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The multitaskers of the brain: glial responses to viral infections and associated post-infectious neurologic sequelae

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Abstract

Many viral infections cause acute and chronic neurologic diseases which can lead to degeneration of cortical functions. While neurotropic viruses that gain access to the central nervous system (CNS) may induce brain injury directly via infection of neurons or their supporting cells, they also alter brain function via indirect neuroimmune mechanisms that may disrupt the blood-brain barrier (BBB), eliminate synapses, and generate neurotoxic astrocytes and microglia that prevent recovery of neuronal circuits. Non-neuroinvasive, neurovirulent viruses may also trigger aberrant responses in glial cells, including those that interfere with motor and sensory behaviors, encoding of memories and executive function. Increasing evidence from human and animal studies indicate that neuroprotective antiviral responses that amplify levels of innate immune molecules dysregulate normal neuroimmune processes, even in the absence of neuroinvasion, which may persist after virus is cleared. In this review, we discuss how select emerging and re-emerging RNA viruses induce neuroimmunologic responses that lead to dysfunction of higher order processes including visuospatial recognition, learning and memory, and motor control. Identifying therapeutic targets that return the neuroimmune system to homeostasis is critical for preventing virus-induced neurodegenerative disorders.

Graphical Abstract

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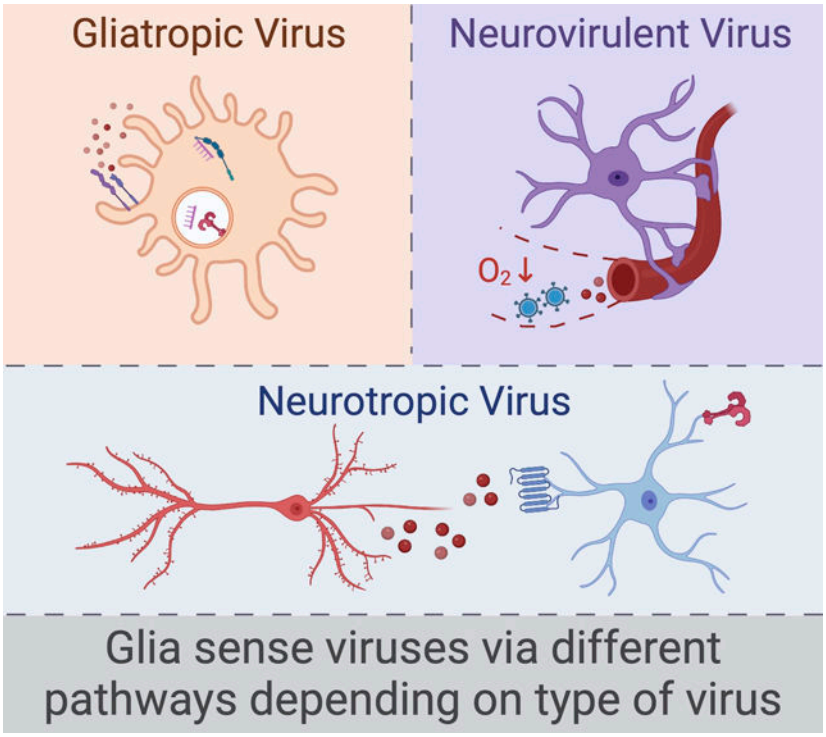

Introduction

A new paradigm in neuroimmunology has emerged whereby innate immune molecules are recognized as modulators of a variety of central nervous system (CNS) functions throughout life. These include the maintenance of blood-brain barrier (BBB) function (Jung et al., 2012; Wosik et al., 2007), synaptic networks (Filiano et al., 2016), microglial physiology (Butovsky & Weiner, 2018; Hickman et al., 2013; Yeh & Ikezu, 2019), astrogenesis and glial-mediated synapse remodeling (Kanski, Strien, Tijn, & Hol, 2013; Vainchtein et al., 2018), and repair (Amor & Woodroofe, 2014; Z. Chen & Palmer, 2008; Cossetti, Alfaro-Cervelló, Donegà, Tyzack, & Pluchino, 2012; Healy, Yaqubi, Ludwin, & Antel, 2019). Within the normal brain, innate immune molecules are expressed by resident cells, including perivascular myeloid and ependymal cells, microglia, astrocytes, oligodendrocytes, and neurons (Adelson et al., 2016; Blank et al., 2016; Cheng, Jin, Zhang, Tian, & Zou, 2011; Datwani et al., 2009; Dixon-Salazar et al., 2014, p.; Ejlerskov et al., 2015; Fourgeaud et al., 2010; Glynn et al., 2011; Green et al., 2012; Hirsch et al., 2009; Michelucci et al., 2015; Peferoen, Kipp, Valk, Noort, & Amor, 2014; Rey, Balschun, Wetzel, Randolf, & Besedovsky, 2013; C. Wang et al., 2020). The cellular source of these molecules, which include classical pattern recognition receptors (PRRs), complement proteins (C1q, C3, C4), major histocompatibility (MHC) I, cytokines (i.e. type I interferon (IFNαβ), interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF), transforming growth factor (TGF)-β), and chemokines (CXCL12, CXCL1), determine their effects on normal brain function. Some innate immune molecules, such as C1q and C3, are produced within the normal CNS (Veerhuis, Nielsen, & Tenner, 2011), contributing to CNS glial communication and synapse loss during normal forgetting, sleep and aging (Clark et al., 2021; Datta et al., 2020; Shi et

al., 2015; Stephan et al., 2013; C. Wang et al., 2020), and increase in diseases with cognitive deficits (Hong et al., 2016; Michailidou et al., 2015; Vasek et al., 2016). Locations and levels of cytokine expression in the brain may also differentially impact their effects. For example, low basal levels of IFNβ promote neuronal survival and neurite outgrowth within the hippocampus (Ejlerskov et al., 2015), and disruptions to the IFNβ-IFNAR signaling promote Parkinson's disease-like phenotypes (Magalhaes et al., 2021). Conversely, increased expression of IFNβ within the choroid plexus during aging is associated with decreased hippocampal neurogenesis (Baruch et al., 2014), which is critical for the formation of new memories. Similarly, IFNα treatment suppresses behavioral activity and reduced hippocampal neurogenesis in primates (Kaneko, Nakamura, & Sawamoto, 2020). These data suggest that the IFNAR signaling pathway may mediate both neurogenic and anti-neurogenic effects depending on the context. Factors that influence the effect of a cytokine signaling pathway could include variations in the cytokine and cellular milieu, the cytokine and receptor expression levels, and the microanatomical location of cytokine production within the CNS. This paradigm contrasts with previously held beliefs that innate immune responses within the CNS always induce pathology (Fig. 1). It also provides a framework for exploring mechanistic links between host-pathogen responses and neurodegenerative diseases, especially those that impact cognitive function.

Viruses are an underappreciated factor in the development of neurodegenerative diseases, and many classes of viruses are associated with long-term neurologic symptoms (Table 1). A major example is the neuroinvasive RNA arboviruses, which include members of the *Bornaviridae, Flaviviviridae, Phenuiviridae, Paramyxoviridae, Picornaviridae, and Togaviridae* families (Table 1). The flaviviruses are transmitted by arthropod vectors and associated with neurocognitive impairments in the majority of survivors. These viruses may be associated with acute neuroinfectious diseases, such as meningitis and encephalitis, and include viruses that target neurons and/or glia. Members of the *Flaviviridae* family, West Nile (WNV) and Zika (ZIKV) viruses, invade the CNS via retrograde transport along neurons or cross the BBB within arthropod exosomes (Zhou et al., 2018). Diseases of pathological forgetting and dysexecutive function have also been reported in patient survivors of respiratory viruses that may not undergo neuroinvasion. Members of the *Pnemoviridae*, *Orthomyxoviridae*, and *Coronaviridae* families that cause infections of the upper and lower respiratory tract, including metapneumovirus, influenza A virus (IAV), and Severe acute respiratory syndrome coronavirus (SARS-CoV)-2, may also lead to long-term neuropsychiatric sequelae. Survivors of severe IAV, which may be neuroinvasive, may develop prolonged cognitive impairment and psychiatric disorders (Denke et al., 2018), although this has not been extensively studied and hypoxia is likely a contributing factor. Recovery of SARS-CoV-2 has been associated with a variety of neuropsychiatric diseases, even in those that do not experience severe symptoms acutely (Taquet, Geddes, Husain, Luciano, & Harrison, 2021).

Neuroimmune mechanisms that lead to neurological sequelae in the setting of recovery from infections with emerging RNA viruses are not well understood. Given that these mechanisms may be generalizable to multiple diseases of cognition or motor dysfunction, and that there are no treatments that reverse deficits, there is a pressing need to define the mechanisms that promote cognitive recovery from neurotropic viral infections and

to identify biomarkers that identify patients at risk for memory disorders. Building on prior reviews (Klein et al., 2019; A. Soung & Klein, 2018), we will discuss recent data on alterations in glial functions that underlie defects in higher order processes including visuospatial recognition, learning and memory and motor control that occur as a result of infections with emerging RNA viruses.

RNA viruses linked to neurological sequelae

WNV, which emerged in North America in 1999, is the leading cause of domestically acquired arboviral disease in the United States (Sejvar, 2014), while ZIKV, the cause of a 2015 epidemic in South America, is still emerging (Weaver, 2017). WNV targets neurons throughout the adult human CNS, while ZIKV more specifically targets neurons in the hippocampus and cortex (Figueiredo et al., 2019). Both viruses are associated with neurological sequelae (Nicastri, Castilletti, Balestra, Galgani, & Ippolito, 2016; Sejvar, 2014; Zucker et al., 2017), which has been most extensively studied in WNV survivors. Studies evaluating rates of persistent memory impairment in patients previously diagnosed with WNV neuroinvasive disease (WNND) using neuropsychological testing report that 40–70% exhibit cognitive symptoms than continue to worsen for years after recovery from acute infection (Murray et al., 2018; Sadek et al., 2010; Weatherhead et al., 2015). Other neurotropic encephalitic arboviruses that lead to neurocognitive sequelae in US patients include LaCrosse, Eastern Equine Encephalitis, and Powassan viruses (Byrd, 2016; Hermance & Thangamani, 2017; Ronca, Dineley, & Paessler, 2016). Worldwide, neuroinvasive encephalitic arboviruses cause 50–100,000 cases/year with neurocognitive sequelae in most survivors (LaBeaud, Bashir, & King, 2011). Human immunodeficiency virus (HIV)-1, a retrovirus that invades the CNS via infected monocytes (Davis et al., 1992) leads to HIV-associated neurocognitive disorders (HAND), whose incidence has not decreased in the era of combination antiretroviral treatment (cART) (X. Chen, Zhang, & Zhang, 2020).There are currently no vaccines and treatments that mitigate persistent neurocognitive impairments associated with these neuroinvasive viral infections.

IAV and SARS-CoV-2, in particular, are the causes of worldwide pandemics with persistent neurocognitive diseases in survivors (Frontera et al., 2020; Heneka, Golenbock, Latz, Morgan, & Brown, 2020; Needham, Chou, Coles, & Menon, 2020; Serrano-Castro et al., 2020; Tansey et al., 2022). Pandemic H1N1 IAV RNA has been detected within the CNS of deceased patients who developed myelitis, meningitis, seizures, and acute necrotizing encephalopathy (Bohmwald, Gálvez, Ríos, & Kalergis, 2018; Liang, Yang, & Lin, 2018; Muhammad Ismail, Teh, & Lee, 2015; Ruisanchez-Nieva, Martinez-Arroyo, Gomez-Beldarrain, Bocos Portillo, & Garcia-Monco, 2017; Simon et al., 2013; Xia, Zhu, Hu, Wang, & Zhang, 2014). Patients that survive acute neurologic disease may also develop idiopathic Parkinson’s disease (Jang et al., 2009). Following acute SARS-CoV-2 infection, a majority of people recover within a few weeks; however >50% of recovered individuals continue to experience neurological diseases, which has been termed post-acute coronavirus syndrome (PACS) (Mehandru & Merad, 2022; Taquet, Luciano, Geddes, & Harrison, 2021; F. Wang, Kream, & Stefano, 2020). Vaccinated individuals continue to experience breakthrough infections, which reportedly reduces PACS by only 50% (Antonelli et al., 2022; Taquet, Luciano, et al., 2021). While there is little evidence of SARS-CoV-2

neuroinvasion (Espíndola et al., 2021; Paterson et al., 2020; Thakur et al., 2021), clinical studies report blood-brain barrier (BBB) disruption, and microglial activation in various brain regions upon post-mortem examination. In addition, a subset of individuals, including those with milder symptoms, suffer from a dysexecutive syndrome consisting of memory and learning impairments, inattention, disorientation, or poorly organized movements (Ortelli et al., 2021).

Higher cortical functions and systems impacted by infection with emerging neurotropic RNA viruses

Neuroimaging findings in patients with neuroinvasive viral diseases often reveal inflammation within various parts of the limbic system, including the cingulate gyrus/cortex, basal ganglia, thalami, and hippocampus (HPC). The HPC, in particular, exhibits higher susceptibility to viral infection, blood-brain barrier dysfunction, and inflammation (Chapman et al., 2012; Ivanidze et al., 2019; Johnston & Webster, 2009; Petito, 2004). The primary circuitry of the HPC includes trisynaptic sequential synapses between the entorhinal cortex (EC), the dentate gyrus (DG) granule cells, and pyramidal cells of the cornu ammoni (CA3 to CA1) (Basu & Siegelbaum, 2015; Chauhan, Jethwa, Rathawa, Chauhan, & Mehra, 2021). The HPC processes information derived from the EC and in turn influences cortical and subcortical areas that modulate complex behavioral processes involving recognition, formation and retrieval of declarative memories and spatial relationships. These circuits utilize excitatory amino acids aspartate or glutamate. Inhibitory GABAergic interneurons within the HPC modulate local synaptic transmission within this structure (Fazekas et al., 2022). Thus, alterations in the synthesis, storage, release, or inactivation of either the excitatory or inhibitory amino acids could lead to localized excitotoxicity with disruption of the circuit. Neural precursor cells that reside within the subgranular zone (SGZ) of the DG generate new neurons throughout life (Boldrini et al., 2018; Tartt et al., 2018). Studies in animal models indicate that adult neurogenesis is essential for visuospatial learning.

While most arboviruses infect neurons and/or astrocytes across brain regions, animal studies of ZIKV infection demonstrate high tropism to adult hippocampal neurons (Figueiredo et al., 2019; Garber et al., 2019), SGZ neural progenitor cells (H. Li et al., 2016), astrocytes (van den Pol, Mao, Yang, Ornaghi, & Davis, 2017), and glial progenitor cells (C. Li et al., 2018; Schultz et al., 2021), consistent with reports of damage and dysfunction of this brain region leading to neurocognitive sequelae (da Silva, Frontera, Bispo de Filippis, Nascimento, & for the RIO-GBS-ZIKV Research Group, 2017; Zucker et al., 2017). Damage to the HPC produces large and persistent effects on behavior, with cognitive impairments similar to those observed in human dementias. Consistent with this, survivors of arboviral infections exhibit features that overlap with neurodegenerative dementias such as Alzheimer's disease (AD) and Parkinson's disease (PD). Magnetic resonance imaging (MRI) of patients that have recovered from WNV, including those without neuroinvasive disease, report atrophy of the posterior cingulate and insular cortices, and the hippocampus and entorhinal regions in the temporal lobe (Rev in (Borisow, Mori, Kuwabara, Scheel, & Paul, 2018), as observed in AD (Ledig, Schuh, Guerrero, Heckemann, & Rueckert, 2018). Involvement of the substantia nigra, which exhibits degeneration in patients with PD, has also been reported (Bosanko et al., 2003; Schafernak & Bigio, 2006) as has

parkinsonism (Lenka, Kamat, & Mittal, 2019). While learning and memory disorders appear to worsen over time in WNV-recovered patients, parkinsonism and other movement disorders eventually resolve (Lenka et al., 2019). Recently, MRI-based studies examining 60 COVID-19-recovered patients at three months after acute infection reveal micro-structural alterations within gray matter areas involving the olfactory system, hippocampus and cingulate cortex, consistent with ongoing anosmia, tremors, impaired mobility and memory loss (Lu et al., 2020). Overall, these findings support the need for larger studies utilizing neuropsychological testing and neuroimaging in patients with post-infectious neurologic dysfunction after recovery from respiratory viruses.

Glia recognize neuroinvasive viral infections via pattern recognition, cytokine signaling, and damage sensing

Viruses that invade the CNS may infect glia, neurons, or both, leading to inflammation, tissue damage, or cell death (Fig. 2). Depending on the type of virus, glia use a variety of mechanisms to detect neuroinvasive viruses. One such mechanism is through the expression of pattern recognition receptors (PRRs), surface-expressed or cytosolic receptors that recognize common and conserved elements of pathogens that are not generally shared by host cells. PRR engagement generally leads to a downstream signaling cascade resulting in the expression of many host genes with antiviral effects. Neurons and glia express a range of PRRs in both humans and mice, as recently reviewed (Gern et al., 2021; L. Li, Acioglu, Heary, & Elkabes, 2021). Microglia especially express a wide breadth of PRRs, including toll-like receptors (TLRs) 1–10, allowing recognition of viral double-stranded RNA, single-stranded RNA, and viral envelope proteins (Gern et al., 2021; Martín-García & González-Scarano, 2009). Interestingly, astrocytic expression has also been reported for almost all of these TLRs (Furr & Marriott, 2012; Gern et al., 2021), albeit at lower levels than that observed in microglia. Oligodendrocytes, conversely, do not appear to express significant numbers or amounts of PRRs, but have been reported to express low levels of TLR-2 and TLR-3 (Martín-García & González-Scarano, 2009). The importance of TLRs in specifically protecting the CNS against viral encephalitides is clearly illustrated by the fact that TLR-3 deficiency in mice and humans confers heightened risk of herpes simplex virus 1 (HSV-1, a DNA virus) encephalitis without major alterations in peripheral infection severity (Reinert et al., 2012; Zhang et al., 2007). In fact, in the absence of TLR-3, astrocytes fail to mount an innate response to HSV-1 while microglia retain the ability to respond, likely reflecting differences in their PRR repertoires (Sato et al., 2018).

Upon PRR engagement, microglia and astrocytes produce cytokines and other inflammatory mediators such as TNF-α, IL-12, CXCL2, CXCL10, and cyclooxygenase-2 (Chung & Benveniste, 1990; Esen & Kielian, 2006; J.-I. Kim et al., 2007; Phares, Stohlman, Hinton, & Bergmann, 2013; Walsh, Perry, & Minghetti, 2000). Likewise, TLR engagement can also trigger the type I interferon pathway (Zheng, Chen, Chu, Zhu, & Jin, 2019), leading to secretion of interferon-α and interferon-β (IFN-α/β). These cytokines signal through the interferon-α receptor (IFNAR) in both an autocrine and paracrine fashion, initiating a regional state of antiviral alarm by causing the upregulation of hundreds of interferon stimulated genes (Schneider, Chevillotte, & Rice, 2014). Therefore, TLR signaling in CNS cells can directly lead to neuroinflammation, with impacts on cognition and behavior. Mice

treated systemically or intracranioventricularly with lipopolysaccharide, a potent bacterial TLR-4 ligand, displayed microglial activation and acute underperformance in Morris water maze, passive avoidance, and pole climb tests of memory and motor coordination (Zhao et al., 2019). In an *in vitro* assay of BBB permeability, exposure to agonists for TLR7 or the intracellular PRRs MDA5 or RIG-I increased barrier permeability in an IFNAR-dependent fashion (Daniels et al., 2014).

The neuroinflammatory effects of neural cell PRR engagement can contribute to neurologic disease. For example, TLR-7 contributed to pathogenesis in an animal model of enterovirus 71 (EV71) in which neonatal mice were infected intracranially (Luo et al., 2019). In this study, mice deficient in TLR-7 exhibited enhanced infection of astrocytes, enhanced neural cell apoptosis, and reduction in the integrity and amount of neurofilament protein (Luo et al., 2019). Interestingly, these changes in viral tropism and neuronal damage occurred in the absence of overall changes in viral titer in the brain (Luo et al., 2019).

In cases in which glia do not directly play host to viral infections, glia may rely on similar signals from infected neurons to initiate an immune response (Fig. 2). Like glia and immune cells, neurons also express PRRs that can lead to the production of cytokines that signal to nearby glia. Infected cells may suffer injury and consequently release proteases, complement factors, and damage-associated molecular patterns (DAMPs) such as host DNA, ATP, and chaperone proteins (Karve, Taylor, & Crack, 2016). These factors can signal to glial cells through complement receptors, purinergic receptors, TLRs, double-stranded DNA receptors, and others (G. Y. Chen & Nuñez, 2010; Davalos et al., 2005; Kanmogne & Klein, 2021). DAMPs are produced by damaged or dying cells during infection as well as other sources of CNS insult, such as neurodenerative disease, sterile inflammation, ischemic stroke, or traumatic injury (Bradbury & Burnside, 2019; Kigerl, de Rivero Vaccari, Dietrich, Popovich, & Keane, 2014; Yates, Anthony, Ruitenberg, & Couch, 2019). Therefore, damage-detection receptors may be one mechanism explaining similarities between the downstream cognitive sequelae of diverse types of CNS insults. This principle is illustrated by studies of traumatic spinal cord injury that link acute damage to TLR-4 signaling, astrocytic production of IL-1β and other cytokines, and leukocyte recruitment (Dickens et al., 2017; Didangelos et al., 2016).

Finally, mammalian mechanisms of viral detection are still being discovered. A recent report found that monocytes can respond to HSV-1 independent of PRRs via viral-mediated degradation of a negative regulator of the type I interferon pathway (Gaidt et al., 2021). This so-called “self-guarding” could play a similar role in allowing cells of the CNS to detect viral infection and other types of neuronal injury.

Astrocytes regulate the blood-brain barrier and respond to viral infection via cytokine signaling

Glia cooperate with endothelial and mural cells to regulate the blood-brain barrier (BBB) (Daneman & Prat, 2015). In the CNS, BBB regulation is essential to the immune response to viruses; a permeable BBB may allow pathogen entry to the CNS via passive diffusion or host cell transport (Ayala-Nunez & Gaudin, 2020), but is also necessary to allow peripheral immune cells to enter the CNS to aid in pathogen clearance. In response to signals from

neurons and immune cells, astrocytes regulate BBB permeability via their cellular processes, which ensheath blood vessels and vascular tubes (Daneman, 2012; Daneman & Prat, 2015).

Neuroinvasive infection may either precede or follow a change in BBB permeability. Once a viral infection has been established in the brain, cytokine signals derived from within the CNS can lead to alterations in BBB permeability. For example, IFNAR signaling in cerebellar astrocytes leads to an decrease in BBB permeability after intracranial inoculation of West Nile virus (Daniels et al., 2017). Astrocytic type I interferon signaling is also necessary to activate microglia and recruit peripheral immune cells after vesicular stomatitis virus (Chhatbar et al., 2018), and is critical for protection and herpesvirus encephalitis (Hayes, Giraldo, Wilcox, & Longnecker, 2022). Similarly, interferon lambda (IFNλ) signaling via the interferon lambda receptor (IFNLR1) is critical for BBB integrity during WNV infection (Lazear et al., 2015), but the role astrocytes play in this signaling pathway has not yet been fully elucidated.

In the opposite case of peripheral or systemic viral infection preceding neuroinvasive infection, cytokines in serum may signal via the luminal side of the BBB to cause an increase in permeability, facilitating viral entry. *In vitro* models of the BBB suggest that exposure to human serum may increase BBB permeability, and the extent of this effect was correlated with levels of chemokine ligands 12 and 7 (CCL12 and CCL7), interleukin 13 (IL-13), and interleukin 1β (IL-1β) (Ho & Kelly, 2020). In SIV infection of non-human primates, changes in microglial interleukin-6 (IL-6) were found to precede viral invasion into the CNS (Gopalakrishnan et al., 2021). Proper regulation of leukocyte extravasation through the BBB is essential for viral control and prevention of serious encephalopathies, as indicated by the association between Natulizumab blocking leukocyte extravasation into the brain and risk of serious opportunistic CNS infections by human polyomavirus 2 (Bloomgren et al., 2012).

Astrocytes have a variety of roles during viral infection of the CNS beyond regulating permeability of the BBB. Notably, astrocytes undergo proliferation and other reactogenic changes following viral infection and other insults to the CNS, collectively referred to as astrogliosis or reactive astrogenesis (Escartin et al., 2021). In the context of viral infection, reactive astrogenesis may be triggered by direct infection of astrocytes or by pro-inflammatory signals from neighboring neurons, glia, or infiltrating immune cells. Reactive astrocytes produce cytokines with complex roles including promoting viral clearance as well as mediating adverse neurologic changes. After infection with a gliotropic variant of the betacoronavirus mouse hepatitis virus (MHV), astrocytic CXCL9 and CXCL10 promotes the accumulation of virus-specific IgG and antibody secreting cells within the CNS (Phares et al., 2013), supporting viral clearance. Conversely, astrocyte-derived IL-1β during a model of West Nile neuroinvasive disease is required for synapse elimination and post-infectious deficits in hippocampal neurogenesis and spatial learning (Garber et al., 2018). In this example, astrocyte IL-1β may signal directly to neural stem cells, promoting further generation of IL-1β+ reactive astrocytes at the expense of normal neurogenesis (A. L. Soung et al., 2022). Likewise, astrocyte NFκB signaling promotes astrogliosis, α-synuclein aggregation, and neuronal loss during recovery from Western equine encephalitis virus (Bantle et al., 2021). In a mouse model of encephalitis caused by the DNA virus

herpes simplex virus, astrocytes produced CXCL1, recruiting neutrophils that further enhanced disease severity (Michael et al., 2020). Conversely, after intracranial infection with the RNA virus human enterovirus A71 (a cause of hand, foot, and mouth disease with occasional severe neuropathology), mouse astrocytes produced high levels of CXCL1, mimicking results observed in cerebrospinal fluid of patients, without significant neutrophil recruitment (Gunaseelan et al., 2022). Pharmacologic perturbation of this pathway lessened disease severity, suggesting that astrocyte-derived CXCL1 could promote neuropathogenesis either by direct effects on neurons or by recruitment of pro-inflammatory immune cells (Gunaseelan et al., 2022). The interferon-stimulated gene viperin is induced in astrocytes and other CNS cell types during viral infection, and restricts replication of the neurotropic flaviviruses TBEV, ZIKV, and Langat virus, although it remains unclear if astrocytic expression specifically is necessary for this protective effect (Lindqvist, Kurhade, Gilthorpe, & Överby, 2018; Lindqvist et al., 2016). These studies illustrate the complex context-dependence of astrocyte cytokine responses.

Astrocytes also participate in the phagocytosis and clearance of debris during viral encephalitides, a role shared with microglia. This process may be imperative for recovery but may also damage synapses. In the context of microglial depletion during ZIKV infection of the adult mouse brain, astrocytes appeared to increase their phagocytic capacity, suggesting a compensatory mechanism with unknown effects on neuronal health (Enlow et al., 2021). In another study of neonatal mice infected with ZIKV, convalescent mice maintained small parenchymal foci of viral material surrounded by activated astrocytes and microglia up to one year after recovery (Ireland et al., 2020). Astrocytes appear to regionally upregulate superoxide dismutase in response to viral infection in a non-human primate model of HAND, suggesting a role for astrocytes in quenching reactive oxygen species and reducing neuroinflammation (Sullivan et al., 2020), yet also contribute to amyloidosis in a similar model (Sil et al., 2020). Together, these studies highlight that reactive astrocytes affect both response and recovery during viral infections in a manner that is highly dependent on the host context and specific viral pathogen (Fig. 1).

Microglial activation affects neuroinvasive viral clearance and neurocognitive recovery

Microglia are resident myeloid cells that enter the brain during early development (Ginhoux et al., 2010). While they are not glia, they exhibit many neuroprotective functions similar to astrocytes, especially with regard to synaptic plasticity (Colonna & Butovsky, 2017; Nguyen et al., 2020; Sipe et al., 2016; Waltl & Kalinke, 2022). Microglia are key players during viral infection of the CNS, with both therapeutic and pathogenic roles depending on the context (Chhatbar & Prinz, 2021). For example, microglia are essential to the early immune response to MHV infection; mice succumb to intracerebral infection if microglia are depleted prior to infection using an inhibitor of colony stimulating factor 1 receptor (Wheeler, Sariol, Meyerholz, & Perlman, 2018). Likewise, microglial depletion affects virologic control in mouse models of DENV, ZIKV, WNV, and JEV (Enlow et al., 2021; Funk & Klein, 2019; Seitz, Clarke, & Tyler, 2018; Tsai et al., 2016). During vesicular stomatitis virus infection, microglia initiate a type I interferon response that limits transsynaptic viral spread (Drokhlyansky et al., 2017).

In some cases, microglia appear to have beneficial roles not just in viral clearance, but also in promoting neurologic and cognitive recovery. Depletion of microglia during MHV clearance impaired remyelination, suggesting that microglia guide oligodendrocyte remyelination after viral infection by clearing myelin debris and upregulating factors that promote oligodendrocyte maturation, such as galectin-3 and insulin-like growth factor 1 (Sariol et al., 2020). During ZIKV infection of adult mice, microglia undergo activation, correlate with virologic control, and appear to phagocytose debris (Enlow et al., 2021). Depletion of microglia during TMEV infection similarly allowed increased viral spread and exacerbated post-infectious seizures and hippocampal damage (Waltl et al., 2018). However, genetic deletion of CCR2 or CX3CR1 (which impacts both microglial and other myeloid responses) prevented hippocampal damage but did not affect seizure development, illustrating the complexity of the role of microglia in viral infection of the CNS (Käufer et al., 2018).

Microglia have also been implicated in detrimental neurologic outcomes of CNS viral infection. In a mouse model of post-infectious West Nile neurologic disease, microglia contribute to aberrant synaptic pruning after viral clearance via complement proteins C1q and C3 (Vasek et al., 2016). Microglia responding to T cell-derived IFNγ were also implicated in learning deficits and elimination of neuronal nuclei and post-synaptic terminals after ZIKV infection (Garber et al., 2019). In mice that recovered from West Nile neurologic disease, single cell RNA sequencing revealed that microglia underwent sustained changes, with transcriptional profiles that resembled those found in neurodegenerative diseases (Rosen et al., 2021). Similarly, unique microglial transcriptomic profiles were also observed after neurotropic MHV infection and glycoprotein-deleted Rabies virus infection (K. W. Huang & Sabatini, 2020; Syage et al., 2020). These studies illustrate how advances in single-cell transcriptomics have facilitated the differentiation of microglia from infiltrating macrophages, allowing more in-depth characterization of microglia in infected animals.

Microglia can also be directly infected by viruses, and serve as an important latent reservoir for HIV as well as a potential barrier to HIV cure strategies (Cosenza, Zhao, Si, & Lee, 2002). Astrocytes may similarly contribute to the cellular HIV reservoir (Lutgen et al., 2020; Valdebenito, Castellano, Ajasin, & Eugenin, 2021). The emerging RNA viruses Oropouche virus and Middle Eastern respiratory syndrome coronavirus infect neurons and glia in humanized mice or human brain slice cultures, leading to complement-mediated BBB changes and microglial activation (Almeida et al., 2021; Jiang et al., 2021). Future studies will determine whether these effects are also observed in human patients.

A Potential Role for Glia in Post-Acute Coronavirus Syndrome

Infection with SARS-CoV-2 has been associated with a variety of post-infectious syndromes including the development of new autoimmune conditions, ongoing respiratory deficiencies, and adverse cognitive and neurologic sequelae. Collectively, these conditions have been termed “long COVID” or post-acute coronavirus syndrome (PACS). Notably, these post-infectious syndromes can include stark changes to the CNS, including splenial alterations to the corpus collosum, reduction in grey matter thickness, diffuse edema, gliosis, microglial and astrocyte activation, and reductions in brain size (Abdel-Mannan et al., 2020; Douaud

et al., 2022; Pajo, Espiritu, Apor, & Jamora, 2021; Schwabenland et al., 2021). Current evidence largely suggests that SARS-CoV-2 does not typically infect or invade the central nervous system and viral material is very rarely found in the brain parenchyma of patients (Pajo et al., 2021; Poloni et al., 2021; Solomon, 2021). However, unique clusters of activated microglia, astrocytes, and CD8+ T cells have been identified in the brain stem and olfactory bulb of deceased patients (Schwabenland et al., 2021). These cellular “nodules” differed from those observed in multiple sclerosis or non-viral severe respiratory failure patients, and correlated with axonal damage as well as the presence of SARS-CoV-2 viral components in the vascular compartments of the CNS (Schwabenland et al., 2021). There are many open questions about how SARS-CoV-2 infection leads to neurologic and cognitive sequelae. A variety of potential explanations have been proposed, including hypoxia, cytokine storm, low levels of viral invasion into the CNS, or induction of autoimmunity (Franke et al., 2021; Kumar et al., 2021; Meinhardt et al., 2021; Vargas et al., 2020). Glia could play a role in several of these potential pathways (Fig. 2), and early results from single nucleus RNA sequencing studies of COVID-19 patient brains indeed point to glial alterations associated with SARS-CoV-2 infection (Yang et al., 2021).

Hypoxia after non-infectious injury (cardiac arrest, ischemic stroke, and traumatic brain injury) is associated with adverse neurologic and cognitive sequelae including neuronal dysfunction and death, cerebral edema, and Parkinson’s disease (Brownlee, Wilson, Curran, Lyttle, & McCann, 2020; Nalivaeva & Rybnikova, 2019; Sekhon, Ainslie, & Griesdale, 2017). Even in the absence of infection, hypoxia has diverse effects on both the blood-brain barrier and CNS cytokine profiles. Experimentally-induced hypoxia leads to vascular remodeling and an increase in vascular permeability, an effect attributed to pericytic rather than astrocytic hypoxia inducible factor 1 (Baumann et al., 2022). In patients recovering from cardiac arrest, hypoxia but not normoxia was associated with cerebral release of IL-6, glial fibrillary acidic protein, tau, and other biomarkers of neuroglial injury (Hoiland et al., 2021). Respiratory distress, hypoxia, and induction of a pro-thrombotic state are associated with severe COVID-19 (Mehandru & Merad, 2022; Serebrovska, Chong, Serebrovska, Tumanovska, & Xi, 2020), and evidence from other non-neuroinvasive viral infections such as respiratory syncytial virus supports the theory that virus-mediated lung pathology can lead to increased BBB permeability and neuroinflammation (Bohmwald et al., 2021). In PACS, symptoms such as brain fog occur even following mild cases (Bliddal et al., 2021), suggesting that severe hypoxia is not critical to the development of PACS. Subclinical hypoxia could still play a role in post-infectious sequelae.

Altered soluble mediator or immune cell levels in the circulation following infection with SARS-CoV-2 could also underly the development of neurologic and cognitive symptoms associated with PACS. Severe COVID-19 is characterized by cytokine storm, a condition in which levels of circulating immune mediators, including TNF-α, IL-1, and IL-6, reach levels elevated enough to be life-threatening (Fajgenbaum & June, 2020; Kumar et al., 2021; Merad, Blish, Sallusto, & Iwasaki, 2022). Cytokine storm is not necessary for the development of PACS (Taquet, Geddes, et al., 2021). However, even in mild SARS-CoV-2 infection, mild hypoxia combined with circulating immune factors could synergize in their signaling to pericytes and astrocytes, leading to opening of the BBB (Reynolds & Mahajan,

2021) and resulting cytokine and immune cell infiltration, neuroinflammation, and adverse effects on neuronal circuits.

Future Outlook

Glial cells play diverse roles during viral infections, functioning as target cells, pro-inflammatory bystanders, mediators of neurologic damage, and facilitators of neurologic recovery depending on the host, immune context, and pathogen. Many open questions remain regarding the functions of glia during viral infections, including how they interact with infiltrating immune cells, how they promote neuronal survival vs. synaptic damage, and how they participate in brain recovery after viral clearance. In addition, the COVID-19 pandemic has firmly demonstrated that even in the absence of viral neuroinvasion, viral infections can still lead to significant cognitive impairments, a process which likely involves glia. Future research into these topics must employ a mixture of patient sample analysis, *ex vivo* organoid models, and animal models, as no single approach can fully shed light on the complex relationship between glia, neurons, and immune cells in the human brain. As research into the role of glia during viral infections continues, we anticipate the advent of pharmacologic interventions that will modulate glial functions during viral infections to promote neuronal and cognitive health.

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Main Points

- Neuroinvasive and neurovirulent viral infections lead to acute and chronic neurologic sequelae
- Glia use distinct viral sensing pathways depending on the tropism of the virus
- Glial immune responses can both protect and damage neuronal tissues

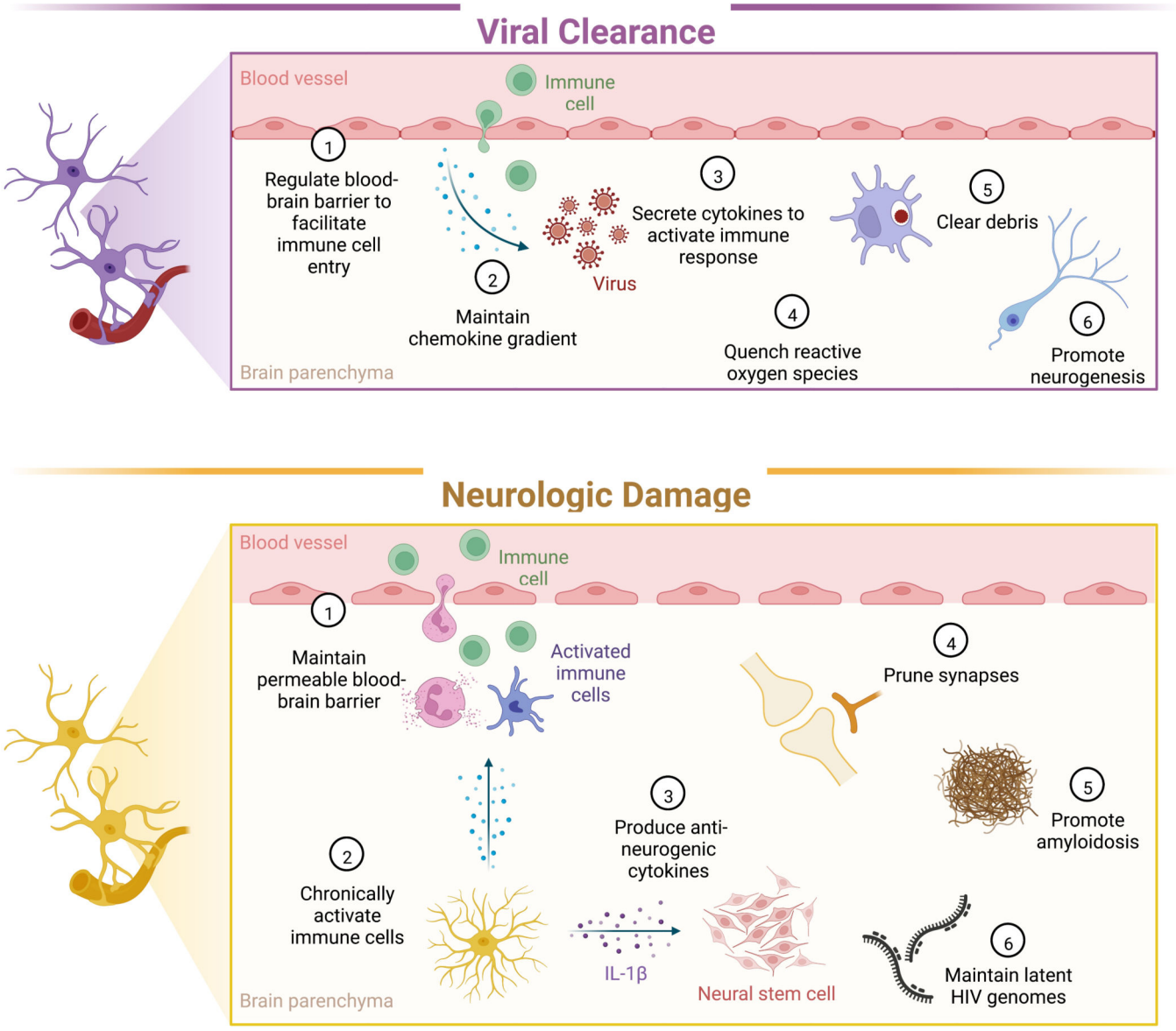

Figure 1. Glia facilitate clearance of CNS viral infections, but also mediate neurologic damage.

During neuroinvasive and neurovirulent viral infections, glia perform functions that are essential to viral clearance and neurocognitive recovery, such as regulating the BBB, maintaining chemokine gradients, and phagocytosing debris. However, these responses can also damage neuronal tissue by promoting chronic inflammation, impeding neurogenesis, and pruning synapses.

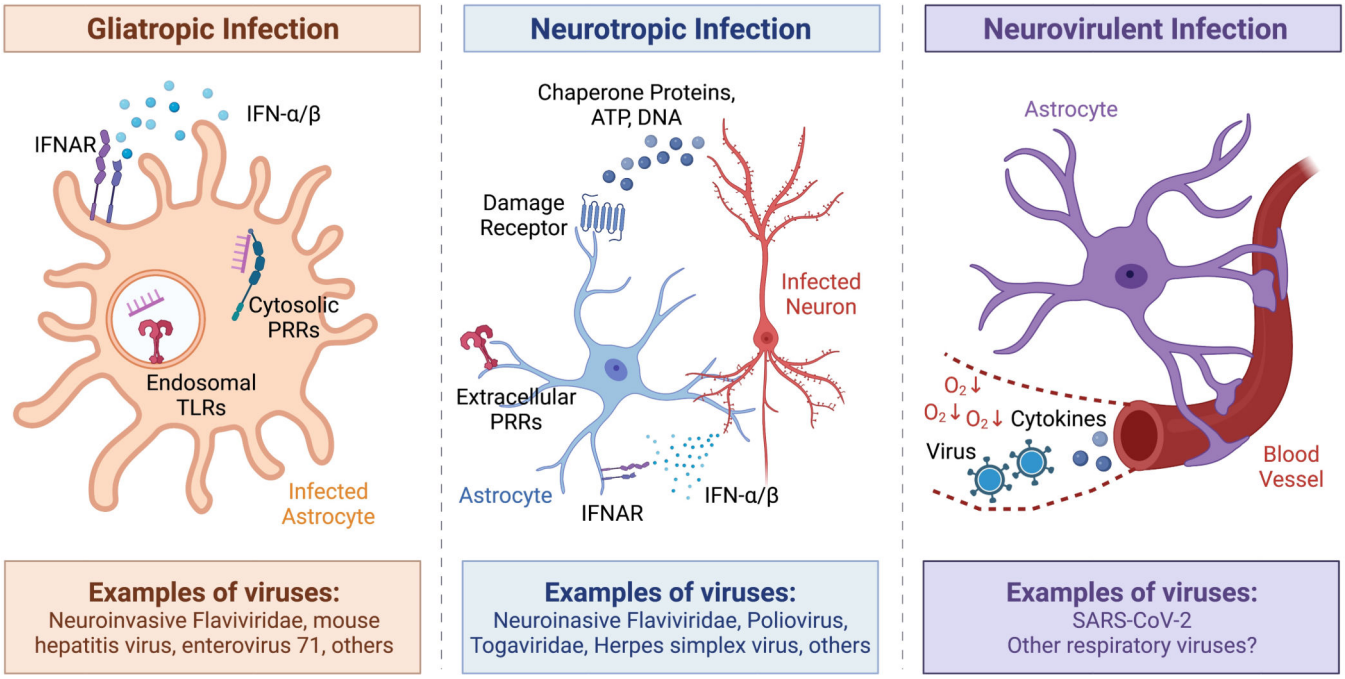

Figure 2. Glia use distinct detection pathways to respond to different types of viral infection.

Viruses associated with neurocognitive sequelae may be gliatropic, neurotropic, neurovirulent, or some combination of each. Glia can recognize gliatropic viruses (left) via intracellular innate sensing receptors, such as endosomal Toll-like receptors or cytosolic pattern-recognition receptors that bind to viral nucleic acids. Infected glia can further amplify their innate immune response via autocrine cytokine signaling. Glia may recognize neurotropic viral infection (middle) via paracrine cytokine signaling. Infected neurons may also signal to glia via the release of damage-associated molecules such as chaperone proteins, host DNA, or ATP. Finally, glia may mediate neuroinflammation in response to neurovirulent viruses (right) via the sensing or translocation of viral particles or cytokines from the circulation. Hypoxia resulting from respiratory disease could amplify these signals via alterations to the blood-brain barrier.

Table 1.

RNA viruses associated with neurologic and cognitive sequelae.

Virus	Family	Genome Structure	Neuroinvasion	Neurologic sequelae	Refs
West Nile virus (WNV)	*Flaviviridae*	Positive-strand RNA	+	Parkisonism, memory impairment	(Weatherhead et al., 2015)
Dengue virus (DENV)	*Flaviviridae*	Positive-strand RNA	+	Guillain-Barré syndrome	(Carod-Artal, Wichmann, Farrar, & Gascón, 2013)
Zika virus (ZIKV)	*Flaviviridae*	Positive-strand RNA	+	Guillain-Barré syndrome, memory impairment	(da Silva et al., 2017)
Tick-borne encephalitis virus (TBEV)	*Flaviviridae*	Positive-strand RNA	+	Effects on vision, balance, neuropsychiatric complaints	(Bogovic & Strle, 2015)
Japanese encephalitis virus (JEV)	*Flaviviridae*	Positive-strand RNA	+	Movement disorders	(Turtle & Solomon, 2018)
St. Louis encephalitis virus (SLEV)	*Flaviviridae*	Positive-strand RNA	+	Convulsive and motor disorders	(Palmer & Finley, 1956)
Eastern equine encephalitis virus (EEEV), Western equine encephalitis virus (WEEV), Venezuelan equine encephalitis virus (VEEV)	*Togaviridae*	Positive-strand RNA	+	Convulsions, somnolence, intellectual disability, confusion, emotional instability, behavioral changes	(Ronca et al., 2016)
Poliovirus (PV)	*Picornaviridae*	Positive-strand RNA	+	Motor neuron disorders, word finding difficulties, concentration difficulties, memory impairment	(Li Hi Shing et al., 2019)
Enterovirus 71 (EV71)	*Picornaviridae*	Positive-strand RNA	+	Acute flaccid paralysis	(Hu, Jiang, & Peng, 2015; P.-N. Huang & Shih, 2014)
Measles virus (MV)	*Paramyxoviridae*	Negative-strand RNA	+	Movement disorders, acute disseminated encephalomyelitis, subacute sclerosing panencephaltis (SSPE)	(Buchanan & Bonthius, 2012; Fisher, Defres, & Solomon, 2015)
HIV	*Retroviridae*	Positive-strand RNA	+	HIV-associated neurocognitive disorder (HAND)	(Holroyd, Vishnevetsky, Srinivasan, & Saylor, 2020)
Influenza A virus (IAV)	*Orthomyxoviridae*	Segmented RNA	Atypical	Seizures, altered mental states	(Ekstrand, 2012; Liang et al., 2018; Muhammad Ismail et al., 2015)
Mouse hepatitis virus (MHV)	*Betacoronaviridae*	Positive-strand RNA	+	In rodents, demyelinating disease resembling multiple sclerosis	(Bergmann, Lane, & Stohlman, 2006)
Middle Eastern respiratory syndrome coronavirus (MERS-CoV)	*Betacoronaviridae*	Positive-strand RNA	Reported in animal models	Guillain-Barré syndrome, movement disorders	(Jiang et al., 2021; J. E. Kim et al., 2017)
Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)	*Betacoronaviridae*	Positive-strand RNA	Atypical	Headache, brain fog, changes in brain morphology	(Solomon, 2021)

Virus	Family	Genome Structure	Neuroinvasion	Neurologic sequelae	Refs
Respiratory syncytial virus (RSV)	*Pneumoviridae*	Negative-strand RNA	-	Seizures, lethargy, strabismus, swallowing difficulties	(Bohmwald et al., 2018)