Human Genetics (2023) 142:1317–1326
https://doi.org/10.1007/s00439-023-02549-x

REVIEW

Direct and indirect impact of SARS-CoV-2 on the brain

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Received: 7 January 2023 / Accepted: 22 March 2023 / Published online: 1 April 2023

Abstract
Although COVID-19 is mostly a pulmonary disease, it is now well accepted that it can cause a much broader spectrum of signs and symptoms and affect many other organs and tissue. From mild anosmia to severe ischemic stroke, the impact of SARS-CoV-2 on the central nervous system is still a great challenge to scientists and health care practitioners. Besides the acute and severe neurological problems described, as encephalopathies, leptomeningitis, and stroke, after 2 years of pandemic, the chronic impact observed during long-COVID or the post-acute sequelae of COVID-19 (PASC) greatly intrigues scientists worldwide. Strikingly, even asymptomatic, and mild diseased patients may evolve with important neurological and psychiatric symptoms, as confusion, memory loss, cognitive decline, chronic fatigue, associated or not with anxiety and depression. Thus, the knowledge on the correlation between COVID-19 and the central nervous system is of great relevance. In this sense, here we discuss some important mechanisms obtained from in vitro and in vivo investigation regarding how SARS-CoV-2 impacts the brain and its cells and function.

Introduction

With more than 650 million cases and 6.5 million deaths, COVID-19 still intrigues researchers and physicians worldwide. Despite being essentially a lung/respiratory disease, the fact that SARS-CoV-2 may affect other organs and tissues is long unquestionable, as reviewed (Gupta et al. 2020). From in vitro experiments to clinical epidemiological data, it is now clear that patients may suffer from a variety of other symptoms, from anosmia and ageusia, to heart disease, kidney disease, vascular disease, gastrointestinal disease or, more severely, to stroke and systemic cytokine storm. This clearly evidences the complex biology of SARS-CoV-2 within the host and calls the attention of physicians and other health professionals for unexpected signs and symptoms.

Since the beginning of the pandemic, patients suffered either from mild neurological symptoms, as anosmia and ageusia (Mao et al. 2020; Zazhytska et al. 2021; de Melo et al. 2021), to more rare but severe cases of encephalopathies, meningitis, and stroke (Mao et al. 2020; SVIN Multinational Registry and Task Force et al. 2021). Whereas many of the coagulopathy-associated complications caused by COVID-19, as the ischemic stroke, was significantly reduced by the early use of anti-coagulants (Ortega-Gutierrez et al. 2021), the understanding on the biology of neurological problems associated with COVID-19, and mainly long-COVID, still intrigues scientists and physicians.

What is very intriguing is the fact that even patients with mild lung disease may still suffer from neurological symptoms, ranging from headache, dizziness, seizures, to encephalopathies, vasculopathies, and stroke (Mao et al. 2020; Brucki et al. 2021). Moreover, the proportion of patients with long-COVID or post-acute sequelae of COVID-19 (PASC), especially women, have highly increased. These patients develop neurological or psychiatric features, as memory loss, confusion, depression, associated or not with chronic fatigue (Del Brutto et al. 2021).

This raises many questions: is there an acute vs a late onset brain impact during COVID-19? Does it correlate with the presence of the virus in the brain? If so, which cell population harbors viral replication? Or, these are only secondary and indirect responses caused by peripheral inflammation or vascular damage? These are important questions to be answered for us to understand and mitigate the impact SARS-CoV-2 can cause to the human brain. Here we discuss some mechanisms on how SARS-CoV-2 impacts the brain, either directly or indirectly.

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SARS-CoV-2 and the paths to the brain

The paths to the brain tissue is a great matter of debate, as reviewed (Chen et al. 2022). Mostly accepted is that SARS-CoV-2 may reach the brain tissue by the transmucosal route through the cribriform plate into the olfactory bulb (Meinhardt et al. 2021; Jiao et al. 2021). Direct invasion from the blood stream has also been proposed, either by transcytosis through endothelial cells (Rhea et al. 2021), or the disruption of the blood brain barrier (BBB) (Nuovo et al. 2021; Yang et al. 2021; Wenzel et al. 2021). This disruption may be either caused by direct infection of cells at the neuro vascular junction, as endothelial cells and astrocytes (Jacob et al. 2020; Yang et al. 2021; Wang et al. 2021b) or due to systemic inflammation, and hypoxemia (Monje and Iwasaki 2022).

Recent reports have also shown that during a crosstalk with alveolar macrophages, $CD4^+$ lymphocytes may get infected with SARS-CoV-2 (Grant et al. 2021) and that it occurs in an ACE-2 independent fashion (Brunetti et al. 2020; Shen et al. 2022). This leads us to speculate whether lymphocytes may carry viral particles to the brain. In fact, it has been recently demonstrated that not only microglia may be infected with SARS-CoV-2 (Jeong et al. 2022b), but that niches of highly activated microglia nearby T $CD8^+$ lymphocytes are abundant in the brain of COVID-19 patients (Schwabenland et al. 2021).

SARS-CoV-2 invades host cells after the interaction of the SPIKE (S) protein with the membrane receptor Angiotensin Converting Enzyme-2 (ACE-2) and further proteolytic cleavage of the S1/S2 domains of S by the protease TMPRSS2 for further fusion and release of the viral genome (+) RNA strand into the cytoplasm, as reviewed (Peron and Nakaya 2020; Tay et al. 2020). Recent findings have demonstrated that Neuropilin-1 may also serve as an entry receptor, and probably more relevant in the CNS (Cantuti-Castelvetri et al. 2020), as ACE-2 expression is very low in many brain areas, as reviewed (Chen et al. 2021).

It is worth mentioning that wild type mice are not permissive to SARS-CoV-2 infection due to structural differences on ACE-2, although the use of the Variant of Concern (VOC) Delta B1.617.2 (Yang et al. 2023), or a mouse adapted strain (MA10) (Amruta et al. 2022) had indicated otherwise. For this reason, most in vitro studies used primary cells either from K18-ACE-2 transgenic mice, hamsters (Rothan et al. 2022; de Oliveira et al. 2022) or wild-type animals pre-treated with an adenovirus (AAV-hACE-2) as a vector to induce the expression of hACE-2 (Song et al. 2021b; Monje and Iwasaki 2022). Other studies also used human-derived induced-pluripotent stem cells (iPSCs) as well as brain organoids (Ramani et al. 2020, 2021; Jacob et al. 2020; Song et al. 2021b; Samudyata et al. 2022; Kong et al. 2022), which are useful tools for the study of many aspects of brain development, function, metabolism and has already been used for the studies of other viral infection, including ZIKA virus (Cugola et al. 2016), dengue virus, influenza virus and also SARS-CoV-2, as reviewed (Harschnitz and Studer 2021).

An interesting work used cortical organoids supplied with pericyte-like cells (PLCs) forming a structure named three-dimensional neural-perivascular assembloid to address the role of the vasculature during SARS-CoV-2 infection (Wang et al. 2021b). PLCs and astrocytes are actively infected with the virus, as assayed by viral RNA detection and Plaque Forming Units Assay (PFU). More interesting, cortical organoids in the presence of PLCs were highly infected when compared to regular organoids, evidencing an important role for endothelial cells in viral replication. This was associated with an increased non-autonomous neuronal cell death, as well as to a robust Type I interferon immune response (Wang et al. 2021b). Due to the lack of vasculature-like structures in regular brain organoids, this research calls the attention to the importance of endothelial and pericytes to the neurobiology of COVID-19. However, due to differences in origin, gene expression, cell type distribution, metabolism, and many others, studies using brain organoids still need further confirmation in vivo.

Many different animal models were established to investigate the biology of SARS-CoV-2 in vivo; from zebrafish (Ventura Fernandes et al. 2022; Kraus et al. 2022), mice (Kumari et al. 2021; Rhea et al. 2021) and hamsters (Rosenke et al. 2020; Zazhytska et al. 2022; de Oliveira et al. 2022) to ferrets (Kim et al. 2022) and macaques (Rutkai et al. 2022; Beckman et al. 2022), as reviewed (Muñoz-Fontela et al. 2020).

Most models used the intranasal inoculation of viable SARS-CoV-2 viral particles either in K18- hACE-2 transgenic mice or after the delivery of an adenovirus carrying the hACE-2 gene (AAV-K18–hACE-2). Hamsters and Rhesus monkeys are also powerful tool to investigate COVID-19, not only because they are naturally susceptible to infection (Imai et al. 2020; Song et al. 2021c; de Oliveira et al. 2022) but also because they develop many similar features to the human disease. These models have given evidence supporting both the presence (Kumari et al. 2021; Song et al. 2021b; Jiao et al. 2021; de Oliveira et al. 2022) and the absence (Fernández-Castañeda et al. 2022; Soung) of neuroinfection. When present, viral particles are detected between 3 and 14 days after inoculation, with a peak no later than day 5th, depending on the animal (Kumari et al. 2021; Rothan et al. 2022; de Oliveira et al. 2022; Amruta et al. 2022). Interestingly, some reports have also called the attention to the presence of viral genome in the eyes of mice, hamsters (Meinhardt et al. 2021; Jeong et al. 2022a), further

confirmed in the human cornea and conjunctiva (Meinhardt et al. 2021).

Non-human primates have also been used to address the neurobiology of COVID-19 (Jiao et al. 2021; Rutkai et al. 2022; Beckman et al. 2022). As observed in mice (Song et al. 2021b) and hamsters (Zazhytska et al. 2021; de Oliveira et al. 2022), in rhesus monkeys (Jiao et al. 2021; Beckman et al. 2022), the olfactory epithelium seem to be the first line of infection, and a probable way of spreading to the brain after intra-nasal inoculation of viral particles. Another similarity with the small animal models was that monkeys also had an increased secretion of innate immunity cytokines, associated with a robust microglial activation (Jiao et al. 2021). Transmucosal route of infection was further confirmed in human samples, as viral RNA was detected by in situ hybridization of the olfactory epithelium. Moreover, S protein was detected in $Tuj1^+$ and $NF200^+$ cells of neuronal origin (Meinhardt et al. 2021). Interestingly, infection of the olfactory epithelium is primarily mediated by neuropilin-1 instead of ACE-2 (Cantuti-Castelvetri et al. 2020), which is similar to observations on brain organoids and human astrocytes (Crunfli et al. 2022; Kong et al. 2022).

Disruption of the microvasculature or the neurovascular unit is often observed, usually associated with microglial (Schwabenland et al. 2021) and astroglial activation (Beckman et al. 2022), suggesting that this could be a viable route of neuroinvasion. Cortical disruption of the vasculature was also observed in AAV-hACE-2 treated and infected mice, evidenced with anti-CD31 and anti-podocalyxin staining followed by iDISCO clearing of the brain tissue (Song et al. 2021b).

Consistently, many clinical findings have corroborated the presence of vascular damage, associated or not with microhemorrhages and endothelial infection in the brain of COVID-19 patients (Conklin et al. 2021; Meinhardt et al. 2021; Song et al. 2021b). Interesting research dissected the direct impact of SARS-CoV-2 on brain endothelial cells on human brains. Through immunofluorescence staining for CD34 and collagen-IV, markers of endothelial cells and basement membrane, respectively, the authors demonstrated a higher presence of *string vessels*, i.e., vascular structures positive for basement membrane (collagen IV^+) but lacking endothelial cells ($CD34^-$) (Wenzel et al. 2021). It suggests a depletion of endothelial cells, probably caused by direct SARS-CoV-2 infection, as $CD34^+$ cells were positive for neuropilin-1.

The mechanism was directly mediated by one of the viral proteases coded in the viral genome, M^{pro} (Nsp5). The authors show that M^{pro} cleaves nuclear factor-κB essential modulator (NEMO), a regulator of IKK and the further phosphorylation of NF-κB, a pivotal pro-inflammatory and pro-survival transcription factor. More important, the appearance of the string like vessels was dependent on the interaction with receptor interacting protein-3 (RIPK3), a well-known modulator of necroptosis. Thus, SARS-CoV-2 infection of brain endothelial cells may not only directly correlate with vascular damage, but with the facilitation of neuroinvasion.

A recent report performed brain autopsies of 11 patients that died of COVID-19 and confirmed the presence of sub-genomic viral RNA, an indicative of viral replication, in different areas of the brain, especially the cortex, thalamus, hypothalamus and the dura-mater (de Melo et al. 2021). More strikingly, although with very low viral loads (< 0.5 copies of N per nanogram of RNA), some patients had detectable viral RNA in the brain up to 239 days after disease onset. Viral N protein was confirmed by immunofluorescence in the cortex and spinal cord of two patients at earlier timepoints. This report shows that, although rare, neuroinvasion may be long-lasting. However, as the study was performed with deceased patients with severe COVID-19, further investigation is needed concerning viral persistence in the brain of long-COVID patients.

SARS-CoV-2 and the impact on brain cells

Although neuroinvasion may vary, what is unquestionable is the presence of constant neuroinflammation, with local cytokine production, microglial activation and secondary neuronal cell death (Song et al. 2021b; Fernández-Castañeda et al. 2022; Soung). Thus, it seems clear that ependymal cells, glial cells and neurons may also suffer an impact during COVID-19.

Cells of the choroid plexus (CP) are among the most permissive cell populations to SARS-CoV-2 infection in vitro, corroborated by the expression of ACE-2, TMPRSS2 and Neuropilin-1 (Jacob et al. 2020). CP organoids were positive for both viral genome and nucleocapsid protein. Transcriptional analyses evidenced a robust change in the overall gene expression, with an up-regulation of genes related to inflammation, mostly Type I interferons, response to stress, regulation of cell death and a down-regulation of genes related to ion transport and ion binding. Moreover, CP had a 3 times increase in cell death when compared to non-infected control cultures (Jacob et al. 2020).

Recent research performing a secretome analysis demonstrated that whereas other cell types reduced cellular interactions after SARS-CoV-2 infection, CP gained (Samudyata et al. 2022). Interestingly, most of these interactions correlated with extracellular matrix, barrier maintenance and solute homeostasis, confirming findings in the human brain (Yang et al. 2021). This may indicate that the CP at the brain-cerebrospinal-fluid-barrier may undergo changes to avoid viral invasion of the brain parenchyma, which may also be corroborated by the modulation of Vascular

Endothelial Growth Factor (VEGF) expression, very important for the maintenance of CP and blood brain barrier (BBB) integrity. Thus, the CP may also serve as an entry route to neuroinvasion.

One of the most detailed studies on the COVID-19 brain performed single cell transcriptomics analysis of brain samples from 8 patients that died of severe disease. At first, the data corroborated many of the findings in brain organoids (Jacob et al. 2020) and in mice (Kumari et al. 2021; Song et al. 2021b; Rothan et al. 2022), showing a robust enrichment in the expression of genes of innate immunity and, as expected, a significant impact on the CP (Yang et al. 2021) which was further, corroborated in multiple sclerosis patients with COVID-19 (Fuchs et al. 2021). It also confirmed other research that claimed the absence of neuroinvasion (Fernández-Castañeda et al. 2022) although with important microglial activation (Samudyata et al. 2022; Beckman et al. 2022).

Another study also performed single cell transcriptomics analysis of brain organoids infected with SARS-CoV-2 (Song et al. 2021b). Twenty-seven different cell clusters were identified, of which 5 were more than 15% infected after 96 h, which are the following: outer radial glia-3; intermediate progenitor-2; neuronal precursor cells; transitional cell-4 and neuronal precursor cell-4, from lower to higher viral loads. More interesting, there was a differential gene expression when ZIKV vs SARS-CoV-2 infected organoids were compared, evidencing a virus-specific transcriptional signature, although both are (+) stranded and enveloped RNA viruses. Also, and corroborating our findings in hamster (de Oliveira et al. 2022), there was a significant change in the expression of genes related to carbon metabolism, tricarboxylic acid cycle (TCA), and pyruvate metabolism, with a rapid modulation of the hypoxia induced factor—1α (HIF-1α), in agreement with a previous report using human monocytes (Codo et al. 2020).

Astrocytes are not only the most abundant cells playing many roles in health and disease (Sanmarco et al. 2021), but also, they are highly metabolic and take place in the BBB and neurovascular unit, becoming an interesting target for viral replication. Despite the very low expression of ACE-2 and TMPRSS2, astrocytes express neuropilin-1, making them permissive to SARS-CoV-2 invasion (Kong et al. 2022). In fact, astrocytes harbor more viral proteins, as nucleocapsid (N) and S than neuronal precursor cells ($Nestin^+$) and neurons ($Map2^+$). Corroborating the findings in CP, astrocytes highly upregulate the expression of Type I interferons, as well as ISGs and ion transport molecules. Another interesting feature was that infected astrocytes induced cell death of the nearby neurons, which may indicate a compromised astrocytic metabolism that indirectly impacts neuronal survival. Interestingly, this non-autonomous neuronal cell death was also observed with CP organoids (Jacob et al. 2020).

An elegant work used organotypic fetal brain slices of the cortical regions from aborted fetuses of 19–23 weeks of gestation. Again, $GFAP^+$ and $AQUA4^+$ cells, i.e., astrocytes, were more infected than neurons or other cell types, as evaluated for the presence of S, N, and viral RNA. Interestingly, perivascular astrocytes as well as vascular cells also harbored more viral antigens. Other precursor cells, as radial glia and intermediate progenitor cells were rarely infected (Andrews et al. 2022). Another striking similarity was that although infected, there was no increase in astroglial cell death, whereas nearby neurons were highly apoptotic, as shown in brain organoids (Song et al. 2021b). Further infection of cortical samples from patients undergoing resection of epileptic areas with SARS-CoV-2 confirmed the tropism for astrocytes, whereas microglial activation was also observed (Samudyata et al. 2022).

Due to the metabolic importance of astrocytes for proper neuronal function, we have investigated protein expression and metabolism of infected hamster's astrocytes (de Oliveira et al. 2022). We observed an important change in the overall expression of proteins related to carbon metabolism, amino acid synthesis, and tricarboxylic acid cycle (TCA). Moreover, targeted metabolomics evidenced intense glutamine consumption, which favors viral replication (de Oliveira et al. 2022). Conversely, blockade of glutaminolysis with L-DON, significantly reduced viral replication, which was already shown in the literature, although using other cell types (Krishnan et al. 2021). It is worth to mention that the use of glutamine as energy source for replication was already observed with other viruses, as vaccinia (Fontaine et al. 2014), cytomegalovirus (Chambers et al. 2010), herpes simplex and influenza (Thai et al. 2015). Glutamine is converted to glutamate and then to alpha-ketoglutarate fueling the TCA cycle through anaplerosis. This is an important alternative source of energy in conditions of low glucose or high inflammation. In fact, the impact on glutamine and glutamate metabolism was elegantly demonstrated through plasma metabolomics, where mild and severe COVID-19 patients were differentially clustered (Krishnan et al. 2021). We believe these metabolic changes are important energy suppliers for viral replication, with special attention to the CNS, as neurons are highly dependent of glutamine and glutamate for proper function and development (Gkini and Namba 2022).

By associating brain organoids with microglia-like cells, it was demonstrated the importance of microglia on viral clearance and tissue damage. Consistent with an anti-viral immune response signature, microglia-like cells highly activated interferon stimulated genes (ISGs), as ISG15. Moreover, there was a significant increase of the microglial activation markers CD68 and TREM2, as well

as of molecules associated with synapse elimination, as C3 and C3AR1(Werneburg et al. 2020). Corroborating this, microglial-like cells were positive for PSD95 puncta, indicating the engulfment of synaptic terminals. As already mentioned, niches of highly activated microglial cells were intimately associated with CD8 + T lymphocytes expressing Eomes, Gramzyme B and CD38 in the brain of COVID-19 patients. Worth to mention that these niches had proximity with BBB disrupted areas (Schwabenland et al. 2021).

Two interesting research showed in mice, hamsters and human samples, that despite the lack of neuroinvasion, there is important neuroinflammation, associated with white matter degradation (Fernández-Castañeda et al. 2022; Soung). By using an adenovirus associated vector (AAV) to induce the expression of hACE-2 (AAV-hACE-2) restricted to the lungs and thus causing only a mild and localized infection, the group observed a robust microglial activation, with increased cytokine and chemokine secretion in the cerebrospinal fluid (CSF), although without neuroinvasion. More interesting, this activation mostly occurred in the white matter when compared to other brain areas, resulting in a reduction of oligodendrocyte precursor cells (OPCs), confirmed in human brain samples, and that correlated with higher CCL11 levels. Also, hippocampal neurogenesis was impaired, as evidenced by a reduced amount of DCX^+ neuroblasts in the dental gyrus (Fernández-Castañeda et al. 2022). Strikingly, this was also confirmed in the hamster model and in human samples. Hippocampal immunofluorescence for IBA-1 and IL-1 evidenced important microglial activation and reduction of hippocampal neurogenesis (Soung).

Important morphological changes were described in neurons of the cerebellum and brainstem of infected monkeys (Rutkai et al. 2022). Most prominent alterations were characterized by pyknotic nuclei and cellular vacuolization, mostly evidenced on Purkinje cells. Apoptotic neuronal death was confirmed through cleaved caspase-3 staining. Also, as already mentioned in other reports, intense microglial activation was evidenced. This is in agreement with other findings, despite that hippocampus, thalamus and midbrain were also affected (Jiao et al. 2021). On the other hand, only a high dose of SARS-CoV-2 (10^6 PFUs) intracranially inoculated caused the dissemination of the virus to other brain areas, as frontal and occipital lobes.

A more detailed study demonstrated the presence of N protein positive cells in the cortex of monkeys infected with 2.5×10^6 PFUs (Beckman et al. 2022). Unexpectedly, neurons were the most infected cell type, followed by astrocytes and microglia. No differences were observed between young and aged animals. An interesting finding was that, whereas double stranded RNA, a marker of viral replication, was mostly found in the neuronal soma, S protein was detected throughout the dendrites. Interestingly, neuroinflammation, astrogliosis and microglial activation was more prominent in aged than in young infected animals. Corroborating previous findings with brain organoids (Samudyata et al. 2022), activated microglia was associated with myelin damage in the white matter (Fernández-Castañeda et al. 2022), decreased synaptic PSD95 staining and increased concentrations of neurofilaments in the serum.

Along with the cells of the choroid plexus, as already discussed, astrocytes were shown to be highly impacted during SARS-CoV-2 infection, as observed in vitro (Andrews et al. 2022; Kong et al. 2022) and animal models (Kong et al. 2022). This was confirmed by two reports using infected brain slices obtained from epileptic patients undergoing surgical resection (Andrews et al. 2022; Crunfli et al. 2022). E and N were detected in around 40% of the astrocytes from infected samples, although no cell death was observed. However, as previously discussed, non-autonomous neuronal cell death was highly detected, which could be caused either by neuroinflammation or tissue hypoxia (Rutkai et al. 2022; Crunfli et al. 2022). Also, both reports confirmed that astrocyte invasion was mediated by neuropilin-1 instead of ACE-2, as previously shown in brain organoids (Kong et al. 2022). The knockdown of CD147, a glycoprotein of the immunoglobulin superfamily and a less known SARS-CoV-2 entry receptor (Wang et al. 2020), also significantly reduced infection (Crunfli et al. 2022). The impact on astrocytes and neurons was also confirmed by the increase in serum levels of glial fibrillary acidic protein (GFAP) and neurofilament (NFL), markers of astrocytic and neuronal degeneration, respectively (Kanberg et al. 2020).

In agreement with our findings in the hamster brain, this research points to a cluster of astrocytes with an increased Type I interferons response and an impaired metabolism of aminoacids and neurotransmitters, especially glutamine and glutamate. Due to the importance of this molecules to the establishment of memory, the authors suggest it may correlate with the cognitive decline and memory loss developed by some patients, especially during long-COVID (Del Brutto et al. 2021). Conversely, we observed a convergence of proteins and pathways related to neurotransmission when we compared their data to hippocampal and cortical proteomics in our model (de Oliveira et al. 2022). Supporting this, a case report of a 29 year old patient with mild disease but with impaired cognition and short term memory loss, demonstrated through magnetic resonance spectroscopy (MRS) a clear reduction in glutamate (GLU), glutamine (GLN) and *N*-acetylaspartate (*N*-AA) in the dorso-lateral pre-frontal cortex (DLPFC) of the patient. Three months later, all neurological symptoms disappeared and GLU, GLN and N-AA returned to normal levels (Yesilkaya et al. 2021). This indicates that a secondary metabolic and neurochemical imbalance may be relevant indicating a possible therapeutic

approach to mitigate some of the neurological and psychiatric symptoms.

In summary, most investigations confirmed that SARS-CoV-2 can directly infect and replicate in certain brain cell types, mostly endothelial cells, CP cells and astrocytes. Also, that they can mount an adequate immune response, with the enrichment of genes related to the innate immune response, especially Type I interferons. This up-regulation of the immune response, especially demonstrated in brain organoids, although relevant to reduce viral loads, seems indirectly deleterious, as it correlated with non-autonomous neuronal cell death.

COVID-19 and systemic impacts: hypoxemia, self-reactivity, reactivation of viral infection

COVID-19 is widely known to cause lung disease, with intense inflammatory infiltrate, alveolitis, hyalin membrane formation and intense mucus production (Barton et al. 2020). In severe cases, this leads to systemic hypoxemia, caused by reduced lung O_2/CO_2 exchange that may indirectly affect the brain vasculature. Corroborating this, SARS-CoV-2 infected rhesus monkeys hypoxemia was associated with increased deterioration of Purkinje cells and a high expression of HIF-1α in endothelial cells and nearby glial cells. Moreover, despite the sparsity, N protein staining was detected in the vasculature of the basal ganglia, cerebellum, and brain stem (Rutkai et al. 2022). Microhemorrhages and leakage of erythrocytes to the brain parenchyma was detected. Of note, increased HIF-1α staining was also observed in mouse brain (Song et al. 2021b).

Confirming this, it was shown that microvascular injury and cerebral blood flow dramatically changes even in patients that recovered from mild COVID-19 infection, without any neurological symptom (Qin et al. 2021). The authors evaluated 51 patients that recovered from either mild or severe COVID-19. Severe diseased patients had a decrease in the cortical thickness after 3 months, whereas mild infection patients had no changes. Sub-cortical nuclei, putamen and thalami were also reduced. Severe diseased patients had a significant overall decrease in the blood flow across the gray matter when compared to mild patients. These findings confirms that reduced O_2 supply to the brain may be greatly relevant, for instance being responsible for the metabolic changes observed (Song et al. 2021b; Yang et al. 2021; de Oliveira et al. 2022). Whether these changes are more prominent in patients during long-COVID was not determined.

Another indirect impact on the brain during COVID-19 was suggested to be mediated by a self-reactive immune response. In fact, the presence of autoantibodies has been described in both mildly and severely infected patients (Wang et al. 2021a). More interesting, it has even been correlated with the chance to develop a more severe disease, as patients may develop antibodies against important molecules of the antiviral immune response, mainly anti-IFN-α (Bastard et al. 2020). Conversely, autoantibodies, as anti-NMDAR and anti-myelin (Franke et al. 2021), have also been described in the cerebrospinal fluid (CSF) on patients with encephalopathies during acute COVID-19 infection.

In this context, a detailed investigation compared B cell clonality in the blood and CSF of COVID-19 patients (Song et al. 2021a). Very unexpectedly, discrepant BCRs were cloned from these two different compartments, evidencing a localized clonal expansion in the CNS. Confirming this, the cloned antibodies obtained from the CSF were capable to immune react against murine whole brain slices, whereas those obtained from the peripheral blood were not. This clearly suggests the presence of intra-thecal antibodies against brain antigens. Using a PhIP-seq platform, where more 730,000 peptides were phage displayed to CSF autoantibodies, two antigen candidates were identified: intraflagellar transport protein 88 homolog (IFT88) and THAP domain containing-3 (THAP3). Although very interesting, the research has a few limitations, as only 5 patients were investigated, and the role of IFT88 and THAP3 on brain function is poorly understood. Also, whether these antibodies are pathogenic and broadly found in vivo has yet to be determined.

Long-COVID-19

Long-COVID or post-acute sequelae of COVID-19 (PASC) is the term used to describe the ongoing symptoms that some people experience after recovering from COVID-19. They usually include chronic fatigue, memory loss, cognitive decline, and confusion, causing the so-called brain fog (Yesilkaya et al. 2021; Del Brutto et al. 2021; Monje and Iwasaki 2022; Fontes-Dantas et al. 2023). Some people may also experience issues such as anxiety and depression (Soltani et al. 2021). What is intriguing is the fact that many of long-COVID patients had asymptomatic do mild disease. This raises the question on how the virus is really impacting brain function? It is suitable to think that many of the mechanisms discussed here, as neuroinvasion, neuroinflammation, brain vascular damage, demyelination and hypoxia are important and greatly contribute with the neurological symptoms. However, most data corroborating these findings were obtained either in experimental models or from samples of patients that succumbed to very severe disease. This raises the question: what is the real cause of long-COVID after asymptomatic or mild disease? Why patients have symptoms for such a long period, as 3–9 months? Does it correlate with viral persistence or latency, as recently proposed? (Chen et al. 2022). Or is it the result of a persistent

neurochemical imbalance caused either a metabolic disturbance or epigenetic changes of neurotrophic genes?

A very recent research immune profiled more than 200 patients with long-COVID with symptoms as chronic fatigue, memory loss and confusion (Klein et al. 2022). The authors described a significant difference in circulating leukocytes, with increased frequency of non-classical monocytes $CD14^{low}CD16^{+}$ whereas $IL\text{-}4^{+}IL\text{-}6^{+}$ double positive CD4 and CD8 lymphocytes were increased. Intriguingly, this was associated with a dramatic reduction of circulating cortisol (around 50%). More strikingly, these patients did not display augmented autoreactivity to self-antigens, as expected. Instead, they had a higher reactivity to Epstein Barr virus (EBV) envelope proteins gp42 and gp350. This report suggests that long-COVID may correlate either with the reactivation of EBV infection or with a clonal expansion of SARS-CoV-2 unrelated B cells that could somehow play a role in long-COVID. More unexpectedly, there was no difference in EBV serology between the groups.

Conclusion

Although there are some discrepancies concerning the prevalence and the importance of neuroinvasion during SARS-CoV-2 infection, either in experimental models or during human disease, the impact of COVID-19 on the CNS is unquestionable, as illustrated in Fig. 1. The questions that remain are: what are the real players? Neuroinvasion, endothelial damage, hypoxemia, peripheral inflammation, auto-immune response, or the reactivation of previous viral infection? In the case of acute neurological consequences, as encephalopathies and stroke, as mostly observed in severe cases of COVID-19, it seems reasonable that a high viremia associated with an exacerbated immune response may be pivotal. However, during long-COVID, it is hard to understand the mechanisms, as many of the patients may have from asymptomatic to mild disease. In fact, even patients with mild COVID-19 had important neurological and psychiatric disorders. Although we have much evolved on the

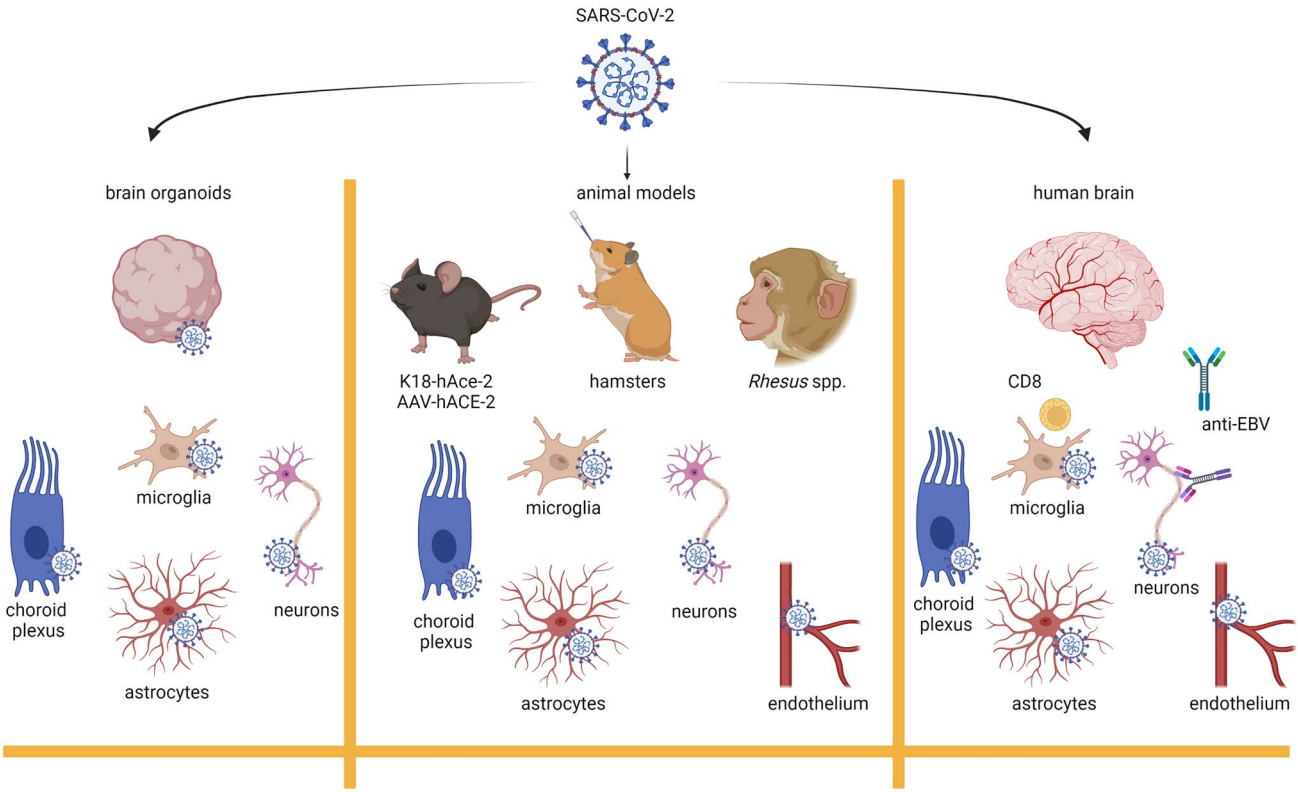

Fig. 1 Experimental approaches for the investigation of SARS-CoV-2 impact on the brain. Left: in vitro models of primary cells or brain organoids infected with SARS-CoV-2. Choroid plexus and astrocytes are the most impacted cells. Microglia may be infected. Neurons are may undergo cell death. Middle: animal models. Mice, hamsters, or rhesus monkeys were infected intra-nasally or intra-cranially with SARS-CoV-2. Choroid plexus and astrocytes are infected whereas neurons may vary between models. Neurons undergo non-autonomous cell death. Endothelial cells may be infected and undergo cell death. Right: human samples. Choroid plexus is infected and disrupted. Astrocytic and neuronal infection may vary between studies. Endothelial cells are infected and undergo cell death. Infected microglia may be surrounded by infiltrating lymphocytes. Presence of autoantibodies against neuronal proteins and EBV glycoproteins were described. Figure made by the author using www.biorender.com

understanding of COVID-19 concerning lung disease, and greatly reduced mortality with vaccine development, a total understanding on the impact of SARS-CoV-2 infection to other organs, especially the brain, is far from being completely understood. This clearly calls the attention not only to the complexity of the disease, but also to scientists, funding agencies, and policy makers, to the necessity for deep further investigation.

Acknowledgements JPSP is funded by Fundação de Amparo a Pesquisa do Estado de São Paulo (FAPESP) grants # 2016/26170-0; 2020/06145-4; by Conselho Nacional de Pesquisa (CNPQ) grant #316646/2021-0 and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior.

Author contributions JPSP wrote the manuscript in full and prepared the figure.

Funding The author has no relevant financial or non-financial interests to disclose.

Declarations

Conflict of interest The author declares to have no conflict of interest.

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