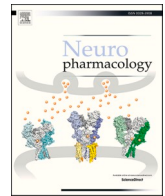




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Inflammation at the crossroads of COVID-19, cognitive deficits and depression

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ABSTRACT

Acute neurological alterations have been associated with SARS-CoV-2 infection. Additionally, it is becoming clear that coronavirus disease 2019 (COVID-19) survivors may experience long-term neurological abnormalities, including cognitive deficits and mood alterations. The mechanisms underlying acute and long-term impacts of COVID-19 in the brain are being actively investigated. Due to the heterogeneous manifestations of neurological outcomes, it is possible that different mechanisms operate following SARS-CoV-2 infection, which may include direct brain infection by SARS-CoV-2, mechanisms resulting from hyperinflammatory systemic disease, or a combination of both. Inflammation is a core feature of COVID-19, and both central and systemic inflammation are known to lead to acute and persistent neurological alterations in other diseases. Here, we review evidence indicating that COVID-19 is associated with neuroinflammation, along with blood-brain barrier dysfunction. Similar neuroinflammatory signatures have been associated with Alzheimer's disease and major depressive disorder. Current evidence demonstrates that patients with pre-existing cognitive and neuropsychiatric deficits show worse outcomes upon infection by SARS-CoV-2 and, conversely, COVID-19 survivors may be at increased risk of developing dementia and mood disorders. Considering the high prevalence of COVID-19 patients that recovered from infection in the world and the alarming projections for the prevalence of dementia and depression, investigation of possible molecular similarities between those diseases may shed light on mechanisms leading to long-term neurological abnormalities in COVID-19 survivors.

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1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic is one of modern society's most significant health crises. According to the World Health Organization (WHO), as of February 2022, over 430 million people have been infected by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), with almost 6 million confirmed deaths worldwide. Beyond causing a prominent respiratory distress syndrome, COVID-19 is a systemic disease that affects multiple organs (Wadman et al., 2020). Severe patients develop peripheral hyper-inflammation,

coagulopathy, hypoxia, hepatic dysfunction, sepsis, and acute kidney failure. Neurological disturbances are frequent in COVID-19 patients and range from relatively mild symptoms, such as headache, anosmia, and ageusia, to severe complications, including encephalopathy, stroke, delirium, and coma (Chen et al., 2020a; Mao et al., 2020; Helms et al., 2020a; Romero-Sánchez et al., 2020; Lechien et al., 2020; Oxley et al., 2020; Poyiadji et al., 2020; Benussi et al., 2020; Chou et al., 2021).

Follow-up studies carried out thus far indicate that a significant proportion of COVID-19 survivors experience persistent neuropsychological alterations, including anxiety, depression, and cognitive impairment (Nath, 2020; Crunfli et al., 2020; Mazza et al., 2021; Taquet

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Abbreviations

ACE2	Angiotensin-Converting Enzyme 2
AD	Alzheimer's disease
BBB	blood-brain barrier
C1q	complement component 1q
CART	Combination Antiretroviral Therapy
CNS	central nervous system
COVID-19	coronavirus disease 2019
CSF	cerebrospinal fluid
EBV	Epstein-Barr Virus
gp130	glycoprotein 130
HAD	HIV-associated dementia
HAND	HIV-associated neurocognitive disorder
HCoV	Human Coronavirus
HIV	human immunodeficiency virus
HSE	herpes simplex encephalitis
HSV	herpes simplex virus
LPS	lipopolysaccharide

IL-1 α	interleukin-1alpha
IL-6	interleukin-6
IL-6R	IL-6 receptor
iPSCs	induced Pluripotency Stem Cells
JAK	Janus kinase
JEV	Japanese Encephalitis Virus
MDD	major depressive disorder
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-1	Severe Acute Respiratory Syndrome Coronavirus 1
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
sIL-6R	soluble isoform of IL-6- receptor
TBEV	Tick Born Encephalitis Virus
TLR	Toll-Like Receptor
TNF- α	tumor necrosis factor-alpha
TNF-R	TNF receptors
WHO	World Health Organization
WNV	West Nile virus
ZIKV	Zika virus

et al., 2021b; Taquet et al., 2021a,b. Both the manifestation of neurological symptoms during hospitalization and the existence of prior neurological diseases, including dementia and neuropsychiatric disorders, are associated with higher mortality by COVID-19 (Chou et al., 2021; Taquet et al., 2021a; Tahira et al., 2021; Romagnolo et al., 2021; Nemani et al., 2021). Likewise, age, diabetes, and maladaptive immune response are risk factors for COVID-19 severity and mortality (Lucas et al., 2020; Webb et al., 2020; Tay et al., 2020). However, the mechanisms by which COVID-19 triggers neurological impairments and its long-term consequences remain to be determined. We and others have shown that depression, dementia, and diabetes share pathophysiological mechanisms leading to brain dysfunction in animal models (Ledo et al., 2013; Neves et al., 2018; Batista et al., 2018; Lourenco et al., 2013). Here, we examine the available evidence on brain infection by SARS-CoV-2, the induction of systemic inflammation, coagulopathy, and blood-brain barrier (BBB) dysfunction as possible mechanisms underlying neurological impairments in COVID-19. Considering the sky-rocketing number of COVID-19 survivors worldwide, it is of utmost importance to understand factors leading to persistent or late-onset neurological outcomes to inform public health policies and develop preventative and treatment strategies for those patients.

2. Viral infections and human neurological diseases

As alarming as it may seem, the fact that COVID-19 induces neurological complications should not come as a surprise. Viruses from diverse families exhibit tropism for the central nervous system (CNS) and have been implicated in acute and persistent neurological alterations in humans.

Herpes Simplex Viruses (HSV-1 and HSV-2) are the leading identified cause of encephalitis in the United States of America, causing a condition termed HSV encephalitis (HSE) (Gnann and Whitley, 2017). HSV belongs to the *herpesviridae* family (Whitley and Roizman, 2001), causes mild mucocutaneous infections in humans and establishes latent infections in sensory ganglia (Whitley and Roizman, 2001). While innate immune responses are important to halt viral replication, HSV-induced CNS pathology results from a combination of viral-driven cytolysis and inflammation-mediated effects (Gnann and Whitley, 2017; Marcocci et al., 2020). HSE survivors frequently experience long-term neuropsychological sequelae and are at risk of autoimmune encephalitis relapses (Gnann and Whitley, 2017). Recurrent HSV infections have been proposed to be a long-term pathogenic mechanism linked to the development of Alzheimer's disease (AD) (Marcocci et al., 2020). Similarly,

infection by Epstein-Barr virus (EBV) has been linked to promoting of neuronal damage in late-onset multiple sclerosis (Bjornevik et al., 2022).

The human immunodeficiency virus (HIV) can also invade the CNS and become latent. Persistent CNS infection, systemic and central inflammation can cause HIV-associated neurocognitive disorder (HAND) (Saylor et al., 2016). Due to the advent of combination antiretroviral therapy (CART) to halt HIV replication, progression of HAND to the most severe HIV-associated dementia (HAD) is now uncommon, occurring just in a subset of HIV+ patients (Saylor et al., 2016).

The *Flaviviridae* family of arboviruses (arthropod-borne virus) includes several members capable of inducing neurological disorders and long-term neurological sequelae, such as Japanese Encephalitis Virus (JEV), tick-borne encephalitis virus (TBEV), and West Nile virus (WNV) (Maximova and Pletnev, 2018; Turtle and Solomon, 2018). A recent Zika virus (ZIKV) outbreak in the Americas led the WHO (2016) to declare a public health emergency of international concern due to neurological disorders associated with the infection. ZIKV infection during pregnancy may cause a complex congenital syndrome, including microcephaly (Souza et al., 2019). In adults, infection may lead to encephalitis, myelitis, and Guillain-Barre Syndrome cases (Souza et al., 2019). Long-term neurological consequences of ZIKV infection, however, are still largely unknown. Animal studies suggest that direct viral cytolysis and neuroinflammation play important roles in flavivirus-induced neurological damage (Maximova and Pletnev, 2018; Turtle and Solomon, 2018; Figueiredo et al., 2019; Souza et al., 2018).

Zoonotic viruses can occasionally cause disease in humans. The most prominent example of a zoonotic virus causing neurological damage is rabies virus (Hemachudha et al., 2013). Another example is Borna disease virus, which causes fatal encephalitis in rare human spill-over infections in endemic areas (Rubbenstroth et al., 2019). Members of the coronavirus family have been introduced to humans from a zoonotic origin and have also been implicated in CNS damage (Li et al., 2020; de Felice et al., 2020; Zubair et al., 2020). Infection by the Severe Acute Respiratory Syndrome (SARS) Coronavirus (SARS-CoV-1), closely related to SARS-CoV-2, has been associated with myopathy, polyneuropathy, seizures, and stroke (Tsai et al., 2005; Lau et al., 2004). SARS-CoV-1 protein and genetic material have been found in patient cerebrospinal fluid (CSF) and post-mortem brains (Lau et al., 2004; Ding et al., 2004; Gu et al., 2005; Xu et al., 2005). Similarly, human coronavirus OC43 (HCoV-OC43) has been reported to invade the brain parenchyma and induce fatal encephalitis (Morfopoulou et al., 2016; Nilsson et al., 2020). HCoV-OC43 and HCoV-229E have been implicated in long-term neurological disease, including a possible role in multiple

sclerosis (Desforges et al., 2019). However, as discussed in the next section, coronaviruses, including SARS-CoV-2, are not primarily neurotropic viruses. Instead, they attack airways and lungs while retaining the capacity of infecting diverse cell types, including CNS cells or endothelia (Puelles et al., 2020; Liu et al., 2021).

3. Evidence of brain infection by SARS-CoV-2

SARS-CoV-2 is a single-stranded RNA virus, a member of the *Beta-coronavirus* genus, of the *Coronaviridae* family within the *Riboviria* realm (Coronaviridae Study Group, 2020). Each virion contains four types of structural proteins, named spike (S), envelope (E), membrane (M), and nucleocapsid (N) (Mariano et al., 2020). Infection by SARS-CoV-2 begins with the interaction of the viral outer-membrane spike protein with angiotensin-converting enzyme 2 (ACE2) at the plasma membrane of host cells. Physiologically, peripheral ACE2 is involved in the conversion of the hormone angiotensin that regulates blood pressure (Alenina and Bader, 2019). In the brain, ACE2 appears to be involved in brain injury recovery, stress response, and memory function (Alenina and Bader, 2019).

Analysis of post-mortem COVID-19 patient brains provided initial evidence of neuroinvasion by SARS-CoV-2 (Crunfli et al., 2020; Puelles et al., 2020; Song et al., 2021; Meinhardt et al., 2021; Matschke et al., 2020). Different routes have been proposed for CNS infection by human coronaviruses, including retrograde transport across peripheral nerves and the intranasal pathway leading to the olfactory bulb (Desforges et al., 2019; Meinhardt et al., 2021; Cooper et al., 2020). Several studies indicate that, although the sustentacular cells of the olfactory epithelium express ACE2, this protein is not present in olfactory receptor neurons (Butowt et al., 2021; Brann et al., 2020; Chen et al., 2020b; Klingenstein et al., 2020). Combined with weak evidence supporting the presence of viral particles in olfactory neurons and bulb, these data indicate that this is not a probable route for CNS infection (Butowt et al., 2021). Alternatively, after reaching the bloodstream, viruses may enter the brain by transport across the BBB via endothelial cells or infected leukocytes, a process referred to as a "Trojan horse mechanism" (Fig. 1), or may reach the CSF by crossing epithelial cells in the choroid plexus

(blood-CSF barrier) (Pezzini and Padovani, 2020).

Brain infection and neurotropism has been demonstrated following intranasal administration of SARS-CoV-2 in mice that overexpress the human isoform of ACE2 (Song et al., 2021). In wild-type mice, the S1 subunit of the spike protein crosses the BBB and reaches the brain parenchyma via a vesicular-dependent transport mechanism known as adsorptive transcytosis (Fig. 1). (Rhea et al., 2020) Due to the limitations of animal models, several groups have used brain organoids derived from human induced pluripotency stem cells (iPSCs) to evaluate the impact of SARS-CoV-2 infection (Crunfli et al., 2020; Song et al., 2021; Ramani et al., 2020, 2021; Zhang et al., 2020; Pedrosa et al., 2021). Although findings diverge, those studies suggest that SARS-CoV-2 could infect human neurons or astrocytes, and lead to inflammation and molecular alterations related to neurodegeneration. Collectively, results support the idea that brain invasion by SARS-CoV-2 or by viral proteins could, at least in part, trigger neurological deficits in COVID-19.

On the other hand, the search for molecular traces of SARS-CoV-2 in post-mortem patient brains and CSF samples has produced inconsistent results, raising the possibility that this is not a primary neuropathogenic mechanism in COVID-19 (Espíndola et al., 2020; Thakur et al., 2021; Yang et al., 2021; Lee et al., 2020). Indeed, unlike the case in HSE, the SARS-CoV-2 genome is rarely found in the CSF of COVID-19 patients presenting neurological symptoms (Espíndola et al., 2020). In two independent studies, Yang et al. (2021) and Lee et al. (2020) found no evidence of SARS-CoV-2 RNA or protein in systematic analyses of post-mortem brain samples (Yang et al., 2021; Lee et al., 2020). Thakur et al. (2021) found low but detectable levels of viral mRNA at multiple brain sites using quantitative real-time PCR (Thakur et al., 2021). Nonetheless, RNA-scope and immunohistochemistry assays targeting nucleocapsid and spike proteins failed to confirm those results. Further, sites of possible infection did not coincide with neuropathology and microgliosis (Thakur et al., 2021). The discrepant results reported in different studies may reflect (1) poor or transient viral invasion of the CNS with fast clearance, leading to low viral levels that approach technical detection limits; (2) methodological issues, such as tissue conservation, blood contamination, and antibody specificity; and (3) positive signals arising from infection of vascular or meningeal cells,

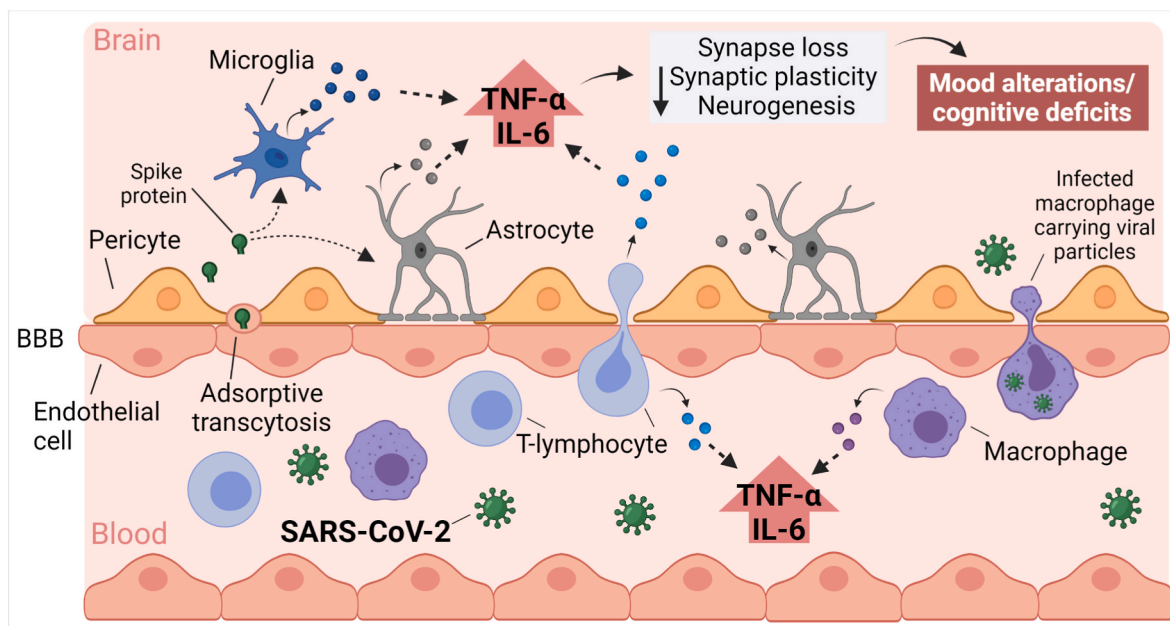


Fig. 1. Proposed mechanisms underlying neurological impact in COVID-19. Systemic inflammation induced by COVID-19, as well as brain invasion by viral proteins or SARS-CoV-2 can add up to cause blood-brain barrier (BBB) dysfunction, brain microvascular damage, and brain inflammation. Activation of toll-like receptors (TLRs) and accumulation of tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6) in the brain, either by local production or from the periphery, triggers synaptic damage, leading to depressive and cognitive symptoms in COVID-19 patients. Created with [BioRender.com](https://www.biorender.com).

rather than in the brain parenchyma.

4. Brain inflammation in infectious diseases

CNS infections cause cognitive, mood, and motor deficits that may persist beyond the acute phase of the disease. In some cases, neurological sequelae may result from irreversible damage and neuronal death triggered by pathogens (van den Pol, 2009). Alternatively, infection-driven inflammation can disturb neuronal function and cause long-term deficits (Figueiredo et al., 2019; Vasek et al., 2016; Frost et al., 2019; De Sousa et al., 2021). Dysregulation of inflammatory responses may cause brain dysfunction and behavioral alterations via multiple mechanisms (Figueiredo et al., 2019; Klein et al., 2017; Garber et al., 2019).

Microglia are the primary neuroimmune cells and perform vital functions in brain homeostasis and defense against pathogens, but they can also contribute to disease processes (reviewed in Hickman et al., 2018; Xie et al., 2019). In response to infection, microglia increase in number, migrate to the primary site of infection and acquire an activated phagocytic phenotype associated with pro-inflammatory cytokine release (Frost et al., 2019; De Sousa et al., 2021; Hickman et al., 2018). Microglia contribute to memory deficits in mouse models of CNS viral infection by actively attacking and eliminating synapses (Figueiredo et al., 2019; Vasek et al., 2016). Once activated, microglia may respond with greater sensitivity to subsequent stimuli (a mechanism known as priming), resulting in exaggerated inflammatory responses and increasing susceptibility to neurodegenerative processes (Frost et al., 2019; De Sousa et al., 2021).

Astrocytes are an essential component of the neurovascular unit and provide a link between neurons and blood vessels. In homeostasis, astrocytes support and maintain BBB integrity, function as well as neuronal connectivity (Matias et al., 2019). In response to infections, astrocytes undergo morphological, molecular, and functional changes that can have beneficial consequences (e.g., pathogen elimination and tissue repair) or detrimental effects (Matias et al., 2019; Escartin et al., 2021). Microglia-released factors, namely interleukin-1 α (IL-1 α), tumor necrosis factor α (TNF α), and complement component 1q (C1q) induce a functional shift of astrocytes to the so-called A1 phenotype, a subtype of astrocytes that lose their physiological roles in neuronal and synaptic maintenance (Liddelow et al., 2017). A1 astrocytes are observed in CNS diseases and injuries, and trigger neuronal and oligodendrocyte loss (Liddelow et al., 2017; Liddelow and Barres, 2017). Astrocytes are involved with both acute and chronic neurological effects, as well as long-term sequelae in neuro-infectious diseases, as several viruses can infect and activate astrocytes, altering BBB permeability and neuronal function (reviewed in Soung and Klein, 2018).

As a consequence of infection or other injuries, monocytes differentiate into macrophages recruited to affected tissues (Wynn et al., 2013). In the CNS, macrophages are present at perivascular spaces, meninges, and the choroid plexus, where they act as scavengers and physiological modulators (Xie et al., 2019). While macrophages are critical for innate immune response, T-lymphocytes are the primary effectors of adaptive immunity. T-lymphocytes also play a role in the CNS, patrolling the meningeal spaces and contributing to normal behavior and cognition. In CNS infections, macrophages and lymphocytes infiltrate the brain parenchyma and contribute to local cytokine release (Klein et al., 2017; Garber et al., 2019; Cusick et al., 2013).

Cytokines play important roles in synaptic plasticity and neuronal physiology (Stellwagen and Malenka, 2006; Cunningham et al., 1996; Habbas et al., 2015; Creed Pettigrew et al., 2016; Hosseini et al., 2020; Ross et al., 2003; Li et al., 1997; D'Arcangelo et al., 2000), but aberrant upregulation of cytokine production and secretion in the CNS interferes with neuronal function and with neurotransmitter-mediated pathways (Klein et al., 2017). As aforementioned, COVID-19 patients experience a hyper-inflammatory syndrome, with increased circulating levels of several cytokines, including TNF- α and interleukin-6 (IL-6) (Lucas et al.,

2020; Webb et al., 2020; Tay et al., 2020). TNF- α is a homotrimer that signals through TNF receptors (TNF-R) 1 and 2 and activates cellular stress response pathways (Wajant et al., 2003; Vanamee and Faustman, 2018). With a broad spectrum of activity, TNF- α may be regarded as a significant pro-inflammatory mediator of the innate immune system (for review, see Wajant et al., 2003 and Vanamee and Faustman, 2018). In brain homeostasis, glial TNF- α contributes to the regulation of synaptic connectivity (Stellwagen and Malenka, 2006). However, upregulation of brain TNF- α impairs synaptic plasticity, motor control, memory and induces microglial and astrocyte activation (Figueiredo et al., 2019; Souza et al., 2018; Cunningham et al., 1996; Habbas et al., 2015; Creed Pettigrew et al., 2016).

Under physiological conditions, IL-6 is present at low levels in the brain and has known roles in neurogenesis, gliogenesis, and regeneration of peripheral nerves (for a review, see Rothaug et al., 2016). IL-6 signaling requires two co-receptors, the IL-6-binding receptor (IL-6R) and the signal-transducing protein, glycoprotein 130 (gp130). Classical IL-6 signaling involves binding IL-6 to IL-6R followed by activation of gp130 and recruitment of Janus kinase (JAK) to initiate intracellular signaling (Rothaug et al., 2016; Erta et al., 2012). Interestingly, neurons do not appear to express relevant amounts of the membrane-bound IL-6R isoform; instead, they express a soluble isoform of the receptor (sIL-6R) (März et al., 1998), which binds circulating IL-6 and activates membrane-bound gp130. This process, known as *trans*-signaling (Rothaug et al., 2016; Erta et al., 2012), has been implicated in cognitive dysfunction caused by lipopolysaccharide (LPS) in aged mice (Burton and Johnson, 2012).

5. Inflammation as a potential driver of cognitive decline and depressive symptoms in COVID-19

Delirium and encephalopathy are commonly reported in COVID-19 hospitalized patients; however, estimates of the incidence of delirium and encephalopathy diverge largely among different cohorts (Chou et al., 2021; Helms et al., 2020b; Ellul et al., 2020). A retrospective cohort study of electronic health records of 236,379 COVID-19 survivors found that one-third of the patients developed neurological or psychiatric conditions within six months of infection (Taquet et al., 2021b; Mahase, 2021). Those rates were higher in severe COVID-19 cases (e.g., individuals admitted to intensive care units) and were higher for SARS-CoV-2 than for influenza infections. Post-mortem analysis of COVID-19 patient brains revealed local inflammation, microglial activation, immune cell infiltration, signs of hypoxia, infarcts, and microvascular damage (Crunfli et al., 2020; Song et al., 2021; Thakur et al., 2021; Yang et al., 2021; Lee et al., 2020). Additionally, COVID-19 patients show elevated blood and CSF biomarkers of inflammation, neuronal damage, and astrocytic activation, associated with neurological symptoms and disease severity (Sutter et al., 2020; Virhammar et al., 2021; Kanberg et al., 2020; Espindola et al., 2021). Molecular and metabolic changes triggered by hypoxia and inflammation may induce encephalopathy and long-term neurological dysfunction independently of CNS infection in critically ill patients (Gofton and Bryan Young, 2012; Sasannejad et al., 2019; Solomon, 2021). Considering that recent findings do not support the presence of SARS-CoV-2 viral material in the brain as the primary source of COVID-19 neuroinflammation (Thakur et al., 2021; Yang et al., 2021), an alternative hypothesis implicates systemic factors as mediators of CNS pathology.

IL-6 and TNF- α are critical mediators of the inflammatory response in COVID-19. Blood levels of IL-6 predict disease progression and correlate with COVID-19 severity and mortality (Santa Cruz et al., 2021; Zeng et al., 2020). Blood TNF- α is high in critically ill COVID-19 patients (Zeng et al., 2020). Evidence supporting the involvement of IL-6 and TNF- α in the progression of COVID-19 has led to ongoing research aimed at inhibiting these cytokines as acute treatment options for severe disease cases (Rubin et al., 2021; Robinson et al., 2020; Angriman et al., 2021). In August 2021, the WHO announced a clinical trial to test three

COVID-19 candidate drugs. One of them was Infiximab, a monoclonal antibody that blocks TNF- α signaling (World Health Organization, 2021) and found to alleviate cognitive deficits in mouse models of brain infection by Zika virus (Figueiredo et al., 2019) and of AD. (Lourenco et al., 2013).

While microglia and macrophages express ACE2, this protein is not abundantly expressed in most blood-derived immune cells (Song et al., 2020a), suggesting that other receptors, including toll-like receptors (TLRs), might be involved in the inflammatory response to SARS-CoV-2. Exposure to Spike protein in microglia, peripheral blood mononuclear cell, and macrophage cultures elicits TNF- α and IL-6 production (Olajide et al., 2021, 2022; Zhao et al., 2021; Shirato and Kizaki, 2021). Interestingly, TLR4 blockage or knockdown decreases the overall immune response, including TNF- α and IL-6 production caused by the Spike protein (Zhao et al., 2021; Shirato and Kizaki, 2021; Olajide et al., 2022), suggesting that TLR4 is a mediator of neuroinflammation promoted by SARS-CoV-2 (Fig. 1). TLR2 activation mediates cytokine production in HSE (Gnann and Whitley, 2017; Marcocci et al., 2020). Similarly, SARS-CoV-2's envelope may activate TLR2 and induce cytokine release (Zheng et al., 2021).

Elevated cytokine levels associated with systemic inflammation may also play a role in long-term brain damage in COVID-19. Mazza et al. (2021) prospectively evaluated psychological and cognitive status in a cohort of 226 COVID-19 survivors in Milan (Italy) for up to three months following hospital discharge. Remarkably, 78% of the survivors performed poorly in at least one cognitive domain, with the most significant impact on executive functions and motor coordination (Mazza et al., 2021). In addition, 36% of the patients self-reported psychopathological symptoms, including persistent depressive traits. Significantly, the persistence of depressive symptoms was associated with systemic inflammation biomarkers during acute infection and in the follow-up visit (Mazza et al., 2021).

Inflammation is a point of convergence between neurodegenerative diseases and mood disorders, particularly major depressive disorder (MDD) (van den Amele et al., 2017; Johnson et al., 2017). MDD patients have upregulation of inflammatory pathways (Miller and Raison, 2015), and psychosocial stress can increase inflammatory response (Pace et al., 2006; Aschbacher et al., 2012). Investigation of the impact of inflammation on brain circuits involved in mood control has elucidated processes underlying resistance to conventional anti-depressants (Miller and Raison, 2015), and has inspired clinical trials using anti-inflammatory strategies to treat subgroups of depressive patients (Köhler et al., 2014). In animals, infections induce a stereotyped and conserved "sickness behavior", characterized by lethargy, anorexia, anhedonia, and depressive-like behavior (Hart, 1988), which has been shown to result from elevated circulating cytokines (Klein et al., 2017; Dantzer et al., 2008). Although it is challenging to mimic the complexity of depression in rodents, work with animal models has helped increase our understanding of the role of pro-inflammatory molecules in MDD (Dantzer et al., 2008; Cheng et al., 2018; Konsman et al., 2008). For example, intracranial administration of IL-6 or TNF- α triggers depressive-like behavior in mice (Sukoff Rizzo et al., 2012; Kaster et al., 2012), and TNF- α blockade rescued memory impairment in a stress-induced rat model of depression (Şahin et al., 2015).

Inflammation is also thought to be a fundamental component of neurodegenerative processes (Heneka et al., 2015; Selles et al., 2018). Plasma TNF- α and soluble TNF- α receptors are typically reported as upregulated in severe AD cases (Zuliani et al., 2007; Ledo et al., 2016; Swardfager et al., 2010; Bonotis et al., 2008; Baranowska-Bik et al., 2008; Álvarez et al., 2007; Lai et al., 2017), and elevated production of TNF- α by peripheral blood mononuclear cells is associated with an increased risk of developing AD. (Tan et al., 2007) Circulating IL-6 levels are elevated in AD patients (Lai et al., 2017; Lyra e Silva et al., 2021), predict cognitive decline later in life (Singh-Manoux et al., 2014), and show a negative correlation with memory scores (Lai et al., 2017; Lyra e Silva et al., 2021). *In vivo* and *in vitro* studies show that both cytokines

trigger stress response mechanisms and disrupt synaptic plasticity, memory formation, and hippocampal neurogenesis (Tancredi et al., 1992; Balschun et al., 2004; Monje et al., 2003). In mouse models of AD, blockage of TNF- α and IL-6 signaling pathways rescues memory (Lourenco et al., 2013; Lyra e Silva et al., 2021; Escrig et al., 2019). Collectively, data indicate that aberrant signaling by TNF- α and IL-6 disturbs memory-related mechanisms and promotes cognitive decline.

Systemic inflammation associated with infections contributes to persistent molecular alterations and functional deficits in the CNS. Sepsis survivors frequently experience neurological sequelae and present an increased risk for developing dementia (Kao et al., 2015; Iwashyna et al., 2010). In mice, sepsis enhances brain amyloid pathology, induces brain metabolic changes and TNF- α upregulation, analogous to what is found in animal models of AD. (Neves et al., 2018; Frost et al., 2019; De Sousa et al., 2021; Basak et al., 2021) Furthermore, sepsis-surviving mice exhibit increased susceptibility to toxicity induced by soluble amyloid- β oligomers, with excessive neuroinflammatory responses and IL-6 upregulation (Frost et al., 2019; De Sousa et al., 2021). Aberrant microglial activation appears to play a central role in sepsis-induced late cognitive impairment (Frost et al., 2019; De Sousa et al., 2021). Similarly, infection by ZIKV induces synapse damage and persistent memory deficits via microglia-mediated synapse engulfment and elimination (Figueiredo et al., 2019). ZIKV infection also induces upregulation of TNF- α , which, in this case, appears to be upstream of microglial activation. Importantly, blockage of TNF- α signaling rescues acute and persistent brain pathology, as well as synaptic plasticity and memory in ZIKV-infected mice (Figueiredo et al., 2019; Souza et al., 2018).

In summary, TNF- α and IL-6 are two major cytokines upregulated in COVID-19 that directly affect brain physiology. Their roles in MDD and AD strongly suggest that these cytokines may drive dysfunctional stress-related responses, mood alterations, and cognitive impairments observed in COVID-19 survivors.

6. BBB dysfunction as a possible mediator of neurological damage in COVID-19

The brain is mainly protected from circulating inflammation via the selectivity of the BBB. Under certain pathological conditions, however, defective BBB function may expose the brain to molecules and cells involved in peripheral inflammation (Galea, 2021). For example, available evidence indicates that BBB alterations in AD allows brain infiltration by immune cells, increases permeability to molecular signals from the periphery, and exacerbates neuroinflammation (Nation et al., 2019; Sweeney et al., 2018). Sepsis and the associated cytokine storm also contribute to vascular damage, coagulopathy, and BBB instability (Cheng et al., 2018; Sharshar et al., 2007). In mice, BBB disruption and TNF- α mediated inflammation contribute to depressive-like behavior (Cheng et al., 2018).

Intriguingly, COVID-19 patients with neurological symptoms frequently present anti-SARS-CoV-2 antibodies in their CSF (Alexopoulos et al., 2020; Garcia et al., 2021; Bernard-Valnet et al., 2021; Song et al., 2020b; Benameur et al., 2020). Possible explanations for this include BBB (Fig. 1) and/or blood-CSF barrier leakage. Although viral particles and RNA have not been detected consistently in CSF and brain tissue from patients (Espíndola et al., 2020; Thakur et al., 2021; Yang et al., 2021; Lee et al., 2020), SARS-CoV-2 spike protein was found to cross the BBB in a rodent model, and to induce functional changes in an *in vitro* model, possibly via a pro-inflammatory response from endothelial cells (Rhea et al., 2020; Buzhdygan et al., 2020). Consistent with this finding, CSF/serum albumin ratio measurement revealed BBB dysfunction in 40% of the individuals in a French cohort of COVID-19 patients with neurological manifestations (Lersy et al., 2020). On the other hand, elevated inflammatory markers in the CSF are verified only in a subset of COVID-19 patients with neurological symptoms, and are independent of circulating cytokine levels (Espíndola et al., 2021; Garcia

et al., 2021; Bernard-Valnet et al., 2021).

7. Concluding remarks

Understanding the neurological consequences of COVID-19 poses several challenges. First, substantial variability is observed regarding the types and frequencies of neurological symptoms. Moreover, the biological impact of COVID-19 on mental health may be confounded by adverse effects associated with social isolation, job/financial insecurity, and other social impacts of the pandemic. From a molecular/cellular standpoint, post-mortem brain analysis is generally limited to severe cases of COVID-19, and pathogenic mechanisms revealed in such studies may differ significantly from mechanisms operating in the brains of COVID-19 survivors. As the COVID-19 pandemic continues to ravage the world in its third year, leaving an unprecedented number of infected survivors, possible late neurological outcomes pose a significant future threat to patients and public health systems. Hopefully, shared efforts by scientists from multiple disciplines to tackle this problem and to anticipate late neurological outcomes of COVID-19 will contribute to a better understanding of disease mechanisms so that treatments can be suggested for this emerging global health problem.

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Declaration of competing interest

The authors have nothing to disclose.

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