






# HIV, HSV, SARS-CoV-2 and Ebola Share Long-Term Neuropsychiatric Sequelae

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**Abstract:** Long COVID, in which disease-related symptoms persist for months after recovery, has led to a revival of the discussion of whether neuropsychiatric long-term symptoms after viral infections indeed result from virulent activity or are purely psychological phenomena. In this review, we demonstrate that, despite showing differences in structure and targeting, many viruses have highly similar neuropsychiatric effects on the host. Herein, we compare severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), human immunodeficiency virus 1 (HIV-1), Ebola virus disease (EVD), and herpes simplex virus 1 (HSV-1). We provide evidence that the mutual symptoms of acute and long-term anxiety, depression and post-traumatic stress among these viral infections are likely to result from primary viral activity, thus suggesting that these viruses share neuroinvasive strategies in common. Moreover, it appears that secondary induced environmental stress can lead to the emergence of psychopathologies and increased susceptibility to viral (re) infection in infected individuals. We hypothesize that a positive feedback loop of virus-environment-reinforced systemic responses exists. It is surmised that this cycle of primary virulent activity and secondary stress-induced reactivation, may be detrimental to infected individuals by maintaining and reinforcing the host's immunocompromised state of chronic inflammation, immunological strain, and maladaptive central-nervous-system activity. We propose that this state can lead to perturbed cognitive processing and promote aversive learning, which may manifest as acute, long-term neuropsychiatric illness.

**Keywords:** HIV-1, SARS virus, virus latency, neuropsychiatry, interoception

## Introduction

COVID-19 and its causative agent, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), have left a mark on the early 21st century. Confronted with a novel pandemic scenario, researchers and scientists worldwide were compelled to work together in analyzing and containing the rapidly spreading disease. This viral pandemic continues to have interlinked effects on a global scale, and its ultimate toll is only beginning to be understood. Beyond the physical and mental strain directly caused by the virus, governmental measures to contain the spread of the disease—such as social-distancing rules, economic lockdowns and the fear-evoking and often uncertain flow of information—may have negatively affected people's wellbeing.<sup>1</sup> Furthermore, the unified focus in fighting against this pandemic has exhausted scientific and medical resources. As such, the extensive attention being paid to this newly encountered pathogen has caused the scientific and medical management of many other diseases to be deferred. For example, in the case of human immunodeficiency virus (HIV), ongoing research has stagnated, and disruptions have occurred in medical supply chains and the intervention programs necessary to contain and treat the disease.<sup>2</sup>

Despite the harmful effects of SARS-CoV-2 and the economic, medical and societal measures associated with the pandemic, highly focused research on SARS-CoV-2 has vastly increased the understanding of viruses and their infectious strategies. Countless studies on COVID-19 were conducted, and reviews were published at unprecedented pace, thereby enabling new knowledge and understanding of human-virus interactions.<sup>3,4</sup>

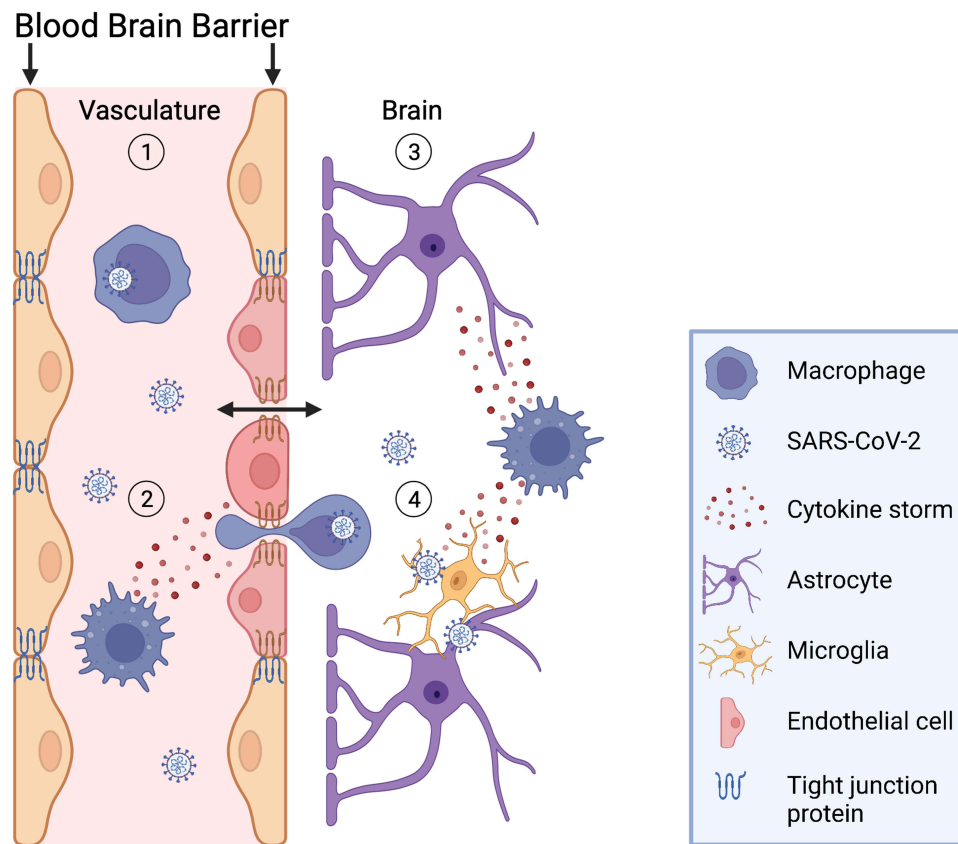
An emerging yet still vastly disregarded aspect of viral infections is their associated long-term neurological/neuropsychiatric symptoms, which can manifest as both neurological illness and psychopathological expression.<sup>1,5,6</sup> The observation of long COVID, also called post-acute sequelae of SARS-CoV-2, has recently revived the focus on the dangers associated with ongoing persistent infection after disease recovery.<sup>6,7</sup> Long-term neuropsychiatric symptoms after viral infection are well-known phenomena that have been thoroughly documented and studied in diseases such HIV-1,<sup>8</sup> herpes simplex virus 1 (HSV-1)<sup>9</sup> and recently Ebola virus disease (EVD).<sup>10,11</sup>

## Common Viral Strategies for Systemic Infection and Neuroinvasion: Primary Effects of Viral Activity

Neuroinvasion of the central nervous system (CNS) and the ability of viruses to “hide” in CNS-resident structures may be a major cause of subliminal infection and persistent disease. Given the scarcely accessible nature of CNS cells behind the blood–brain barrier (BBB) and their cytolytic sensitivity, neuronal cells can provide an ideal protective environment supporting reservoirs of persistent viral replication and latency.<sup>12,13</sup> To exploit this protective niche, viruses have been suggested to use diverse routes of neuroinvasion. HIV-1, for example, targets immune cells, such as lymphocytes (eg, CD4<sup>+</sup> T cells) and monocytes (eg, macrophages and dendritic cells) that express a high surface density of CD4 receptors, which viruses may use for facilitated transport across the BBB as a direct entrance route.<sup>13,14</sup> CD4-expressing immune cells in the brain, such as astrocytes, pericytes, and microglia, may then be recruited and subsequently harbor the viral genome within the CNS.<sup>14–16</sup> Protected by the BBB, the viral genome can then silently replicate in microglia and other CNS-resident structures, thus potentially expanding viral reservoirs and causing persistent deep structural infection and neuronal dysfunction.<sup>12,14</sup> This phenomenon of dormant infection and reactivation has been extensively studied in HIV-1, thus providing a potential explanation for the chronicity of infection and associated cognitive symptoms despite antiretroviral therapy.<sup>8,12</sup>

Similar neurotropic characteristics are increasingly being described for other viruses, such as HSV-1,<sup>17</sup> EVD,<sup>18</sup> and members of the coronavirus family, such as the mouse hepatitis virus, Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV-2.<sup>7,19,20</sup> For example, *in vitro* analysis of infected human organoids has revealed the expression of angiotensin-converting enzyme 2 (ACE2), the main receptor for SARS-CoV-2, in lymph-node-resident macrophages,<sup>21</sup> multiple brain areas, and CNS-resident glial cells, such as astrocytes, thus supporting similar mechanisms of neurovirulence across these viruses.<sup>22</sup> Although the presence of such neuroinvasive pathways remains inconclusive for many viruses, secondary CNS infection via virally induced loss of BBB integrity with elevated CNS influx of inflammatory molecules and viral particles has been widely accepted.<sup>23,24</sup> Thus, subsequent cytokine storms and associated systemic inflammation leading to multiple organ damage, cardiac dysfunction, and CNS inflammation may be a major culprit of interoceptive disturbance and cognitive malfunction (Figure 1).<sup>25</sup>

In line with these findings, we suggest that many viruses have shared neurovirulence and CNS-persistence potential, despite fundamental differences in their specific targeting and immune responses, and that viral latency and chronic CNS inflammation are the likely causes, in part, of long-term neuropsychiatric symptoms.<sup>23,26</sup> Specifically, we propose that viral latency and reactivation in CNS-harbored infected cells hijack the cellular reproductive machinery and energy expenditure and have deleterious effects on host DNA, metabolic tone and cellular communication, activation and proliferation.<sup>7,27–29</sup> The viral interference in metabolic regulatory processes may directly alter intercellular communication and the composition of the extracellular microenvironment, thereby exerting multiple effects on host phenotypic expression and viral replication.<sup>27,30,31</sup> Such dysregulated metabolite generation has been demonstrated in latent HIV-1 infection, in which stress-induced reactivation of the virus is associated with upregulated glycolysis,<sup>32</sup> and the induction of hypoxia-inducible factor 1a (HIF-1a) and mitochondrial reactive oxygen species (ROS).<sup>33,34</sup> These state-dependent shifts in metabolic processing in infected and neighboring cells, and subsequent alterations in metabolite generation, such as increased mitochondrial ROS, gamma aminobutyric acid (GABA) retention and glutamate excitotoxicity, may therefore be responsible for the functional perturbation of brain networks and cognitive disruption dependent on the viral infection phase.<sup>35–38</sup> Indeed, targeting mitochondria may represent a conserved evolutionary strategy given their heteroplasmic informational reservoir.<sup>39</sup> Thus, viruses, including SARS-CoV-2, exhibit extensive artificial intelligence processes, enabling, for example, mitochondrial hijacking.<sup>40</sup>



**Figure 1** Virus-induced enhancement of blood-brain barrier immune cell trafficking. The figure illustrates how a viral organ infection may stimulate white blood cell (eg, macrophage) and chemical trafficking across the BBB. (1) For example, SARS-CoV-2 infection in the periphery (ie, lung/gut) appears to generate an inflammatory microenvironment, releasing increased levels of activated immune cells that can travel to the brain, altering endothelial integrity, and inducing a similar inflammatory phenomenon there. (2) The increased macrophage excitation, number of immune cells and stimulated cytokine release causes this endothelial disruption, diminishing the immune privilege of the brain. (3) Enhanced trafficking of uninfected and possibly infected macrophages may also facilitate the transport of viral particles into the brain thereby altering microglia and astrocytes homeostasis, building viral reservoirs and affecting cellular interaction. (4) Infection-induced cytokine storms in the brain may further aid viral replication by damaging host DNA, stimulating an even greater rate of RNA polymerase errors and thus, enhanced levels of mutation, causing systemic and persistent infection. We surmise this infection stimulated inflammatory neuronal environment alters mitochondrial function either directly or indirectly in that it requires greater levels of metabolic substrates (eg, oxygen and glucose) to sustain normal functionality, thereby competing with normal neuronal energy demands. As a result, stress-induced viral reactivation and subsequent induction of HIF-1 $\alpha$  and mitochondrial ROS may lead to abnormal metabolite generation and distribution, for example, in the form of increased mitochondrial GABA retention and extracellular or cytoplasmic glutamate accumulation, causing functional perturbation of brain networks and disruption in cognitive processing.

## Common Neuropsychiatric Sequelae of Viral Infection: Secondary Effects of Viral Activity

Interestingly, virally induced neurological or neuropsychiatric effects are similar among viruses.<sup>26</sup> Often, the sequelae of infections with viruses suggested to be neurovirulent—such as HIV-1, HSV-1, EVD, MERS-CoV, and SARS-CoV-2—have been reported to include encephalopathies (eg, meningitis or encephalitis, seizures, and strokes) with altered mental status; brain fog; fatigue; and increased neuropsychiatric incidence of anxiety, depression and post-traumatic stress (Table 1).<sup>5,9,11,41–43</sup> The significance level of the following presented data is  $p < 0.05$ .

Notably, a recent follow-up study of 197 EVD survivors two years after their discharge from the Ebola treatment center has reported a prevalence of anxiety, depression, and post-traumatic stress disorder (PTSD) of ( $n = 49$ , 24.9%), ( $n = 93$ , 47.2%), and ( $n = 43$ , 21.8%), respectively, with older survivors ( $\geq 30$  years) demonstrating an increased likelihood of developing anxiety (AOR = 3.04, 95% CI 1.2–7.7;  $p = 0.019$ ) and depression (AOR = 8.5, 95% CI 2.68–27.01;  $p = 0.001$ ) in comparison to younger survivors ( $< 30$  years).<sup>11</sup> In addition, decreased exercise after treatment has been associated with greater risks of anxiety and depression (AOR = 2.63, 95% CI 1.25–5.54;  $p = 0.011$ ).<sup>11</sup> Furthermore, other studies have reported similar neuropsychiatric incidents during and after SARS-CoV-2 infection.<sup>41,44–46</sup> In a systematic analysis of 72 studies including 3559 cases of coronavirus disease (ie, SARS-CoV, MERS-CoV, and SARS-CoV-2) between the ages of 12 and 68 years, Rogers et al have reported a prevalence of anxiety (35.7%; 95% CI 27.6–44.2) and depression (32.6%; 95%

**Table 1** Neuropsychiatric Disorders Associated with Viral Infections

Virus	Neuropsychiatric Disorder					
	Anxiety Disorders (eg, Generalized Anxiety Disorder)		Depressive Disorders (eg, Major Depressive Disorder)		Stress Disorders (eg, Post-Traumatic Stress Disorder)	
	Acute Phase	Latent Phase	Acute Phase	Latent Phase	Acute Phase	Latent Phase
SARS-CoV-2	X	X		X		X
HIV-1	X	X		X		X
EVD	X	X		X		X
HSV-1				X		

**Notes:** The table shows the main neuropsychiatric disorders reported during and after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), human immunodeficiency virus 1 (HIV-1), Ebola virus disease (EVD), and herpes simplex virus 1 (HSV-1) infection. The table is divided into acute-phase presentation and latent-phase presentation (>60 days after initial infection).

CI 24.7–40.9) during acute infection with symptoms of anxiety (12.3%; 95% CI 7.7–17.7), depression (10.5%; 95% CI 7.5–14.1) and trauma (30.4%; 95% CI 23.9–37.3) persisting months (60 days to 12 years) after the illness.<sup>47</sup> A 6-month retrospective COVID-19 cohort study has reported an array of additional neurological issues, such as dementia, encephalitis, intracranial hemorrhage, ischemic stroke, parkinsonism, and myoneural junction and muscle diseases.<sup>48</sup>

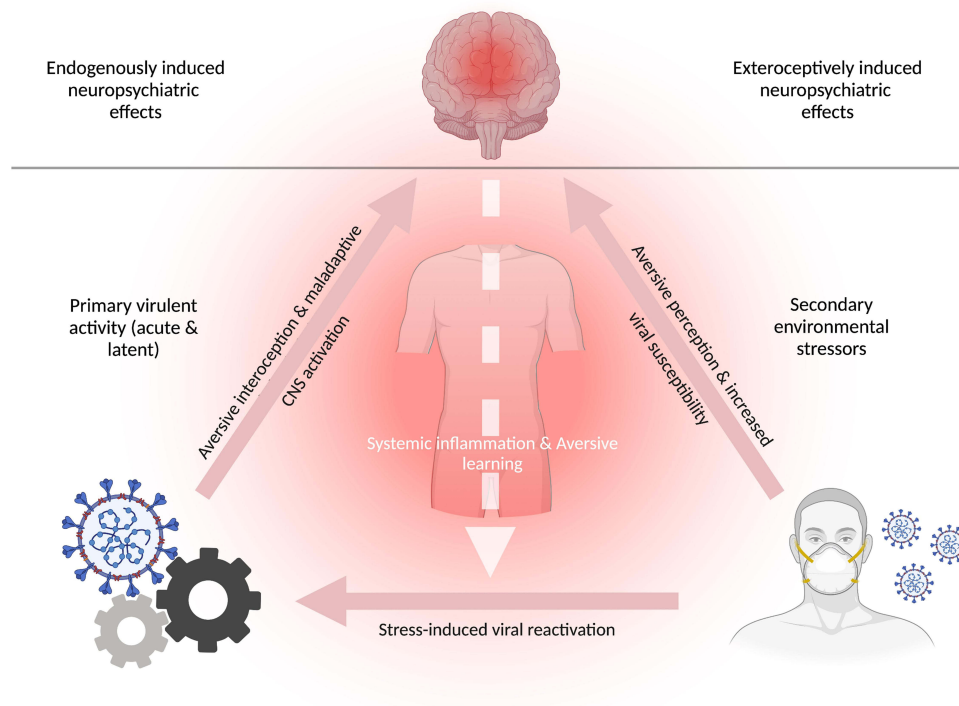
HIV-associated neurological disorders and neuropsychiatric disorders have been observed during the course of life-long HIV-1 infections. Singer and Thames have reported that approximately 24% of the patients with HIV infections display comorbid encephalopathy (eg, aseptic meningitis), with cognitive, motor, and behavioral abnormalities in some cases, despite antiretroviral therapy.<sup>49</sup> Furthermore, progressive dementia, changes in mental status, and a substantial prevalence of mood disorders have been reported in HIV infection.<sup>49,50</sup> A study conducted by Celesia et al including 251 HIV-infected individuals demonstrated the presence of anxiety in 47% of the subjects (n = 118). Interestingly, within the anxiety group only 21.2% (n = 25; p = 0.047) of the subjects were currently receiving antiretroviral therapy compared to 32.3% (n = 43; p = 0.047) within the group without anxiety.<sup>51</sup> It has been shown that up to 20% of HIV-associated anxiety manifests as generalized anxiety disorder.<sup>49</sup> PTSD has been estimated to occur in up to 54% of HIV-infected individuals, with the highest prevalence among minority groups and individuals experiencing persistent pain.<sup>49</sup> A study conducted by Smith et al including 145 HIV/AIDS diagnosed individuals that have been experiencing persistent HIV-associated pain demonstrated that 53.8% (n = 78) of the participants met the diagnostic criteria for PTSD.<sup>52</sup> Major depressive disorder (MDD) is another highly prevalent clinical presentation in HIV infection.<sup>49</sup> A high correlation between anxiety symptoms and depressive symptoms during the course of a life-long HIV infection has been established (p < 0.01).<sup>53</sup> Interestingly, very limited data on neuropsychiatric symptoms are available for HSV despite its high occurrence; HSV-1 infection rates are as high as 80% in the general population.<sup>9</sup> MDD is the only studied and verified neuropsychiatric sequelae of HSV-1 infection that we could find in the literature to date.<sup>54</sup> In a UK Biobank cohort study, Ye et al demonstrated significant associations between depression status and HSV-1 antibody (OR = 1.09, 95% CI 1.02–1.16; p = 0.024) and seropositivity (OR = 1.28, 95% CI 1.12–1.47; p < 0.003).<sup>54</sup>

Although the common neuropsychiatric effects of different viruses indicate the existence of shared neurovirulent processes, other factors may be at play. Mental disorders, such as those described above, are diagnosed based on disease-specific criteria, as defined in diagnostic tools such as the *Diagnostic and Statistical Manual of Mental Disorders*.<sup>55</sup> By implementing psychological tests, life history records and therapist-guided interviews, the psychiatric assessment of mental disorders concentrates largely on externally observable behavior, possibly leaving a physiological causation masked.<sup>55,58</sup> This aspect must be considered when gathering and reporting data, because the observable behavior may be reducible to multiple factors. In a viral pandemic, anxiety, depression, and trauma can be environmentally (eg, exteroceptive) induced in infected and non-infected people alike.<sup>56,59</sup> Therefore, psychopathological expression in infected individuals does not ultimately imply the presence of virulent activity but can also result from unconscious and conscious stress induced, for example, by social stigma, individual behavior (eg, substance abuse), experience with

invasive medical procedures, long-term isolation and medical segregation, inconsistent information or the awareness of one's affliction.<sup>1,49,57</sup> Thus, the frequently observed disease-associated loss of energy (eg, fatigue), diminished interest in one's environment (eg, anhedonia), and diminished ability to think (eg, brain fog)—symptoms that may lead to the diagnosis of MDD in infected individuals<sup>60</sup> may be reducible to purely biological phenomena (eg, infection-stimulated immunological responses), secondary environmentally induced psychological phenomena (eg, exteroceptive responses) or both.<sup>49</sup> Likewise, misattributions can result in the diagnosis of other neuropsychiatric disorders.<sup>49</sup> Especially trauma- and stressor-related disorders (eg, PTSD), which diagnostic criteria are strictly reliant on exteroceptive events (ie, distinct stressors), may be subject to misassessment.<sup>52</sup>

## A Holistic Cycle of Neuropsychiatric Effects and Latent Viral Infection

Understanding the different processes affecting individuals' health and behavioral outcomes is essential for successful disease treatment and containment. Both a virally induced endogenous response that alters neuronal functioning in the CNS and an exteroceptive evolved fear of the disease can establish a neuronal level of activity for maladaptive perception and learning.<sup>23</sup> Furthermore, chronic psychological stress may increase individuals' susceptibility to viral infection or reinfection through proinflammatory responses and suppression of cellular immunity.<sup>61</sup> We surmise that these effects can be detrimental, particularly in infected individuals. We further suggest that, in a positive feedback loop of cyclical reinforcement, psychological stress may foster the reactivation and aggravation of viral activity in infected individuals, thereby increasing acute psychopathological expression and susceptibility to neuropsychiatric sequelae (Figure 2).



**Figure 2** A positive feedback loop of primary virulent activity and secondary stress-induced reactivation with neuropsychiatric sequelae. The figure illustrates two distinct factors (ie, levers) that, after stimulation, may produce neuropsychiatric illness. The figure is divided into exteroceptively induced neuropsychiatric effects (top right) and endogenously induced neuropsychiatric effects (top left). The human mask (bottom right) represents external factors (ie, lever 1), such as social stigma, governmental restrictions, individual- and public behavior, or fear induced by inconsistent information and the awareness of one's affliction; these stressors may cause secondary non-virulent emergence of neuropsychiatric sequelae (eg, anxiety) that can increase susceptibility to viral infection, owing to inflammation-associated immunosuppression, in infected and non-infected individuals. The cogwheels (bottom left) represent virulent activity and the reactivation of latent viruses in the CNS (ie, lever 2), which, after stress-induced activation, may cause shifts in the metabolic processing of infected and neighboring cells, and subsequently alter neuronal metabolite generation and the functionality of brain networks. In a bi-partite manner (ie, via primary virulent activity or secondary exteroceptive stressors), systemic inflammation and aversive perception can be generated, thus providing a basis favoring maladaptive learning. In infected individuals, the activation of each lever may trigger a positive feedback loop of virus-environment-reinforced systemic responses that maintains the host in an immunocompromised state of chronic inflammation (eg, cytokine storm), interoceptive aversion (eg, chronic sympathetic nervous system activation), and maladaptive CNS activity (eg, metabolic disruption of infected CNS-resident glial cells). Therefore, the stimulation of each cyclical element can lead to perturbed cognitive processing and promote aversive learning, which may manifest as acute and long-term neuropsychiatric illness.

In a predictive coding model, virally induced inflammation and disease-associated interoceptive responses (eg, activation of the autonomic nervous system) foster aversive learning by conceptual overgeneralization in a top-down fashion.<sup>62</sup> For example, virally induced chronic states of perceived pain or of anxiety that is not due to a distinct consciously perceived sensory cause may result in the host connecting the aversion to other non-aversive components of higher-order cognition.<sup>23</sup> Consequently, the overgeneralization and association of aversive infection-related interoceptive responses to neutral sensory evidence can be funneled and integrated into various memory components.<sup>62</sup> This maladaptive learning effect may be strengthened by the virulent changes in the neuronal milieu, thus giving rise to, for example, persistent and generalized anxiety, and maintaining the body in an immunocompromised state of chronic viral activity and aversive psychological reinforcement.<sup>23,62</sup>

In a bottom-up fashion, negative external stimuli (eg, shock-like exteroceptive experiences) may similarly prompt the reactivation of latent viral particles with subsequent shifts in metabolic processing in infected and neighboring cells.<sup>32,63</sup> Such stress-induced responses may be driven psychologically (eg, by trauma or anxiety)<sup>64</sup> or physiologically (eg, by muscle injury),<sup>65</sup> thereby inducing effects such as alterations in redox balance and ROS production, and further accelerating the inflammatory cycle of subliminal viral infection.<sup>63</sup> Stress-induced viral reactivation and associated upregulation of pro-inflammatory cytokines can modulate host circulatory barriers (eg, the BBB and gut endothelial cells) and increase their permeability (ie, leakage), thereby enabling unhindered diffusion of viral particles and other exo- and endo-toxins.<sup>66–70</sup> In addition, circulatory barrier disruption may promote microbial dysbiosis and dysregulated interactions among bacteria, bacteriophages, the virus, and the host. Consequently, further upregulation of pro-inflammatory signaling may increasingly induce interoceptive aversion, such as through chronic activation of the sympathetic nervous system.<sup>70–73</sup> Hence, environmentally induced upregulation of virulent activity not only strongly facilitates maladaptive learning but also may directly alter the functionality of affected brain networks, such as by causing acute anxiety states and persistent anxiety traits.<sup>32,74</sup>

## Conclusion

The observation of long COVID, also known as post-acute sequelae of SARS-CoV-2, has recently accelerated scientific interest in the emergence of neuropsychiatric long-term persistent symptoms after viral infections. Although differences exist in viral harboring cells and targeting mechanisms, the neuropsychiatric effects of several viruses on the host are highly similar; the most commonly reported comorbidities with these infections include anxiety, depression, and post-traumatic stress. Although these mutual neuropsychiatric effects can result from primary viral activity and shared neurovirulent processes, secondary induced exteroceptive stress, such as disease-associated uncertainty and fear, may also be a culprit of psychopathological expression that can increase susceptibility to viral infection or reinfection. Importantly, in a positive feedback loop of virus-environment-reinforced systemic responses, we hypothesize that a cycle of primary virulent activity and secondary stress-induced reactivation maintains the host in an immunocompromised state of chronic inflammation, immunological strain, and maladaptive CNS activity. The stimulation of each cyclical element can then lead to perturbed cognitive processing and aversive learning, which may manifest as acute and long-term neuropsychiatric illness. In-depth research on the persistent effects of virulent activity in the CNS on cognitive processing and the adaptive role of mitochondria in health and disease (ie, latent vs active viral infection) is strongly recommended.

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## Data Sharing Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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