins (93-95), whereas the enterovirus EV-A71 may induce oxidative stress both in the ER (96) and mitochondria (97), the latter leading to morphological changes and subsequent functional anomalies in glioblastoma cells.

Viral infection could interfere with neurotransmission. Neurotropic viruses may alter the levels of specific neurotransmitter levels, leading to dysregulation of synaptic nerve signal transmission and subsequent impairment of specific brain functions that may trigger psychotic disorders (52). Specifically, viruses affect pathways that involve dopamine metabolism (98,99) and glutamate transmission via molecular mimicry at N-methyl-D-aspartate receptors (100). JEV infection can significantly increase dopamine production and modulate the rate-limiting enzyme of dopamine biosynthesis, with an increase in phosphorylated tyrosine hydroxylase levels at the early stage of infection (101). JEV may also exploit dopamine-mediated neuronal communication to increase the susceptibility of dopamine D2 receptor-expressing cells to JEV infection, which causes damage to dopaminergic neuron-rich areas such as the thalamus and midbrain, leading to neuronal loss and increasing the fatality rate of JEV-infected mice (101).

3. The quest for establishing an etiological link between viral infection and psychiatric diseases: Conjectures and evidence

The present review has thus far provided a summary of the possible mechanisms with which systemic and/or neurotropic viral infections may contribute to the development of psychiatric disease. Nevertheless, determination of the presence of a virus within the host during an acute, persistent or latent infection that evolved into an early or a delayed psychiatric abnormality is essential to establish the possible contribution of viruses to psychiatric abnormalities. Either seroepidemiological analysis or the direct detection of viral genetic material in appropriate clinical samples, such as the CSF, have been employed thus far in CNS and systemic infections that were

subsequently linked to a psychiatric disease. Significant rates of neuropsychiatric manifestations (43%) have been found in HSV-2, varicella zoster virus (VZV) and enterovirus meningitis cases (102-104). Cognitive impairment in adults shortly after aseptic meningitis and encephalitis caused by HSV, VZV, enteroviruses, HIV, ZIKV and coronaviruses has also been reported (105,106).

Epidemiological and serological evidence about the role of specific viruses in psychiatric disease. Regarding viral infection and its role in the disruption of normal neurodevelopment, as long as 4-5 decades ago, there were initial reports on the greater incidence of patients with schizophrenia who were born during late winter and spring when the risk for respiratory tract infections, and most notably influenza virus infection, is significantly greater (107,108). Numerous studies have subsequently supported this observation (109,110). A significant risk for schizophrenia has also been reported for patients whose mothers were exposed to influenza epidemics during the 2nd trimester of gestation (111). Prenatal exposure to rubella is another suggestion for the increased risk of schizophrenia in the offspring of affected mothers (112). A high frequency of psychiatric disorders has also been reported for patients with a history of chronic hepatitis C virus (HCV) infection (113). Additionally, anti-viral treatment and final HCV clearance have been shown to positively affect the quality of life in these patients (114). Psychotic diseases, such as major depressive disorder, anxiety disorder and HAND, have commonly been reported amongst patients with HIV; however, not much information is currently available about a possible association between HIV infection and schizophrenia (46). Inconsistent results have been reported from such epidemiological studies and their role in identifying the viral connection in psychiatric diseases. For instance, in another large-scale study, no significant association was identified between maternal infection before, during or after the 1957 influenza epidemic, and the development of schizophrenia in offspring (115).

Further serological methods have been employed to decipher an association between prenatal exposure to influenza and an increased risk of schizophrenia. For example, one study based on serological investigation of the mothers of psychiatric patients indicated that the risk of schizophrenia was increased in people exposed to the influenza virus within the uterus during the first trimester of pregnancy (112).

Members of the *Herpesviridae* family are also very well known for their neurotropic properties and their persistence in the host, marked by alternating periods of latency and possible reactivation (116). Elevated IgG antibody levels against HSV-1 and/or cytomegalovirus (CMV) have also been associated with a first episode of schizophrenia, brain morphological changes, increased suicidal tendencies and cognitive impairment (117,118). In another, large-scale serological study of CMV IgG detection in plasma samples from psychiatric patients, high rates of antibody detection (61%) were associated with a variety of different psychiatric disorders (119). An aberrant response to infection by Epstein-Barr virus (EBV) has also been reported in patients with schizophrenia who have been shown to exhibit elevated levels of antibodies against the viral capsid antigen of the virus, but not against the EBV nuclear antigen-1 (120). However,

other studies have shown inconsistent results regarding the potential association of a previous herpesvirus infection with psychiatric disease. In certain studies, no significant association between HSV-2, HSV-6 and VZV infections, and schizophrenia was found (121-123), whereas elevated antibody titers against *Chlamydia trachomatis* were more significantly correlated with schizophrenia than antibodies against other herpesviruses (124).

Arboviruses have also been implicated as etiological agents of psychiatric morbidity in patients with clinical and/or serological evidence of infection. For instance, cognitive difficulties have previously been reported amongst 49 patients with clinical and laboratory classification of a WNV infection (64). Persistence of these cognitive deficits for an extended period of time and their prevalence, irrespective of whether the infection was neuroinvasive or not, has been shown to advocate a systemic pattern of neuropsychiatric disorder manifestation, rather than the result of direct neurotoxicity of WNV. Chikungunya virus is another arbovirus that has been linked with depression, anxiety and somatoform disorders (60), although it has been suggested that prenatal and postnatal exposure to the virus may not be associated with impaired neurodevelopment (125). Nevertheless, such studies regarding the role of these and other arboviruses, such as ZIKV or DENV, in psychiatric disorders are still scarce and further studies must be conducted on larger sample sizes and the pathophysiology of arbovirus infection with psychiatric sequelae.

Direct evidence of the possible implication of viral infection in psychiatric disorders

Detection of viral genes and their products in clinical samples of psychiatric patients. Most of the viral infections that have been recognized so far as contributing factors in the etiology of psychiatric disease are based on epidemiological and serological analyses that provide speculative, and not definitive, evidence of an association between viruses and psychiatric disease. Psychiatric disorders often develop late, after viral infections during critical neurodevelopmental stages. This, combined with other environmental factors, makes it difficult to study the direct connection of viruses to psychiatric disease during the acute infection phase. Moreover, viral persistence through latency means that any viral load, which may be linked with direct neurotoxic, or indirect inflammatory and neurodevelopmental processes that could lead to a psychiatric disease, remains at almost imperceptible levels, posing a significant challenge for their detection, even when using the most modern, state-of-the-art molecular methodologies.

More compelling evidence for the role of viruses in psychiatric diseases comes from studies that detect and analyze viruses directly in the brain or in CNS-associated clinical samples, such as the CSF. These studies use highly sensitive molecular techniques, such as polymerase chain reaction (PCR) and next-generation sequencing (NGS), which can identify viral genes and products even at low levels. The potential conferred by these techniques in accurately detecting and characterizing viral genes and products, even when minimum viral loads persist during a dormant part of the biological cycle of the virus, is significant. A number of viruses, which are not obligate neurotropic viruses, may also be recognized, such as HCV. The psychopathology behind HCV infection is complex

and poorly understood, involving activation of glial and local/systemic inflammatory pathways, as well as metabolic disruptions (126). However, HCV RNA has been detected in brain autopsy samples of patients at a 3-5 log lower load than in hepatocytes (127). Moreover, HCV RNA has been found in astrocytes and microglial cells (128), which may indicate viral spread within the CNS despite the fact that these cells do not express the appropriate receptors on their surface for HCV entry. In addition, HCV RNA has been detected in peripheral blood mononuclear cells (PBMCs), which may conditionally transport viral particles across the BBB (129).

Novel sequencing techniques, based on NGS and whole genome sequencing methodologies, provide a powerful means to delve into the heterogeneous viral populations of the virome and/or acutely infecting viruses within a host with psychiatric disorders, providing a fundamental basis for further analyses and studies of their possible relationship with the disease. However, few studies which either report inconsistent, varying results or are largely incomplete, have been performed to date, and these have reached controversial conclusions about the connection of viruses with psychiatric disease. For instance, in one study, whole-genome and RNA sequencing were employed for the investigation of viral infection directly in brain tissues and its association with schizophrenia, bipolar disorder and autism spectrum disorder (130). Samples from a large number of patients were analyzed; however, despite detection of diverse neurotropic DNA and RNA viruses in the brains of patients with major psychiatric disorders, such as herpesviruses, polyomaviruses, retroviruses, adenoviruses and others, neither significant qualitative (types of viruses detected) nor quantitative (viral load) differences were detected between patients and controls. Therefore, no association between viral infection of the brain and major psychiatric disorders could be inferred.

Another study based on novel sequencing technologies reported on the development of a sequence-capture method and an appropriate bioinformatics analysis pipeline that may perform detailed analysis of the human virome in a variety of clinical samples, with the aim of investigating its possible association with psychiatric disease (131). Detection of HIV-1, Torque teno virus, pegivirus, herpesvirus and human papillomavirus sequences were reported in PBMC, plasma and stool samples, but only Torque tenovirus was detected in psychiatric case samples and not in controls. A limitation of this previous study, however, was the fact that a limited number of samples and patients were examined and, notably, only peripheral samples were analyzed; since viruses present in the CNS may not be present in peripheral tissues, the study of CSF samples with the proposed method may enhance identification of viral activity in the CNS of psychiatric patients (131).

Evidence from research on models using experimental animals. Several studies on experimental animal models have been employed during the last two decades in an attempt to support the viral model of neuropsychiatric abnormalities. For instance, in such an experiment, transgenic mice that were genetically manipulated in order to express the phosphoprotein of Borna disease virus (BDV) in glial cells showed a significant reduction in synaptic density, and the expression of brain-derived neurotrophic factor and serotonin receptor, as well as a decrease in synaptic density (132). These mice then

developed behavioral abnormalities, such as hyperactivity, increased aggressiveness between males and spatial reference memory deficit. In summary, the experiment showed that the expression of BDV phosphoprotein in glial cells may directly induce neuronal degeneration that could lead to disorders resembling those of psychiatric patients. In another model of schizophrenia, where mice were experimentally infected with influenza virus at embryonic days 7, 9, 16 and 18, the mice exhibited significant postnatal brain structural abnormalities that led to abnormal behavior (133). An experimental study carried out with conventional mice (adult male and female C57BL/6J, 129X1/SvJ and nude mice Foxn1nu/Foxn1n, all 8-12 weeks old), infected with chimeric EcoHIV, as a model to reproduce physiological conditions for the development of disease in people on antiretroviral therapy (ART), revealed that ART can prevent AIDS, but not HIV-associated neuropathogenesis (134). This study suggested that, although HIV replication is suppressed by ART, the persistence of integrated, replication-competent HIV in T cells and macrophages may serve an important role in neurocognitive and behavioral aberrations.

HERVs and their role in psychiatric disease. HERVs pose a different challenge from the classical problem of proving a possible association of viral infections with psychiatric disease. They are not the mediators of a viral infection, they are part of the human virome and, as retroviruses, they have permanently integrated cDNA sequences of their RNA into the human genome, comprising 8% of its total nucleotide composition. Therefore, the key point is not to prove any kind of infection by HERVs, but, since partial expression of retroviral genes has been linked to either human health or disease, to determine the association between HERVs and psychiatric disease, HERV transcripts and/or their products should be detected and characterized in appropriate clinical samples (135-138).

Aberrant expression of HERVs has recently been identified in schizophrenia (139). Upregulated transcripts of the polymerase gene of the HERV-W family have also been detected by quantitative PCR methods in the CSF samples from a significant proportion of patients with schizophrenia, or schizoaffective disorder, as well as in the frontal cortex of brains from individuals with schizophrenia (135). In addition, elevated levels of HERV-W transcripts and proteins have been reported in the blood, CSF and brains of patients with bipolar disorder (136,137). In another study, a more detailed association between HERVs and psychiatric disease was reported, where patients with schizophrenia and bipolar disorder could be differentiated into subgroups with differing inflammatory and clinical profiles (e.g. earlier disease onset), on the basis of HERV-W family env protein antigenemia and cytokines (140).

Most studies carried out thus far on the potential association of HERVs with psychiatric disease have implicated HERV-W as the most frequently associated family (138). However, insufficient evidence is available due to the currently limited number of studies and the small sample sizes that have been employed in these studies. Further studies are required in order to obtain more unambiguous data regarding the possible role of HERVs.

The paradigm of SARS-CoV-2: An interplay of neuroinvasive, inflammatory and environmental processes. It has been suggested that the neuroinvasive properties of SARS-CoV-2 in conjunction with hyperactivity of inflammatory responses

may have an impact on the emergence of neuropsychiatric disorders during both the acute and post-infectious phases of COVID-19 (141). Specifically, in long COVID syndrome, it has been proposed that neuropsychiatric sequelae may be mainly associated with inflammatory, metabolic and degenerative processes in brain areas where the presence of the virus receptor ACE2 is significant, extending from the somatosensory cortex to the rectal/orbital gyrus, the temporal lobe, the thalamus and hypothalamus, and further, to the brainstem and cerebellar regions (142). Moreover, the socioeconomic impact of the pandemic has imposed a significant strain on human societies and individual lives due to strict lockdowns, social distancing or isolation measures, incomplete physical health recovery and a worldwide economic crisis. In addition, it has been emphasized that individuals with intellectual and developmental disabilities may be at a greater risk of mental health deterioration during COVID-19 due to the direct effect of anxiety caused by the pandemic itself and the media, as well as to restrictions brought about by lockdown regulations (143-145). These showcase the indirect effects of SARS-CoV-2 on the increase in the prevalence of neuropsychiatric disorders, which differ from the purely biological, neuroinvasive properties of the virus (146-148). Therefore, it is crucial to broaden the current knowledge about the persistence of psychiatric disorders in the post-acute phase of infection, in order to distinguish between the social and the pathophysiological origin of emergent cases, and to develop an appropriate, targeted approach for patients.

In a previous study, it was estimated that the incidence of neurological or psychiatric diagnosis within 6 months after a SARS-CoV-2 infection was 33.62% in ~250,000 patients (149). Depression and anxiety have been reported as the most common psychiatric symptoms in patients with long COVID (150,151). Notably, post-traumatic stress disorder (PTSD) has been recorded following recovery from serious epidemic events in the past and the same applies to the most recent COVID-19 pandemic (152). Sleep disturbances, fatigue, memory impairment, concentration, disorientation, confusion and other serious disorders have been associated with long COVID with debilitating effects on everyday life.

4. Conclusion

The association of viruses with psychiatric diseases still remains controversial, since we have not crossed the borderline from hypothesis to proof yet. In most cases of viral disease and epidemiology, establishing a specific virus as the causative agent depends fundamentally on confirmation in the laboratory. However, most evidence available thus far regarding the possible role of viruses in the development of psychiatric disorders comes mainly from observational, epidemiological and serological studies. A number of older diagnostic approaches, such as serological demonstration of elevated antibody titers against known viruses, are of limited value. They frequently lack high specificity, constitute indirect proof of viral infection, and are ineffective in characterizing novel viruses as potential causes of psychiatric disease.

Accurate diagnosis is complex with a number of parameters, including the patient's medical history and immune status, appropriate sample type and timing of collection, and

the methods used. Despite significant advances in diagnostic laboratory capabilities due to technological advancements in molecular methodologies, challenges remain. These advancements have enabled the high throughput of prompt and more accurate diagnostic results, reinforcing the liaison between laboratory and clinical staff. Quantitative results of viral loads and genotypic characterization of strains relevant to psychiatric or other diseases can now be obtained, further enhancing the clinical utility of diagnostic results. Moreover, they have enabled the recognition of emergent, re-emergent or known viruses that have never been associated with psychopathology before. However, studies focusing on direct virus detection in appropriate clinical samples are still limited, hindering the direct causal connection with disease onset.

Due to notable and inherent difficulties in both virus detection and the establishment of an etiological connection, satisfactory results are yet to be obtained. Firstly, detection of neurotropic viruses is hampered by their ability to establish chronic infections, either latent or with a late-onset. It is frequently difficult to determine the insidious persistence of such neurotropic viruses for months or years within the CNS, something which is attributed to their very low viral loads, particularly during dormancy. Moreover, irrespective of whether there is a direct neuroinvasive effect, or indirect activation of microglial cells and astrocytes through systemic inflammatory and neuroinflammatory processes, there is currently a lack of appropriate methodological approaches to sufficiently understand the progress of these neurotropic infections and the ensuing pathophysiology.

Secondly, the neurodevelopmental model of psychiatric disease suggests that transient viral infections at critical stages during early childhood or the prenatal period may lead to psychiatric disease. However, obtaining and preserving appropriate samples from these critical neurodevelopmental periods is difficult, especially when such viral infections are asymptomatic or subclinical.

Thirdly, the complexity of the virome and the existence of thousands of viral species, a number of which have not yet been fully described, adds to the challenge. The knowledge of viral diversity remains incomplete and numerous novel viruses are yet to be discovered. Additionally, RNA viruses evolve rapidly and novel strains with potential neuropsychiatric virulence, such as SARS-CoV-2, may emerge.

Finally, psychiatric diseases are multifactorial disorders involving a complex mixture of genetic and environmental influences. Viral agents may prime an organism for the development of psychiatric disease rather than causing it directly. Establishing the viral connection is challenging, deviating significantly from a simplistic, direct connection between infectious cause and disease, as described by Koch's postulates (153).

Further experimental research, including larger population sizes, and modern molecular methodologies accompanied by appropriate bioinformatics analysis, is essential for elucidating the complex interactions among genes, pathogens and the immune system in the etiology of psychiatric disease. The advent and further development of multi-omics technology, which collectively includes genomics, transcriptomics, proteomics, metabolomics, interactomics, epigenomics and pharmacogenomics, may enhance understanding of virus-host

interactions; decipher the pathophysiological mechanisms that underlie the role of viruses in various diseases, such as psychiatric disease; identify effective antiviral treatments and vaccines; and identify reliable biomarkers of viral infections (154). Single-cell analysis by multi-omics is particularly promising in the identification of molecular characteristics of pathophysiological processes within specific cell types, which, for example, may be infected by a virus, and how these characteristics are associated with a specific phenotype, such as a psychiatric disease. However, there is still the challenge of analyzing the large amount of biological information collected by single-cell multi-omics, especially when comparison of data from different cell types is made, something which greatly relies on the development of appropriate bioinformatics tools. Moreover, these elaborate molecular methods need to be supplemented with accurate *in vitro* models to obtain a better understanding of the pathophysiology of viral infections in association with neuropsychiatric disorders.

Most of the currently available information about the course of viral pathogenesis in the CNS is limited since it originates only from lesions analyzed by MRI data and postmortem histology (155). Despite the fact that experiments with organoids have been promising for the evaluation of viral dissemination between neuronal cells and the activation of astrocytes, their low level of complexity cannot simulate all cellular factors involved in neuroinvasion and inflammation (156). Moreover, the currently available experimental animal models may not fully replicate the course of neuropathologic conditions in humans for a very important reason. These experiments are carried out under carefully controlled laboratory conditions and may not accurately represent the complexity of those interactions between the human host, the environment and the viruses that may lead to psychiatric disease. More elaborate models are needed that will take into account as many experimental parameters as possible and will more accurately represent these complex interactions. The continuous emergence of novel viral variants with unprecedented virulence potential, as was evident with the recent COVID-19 pandemic, may also add more complexity to the design of satisfactory experimental models. Further studies are needed on the study of viral tropism, and progress before the onset of symptoms and during the course of infection and, secondly, on the identification of genetic and epigenetic host factors that may lead to CNS impairment and subsequent neuropsychiatric disease (91). More extensive, prospective studies are also needed to follow the sequelae of acute viral infections of the CNS in conjunction with other environmental stimuli that may influence the development of psychiatric diseases. By addressing these challenges, research may move closer to understanding the role of viruses in psychiatric disorders, potentially developing targeted interventions that could mitigate their impact.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

NS and CA were major contributors in writing the manuscript. SP, AT, EA and SK were contributors in writing and critical revision of the manuscript. DAS was a contributor in critical revision of the manuscript. ER was a major contributor in providing the subject of this review manuscript, as well as in writing and critical revision of the manuscript. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

DAS is the Editor-in-Chief for the journal but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The authors declare that they have no competing interests

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