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REVIEW

Neurological pathophysiology of SARS-CoV-2 and pandemic potential RNA viruses: a comparative analysis

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SARS-CoV-2 has infected hundreds of millions of people with over four million dead, resulting in one of the worst global pandemics in recent history. Neurological symptoms associated with COVID-19 include anosmia, ageusia, headaches, confusion, delirium, and strokes. These may manifest due to viral entry into the central nervous system (CNS) through the blood–brain barrier (BBB) by means of ill-defined mechanisms. Here, we summarize the abilities of SARS-CoV-2 and other neurotropic RNA viruses, including Zika virus and Nipah virus, to cross the BBB into the CNS, highlighting the role of magnetic resonance imaging (MRI) in assessing presence and severity of brain structural changes in COVID-19 patients. We present new insight into key mutations in SARS-CoV-2 variants B.1.1.7 (P681H) and B.1.617.2 (P681R), which may impact on neuropilin 1 (NRP1) binding and CNS invasion. We postulate that SARS-CoV-2 may infect both peripheral cells capable of crossing the BBB and brain endothelial cells to traverse the BBB and spread into the brain. COVID-19 patients can be followed up with MRI modalities to better understand the long-term effects of COVID-19 on the brain.

Keywords: blood–brain barrier; brain; central nervous system; COVID-19; magnetic resonance imaging; neuropathophysiology; RNA viruses; SARS-CoV-2

Abbreviations
ARDS, acute respiratory distress syndrome; BBB, blood–brain barrier; CendR, C-end rule; CNS, central nervous system; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; FA, fractional anisotropy; HPA, hypothalamic–pituitary–adrenocortical; MRI, magnetic resonance images; MS, multiple sclerosis; MBP, myelin basic protein; NMDAR, anti-N-methyl-D-aspartate receptor; NiV, Nipah virus; PNS, peripheral nervous system; RBD, receptor binding domain; SWI, susceptibility weighted imaging; ZIKV, Zika virus.

Since December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected tens of millions of people globally [1–2]. Coronavirus disease 2019 (COVID-19) has since been the subject of massive scientific endeavor as researchers have pushed to understand its mechanisms of action, rapidly develop vaccines, and seek effective treatments. SARS-CoV-2 shares remarkable similarities to the severe acute respiratory coronavirus (SARS-CoV), which caused a major outbreak in 2003 [3], and Middle East respiratory syndrome coronavirus (MERS-CoV), responsible for sporadic epidemics in the Middle East [3]. Both viral diseases had high mortality rates of 10% and 35%, respectively, causing concern over the potential lethality of SARS-CoV-2 [4]. Previous research has established that coronaviruses are able to breach into the central nervous system (CNS) and induce symptoms of both the compromised CNS and peripheral nervous system (PNS) [5]. Recent studies have reported that infection with SARS-CoV-2, along with respiratory symptoms, results in neurological complications such as ageusia, anosmia, Guillan–Barré syndrome, myasthenia gravis, and encephalopathy [6–9]. This phenomenon, reported in several other RNA viruses (some of which will be further discussed in this review), can be made possible primarily through three potential entry points by which a virus can enter the CNS: (a) by penetrating the blood–brain barrier (BBB), (b) entering through the blood–cerebrospinal fluid barrier, and (c) invasion via cerebral nerve terminals. However, in this review, we will largely be focusing on entry by penetrating the BBB.

The BBB is a highly restrictive region of CNS microvasculature composed of continuous non-fenestrated blood vessels which helps regulate, and in many cases prevent, metabolites, macromolecules, and toxins in the circulating blood from crossing into the extracellular fluid of the CNS where neurons reside [10]. The BBB consists of endothelial cells of the capillary wall, astrocyte end-feet surrounding the capillary, and pericytes embedded in the capillary basement membrane [11]. The BBB protects the brain from the blood milieu, facilitates selective transport, and modifies blood- or brain-borne substances [12]. The BBB restricts the passage of pathogens, the diffusion of solutes in the blood, and the passage of peripheral immune factors [13–14]. Being a semipermeable barrier, it allows for the diffusion of hydrophobic and small polar molecules [15]. The BBB is extremely selective about what it allows to diffuse across it, which adds to the complexity of developing therapeutic agents to treat CNS disorders. This makes it imperative to understand how the virus is able to invade the BBB and develop ways to prevent further damage from occurring [16].

There is currently little known about the mechanism whereby SARS-CoV-2 crosses the BBB; hence, a comparative study of the mechanisms adopted by other viruses could shed some light on this issue. In this review, we elucidate the neuropathological complications caused by RNA viruses that infect the CNS as well as the mechanisms by which they cross the BBB. Through this side-to-side comparison, we aim to provide further points of research in the ongoing journey of understanding the course of SARS-CoV-2 infection.

Coronaviruses (CoVs)

Members of the family *Coronaviridae*, the coronaviruses (CoVs) that we discuss in this review are SARS-CoV, MERS-CoV, and SARS-CoV-2. All of these CoVs are positive-sense, single-stranded RNA viruses with genome sizes around 30 kilobases long [2,17]. These three CoVs make up the subfamily *Betacoronaviridae*, or betacoronaviruses [2,17], which are a class of CoVs known to infect mammals, including humans [18].

Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV)

SARS-CoV is evolutionarily very similar to SARS-CoV-2, binding to the same angiotensin-converting enzyme 2 (ACE2) entry receptor and containing the same four essential structural proteins: the nucleocapsid (N), matrix (M), envelope (E), and spike (S) proteins [19]. Similar to COVID-19, SARS largely manifested as a respiratory disease, infecting the lower respiratory and gastrointestinal tracts, sometimes causing acute respiratory distress syndrome (ARDS) [4]. Some cases of SARS have been associated with the incidence of epilepsy and stroke [20–23]. There is also evidence to suggest that SARS leads to muscle weakness, myopathy, and polyneuropathy [24]. Chronic post-SARS syndrome has also been described, characterized by persistent fatigue, diffuse myalgia, weakness, depression, and disrupted sleep patterns [25].

SARS-CoV is able to infiltrate the CNS through penetration of the BBB through the Trojan horse mechanism, a phenomenon by which infected cells transmigrate across the BBB (Fig. 1A) [26]. SARS-CoV has been shown to infect lymphocytes, granulocytes, monocytes, and monocyte derivatives, which then pass through the BBB and allow for CNS infection [27–29].

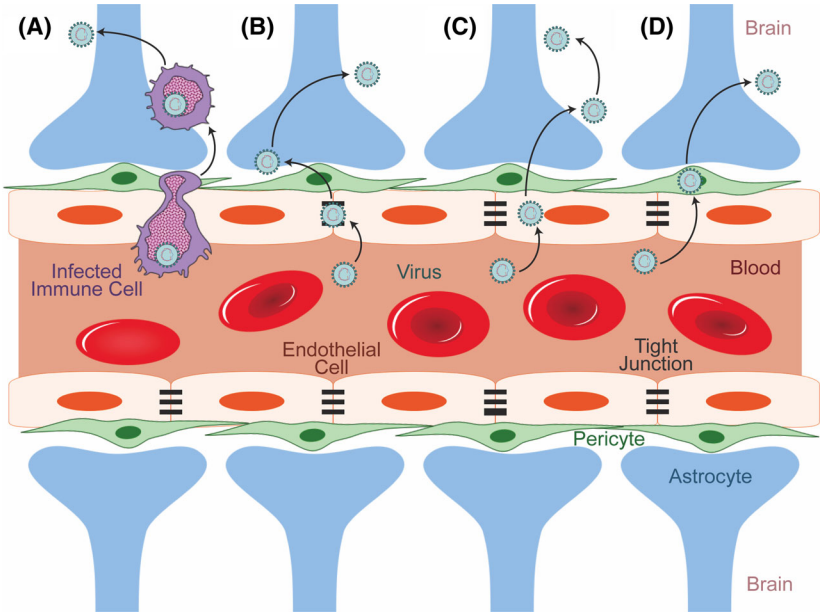

Fig. 1. A Simplified Diagram of the Various Mechanisms by Which Viruses Enter the BBB. (A) The 'Trojan horse mechanism' where a virus-infected immune cell crosses the brain endothelium through the tight junction and releases virus after crossing the BBB, (B) passive viral transport, where a virus passes through the brain endothelium through loosened tight junctions, potentially disrupting the tight junction, (C) infection of the brain endothelium upon which the virus is exocytosed past the BBB, and (D) infection of pericytes leading to invasion of the virus into the BBB.

Middle East Respiratory Syndrome Coronavirus (MERS-CoV)

Though MERS-CoV is phylogenetically related to SARS-CoV-2, it is only 40% similar genetically [30]. MERS-CoV has a six-helix bundle fusion core structure of spike protein [31]. Unlike SARS-CoV and SARS-CoV-2, MERS-CoV binds to the dipeptidyl peptidase 4 receptor (DPP4) to gain entry [32].

MERS-CoV infection has been correlated to incidence of upper respiratory and gastrointestinal tract infections, which are also observed in COVID-19 [4]. Common symptoms associated with MERS-CoV vary from asymptomatic or mild disease to severe illness with risk of progression to respiratory failure due to viral pulmonary infection [33]. The most notable symptoms correlated with MERS-CoV include runny nose, sore throat, low-grade fever, myalgia, and ARDS [33–34].

Nevertheless, clinical, radiological, and laboratory findings have been suggestive of MERS-CoV being associated with neurological illness. However, there is a lack of a confirmatory test of brain infection, especially the presence of the virus in the brain tissue [35]. Currently, there is little evidence to suggest that MERS-CoV causes neurological complications and there is no evidence of direct CNS invasion [36]. Any reported neurological manifestations could be attributed to passive flow through a BBB damaged by disease-mediated inflammation (Fig. 1B) [36].

It has also been hypothesized that, in those with certain genetic predispositions, autoimmunity by host T cells may result in the induction and exacerbation of neuropathologies observed through MERS-CoV infection [37]. Although it is uncommon, the CNS could be involved by MERS-CoV infection through autoreactive T cells which recognize viral and myelin antigens as similar molecules, causing autoreactive inflammation that disrupt the BBB and facilitate uncontrolled transport across the BBB [37–39]. Though little evidence has been presented to support this hypothesis, it is well established that viruses can share certain epitopes with host cells, which could lead to potential autoimmune disorders [40]. In fact, in the case of multiple sclerosis (MS), considered a model for immune cell-mediated CNS disease, several CoVs contain a stretch of six peptides similar to myelin basic protein (MBP) [40-41]. CoVs with at least four of the same peptides in this stretch (ASQKRP) have been established to induce immunity against MBP, meaning that these CoVs could conceivably induce autoimmunity against MBP and subsequent neurodegeneration upon infecting the host. This theory could provide an explanation to the mystery behind the albeit rare neuroinvasive capability of MERS-CoV. This hypothesis has previously been used to explain the resultant neurological complications observed over the course of infection with the H1N1 pdm09 influenza strain [42].

SARS-CoV-2

The genome of SARS-CoV-2 is very similar to SARS-CoV, showing 79.6% homologous sequence [2,43]. SARS-CoV-2 is able to enter cells primarily via

binding to ACE2 though there have been alternate receptors identified, such as lectins [44] and neuropilin 1 (NRP1) [45], which will be discussed further below. One of the divergences from SARS-CoV that can contribute to the enhanced virulence of SARS-CoV-2 is the presence of a furin cleavage site insertion at the S1-S2 junction of the S protein [46]. This furin cleavage site insertion increases the number of polar interaction sites between the virion and the ACE2 receptor, which facilitates viral uptake by the host cell [47]. This insertion is highly conserved in rodent origin embeco lineage (betacoronaviruses) and avian origin gammacoronaviruses, as well as in certain feline and canine alphacoronaviruses [48]. However, though the bat coronavirus RaTG13 and pangolin coronavirus appear to be the closest relative of SARS-CoV-2 [2,47,49–50], this insertion only appeared in SARS-CoV-2, gaining considerable attention to study the possible origin of furin cleavage site in the S protein of SARS-CoV-2.

COVID-19 can be seen as a systemic infection, causing a variety of symptoms in multiple body systems. In particular, systemic inflammation, coagulation, cytokine storm, and lymphopenia are observed as a result of SARS-CoV-2 infection [51]. COVID-19 has also been reported to cause hyperglycemia, elevated transaminase levels, diarrhea, urticaria, rash, perniolike lesions, myocarditis, arrhythmia, pneumonia, ARDS, acute kidney injury, pulmonary embolism, and deep vein thrombosis [51]. Beyond this, symptoms caused by invasion of the virus in the CNS and PNS have also been reported—namely ageusia (loss of taste), anosmia (loss of smell), myasthenia gravis, encephalopathy, and Guillan–Barré syndrome [6–9]. Reports of seizures have also been documented, though occurrence is rather infrequent and further study into this phenomenon is warranted [52]. There have been reports of strokes and other cerebrovascular diseases occurring in several patients infected with SARS-CoV-2, particularly in severe cases of COVID-19 [7,53–54]. SARS-CoV-2 has been shown to cause neuritic degeneration and synaptic loss in neurons, which increases the risk of developing Alzheimer's disease [55–56]. SARS-CoV-2 can gain access to neurons and astrocytes, which do not express ACE2, via the neuropilin 1 (NRP1) protein, which is more readily expressed in the CNS [56]. NRP1 has been established as a co-receptor for SARS-CoV-2 cellular entry and, while it has not yet been established whether its expression in the absence of ACE2 promotes infection, we believe that NRP1 possibly can facilitate viral entry into neurons and astrocytes. Recently, it has been reported that the ApoE4 allele, a genetic risk factor for developing Alzheimer's disease, contributes to enhanced SARS-CoV-2 replication in astrocytes [55,57].

Neuronal damage as a result of SARS-CoV-2 infection has been reported to occur in different ways. Injury from hypoxia, a condition commonly observed in severely ill COVID-19 patients, has been thought to cause damage to the nervous system [58]. Systemic inflammatory response syndrome has been implicated in causing CNS damage, as a result of the secretion of inflammatory cytokines such as IL-6, IL-10, IL-1β, and TNF-α by glial cells [59–60]. These cytokines can lead to activation of the hypothalamic–pituitary–adrenocortical (HPA) axis, releasing norepinephrine and glucocorticoids, which cause mass immune dysregulation [61–67]. SARS-CoV-2 can also lead to shedding of proteins such as high mobility group box 1 (HMGB1) from viral-damaged cells that can leach across the BBB once it has been damaged by systemic inflammation [68]. These proteins, acting as pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), can trigger innate immune response within the brain, leading to inflammation and subsequent damage to the CNS [62,69–71]. It has also been reported that IFN type I response occurs in COVID-19 and, though this effect is thought to be protective, may lead to cognitive impairment [62,72].

Research is still ongoing to determine the mechanism by which SARS-CoV-2 infects the CNS and PNS. However, there are a few mechanisms that have been suggested which may explain complications of the CNS.

One suggested mechanism for SARS-CoV-2 entry to the CNS is penetration of the BBB. This could occur via three potential means: (a) the Trojan horse mechanism (Fig. 2A), (b) infection and invasion through vascular endothelial cells (Fig. 2B), or (c) infection and invasion through pericytes embedded in the endothelial membrane which become exposed from damage to the BBB (Fig. 2D) [73]. It has been shown that SARS-CoV-2 is able to infect monocytes and macrophages, which can be recruited across the BBB, giving credibility to the Trojan horse mechanism theory [74–75]. Given that some endothelial cells along the vascular tree express little to no ACE2 relative to epithelial cells [76], SARS-CoV-2 may infect vascular endothelial cells in order to invade the BBB [77]. Given its genetic similarity to SARS-CoV, which infects many types of immune cells, SARS-CoV-2 may infect similar cell types and utilize the Trojan horse mechanism to enter the BBB. The resulting inflammation would increase BBB permeability and allow SARS-CoV-2-infected immune cells to more easily invade the CNS [78]. The

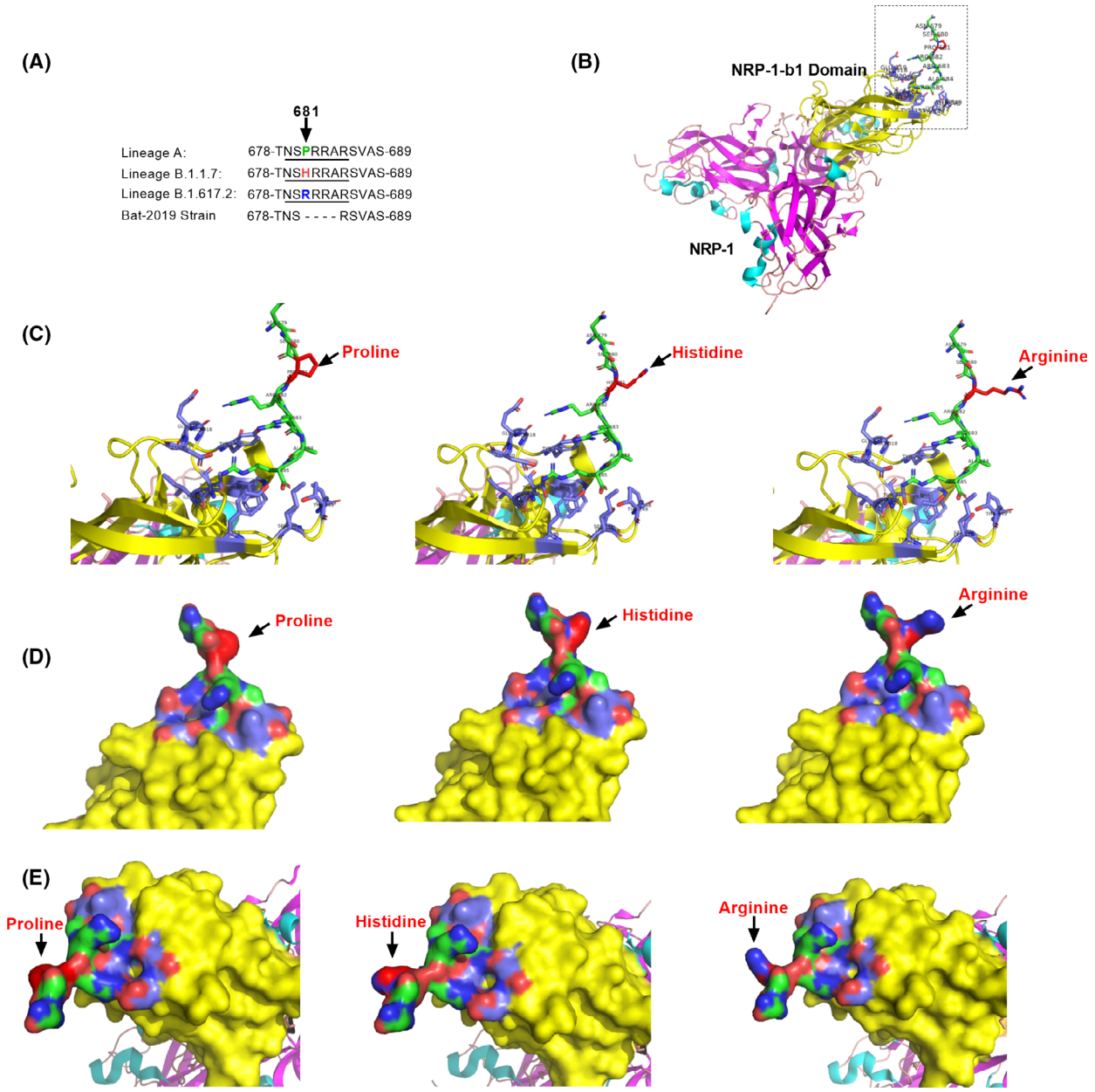

Fig. 2. Computational structure analysis of NRP-1-b1 domain and SARS-CoV-2 spike CendR peptide. (A) Alignment of SARS-CoV-2 spike protein residues between lineage A and lineage B and Bat-2019 strain. (B) Protein structure of NRP-1-b1 interacting with Spike peptide is shown. Crystal structure of S1 CendR motif (PDB accession code 7JJC) was used as a basis to model the protein structures. The inset in panel B is shown in (C) and (D, solid surface model) for proline, histidine, and arginine variants. Proline to histidine or arginine change imparts a hydrophobic to charged side chain, which alters the interaction between NRP-1-B1 with spike CendR peptide. Top-down views of (D) are provided in (E). PyMOL program (the PYMOL Molecular Graphics System, version 2.0 Schrödinger, LLC.) was used for protein structure visualization.

S protein on SARS-CoV-2 has been shown to disrupt the BBB through interactions with brain endothelial cells, resulting in a pro-inflammatory response that damages the cells and reduces BBB integrity, lending credence to the associated theory [79].

Evidence has also been presented that CoVs invade peripheral nerve terminals and spread along synapses, ultimately leading to the CNS without breach via the BBB [80–81]. This mechanism has been observed in several CoVs, herpes simplex virus, and human

immunodeficiency virus (HIV) [82]. Entry of SARS-CoV-2 to the CNS could also occur through the olfactory nerve despite a lack of ACE2 expression, but due to the expression of NRP1 instead, which facilitates SARS-CoV-2 entry into cells [83–85]. NRP1 is expressed in respiratory and olfactory epithelium, as well as neuronal cells [85]. Due to their lack of expression of ACE2, NRP1 in neuronal cells may be a major receptor for SARS-CoV-2 infection of the CNS. Despite this, it has been suggested that the presence of any cells expressing ACE2 is enough for productive infection with SARS-CoV-2 to occur—a requirement satisfied by the presence of pericyte-like cells along the BBB [86]. Infection of pericytes, coupled with alternate entry of SARS-CoV-2 into neuronal cells via NRP1, may facilitate entry of the virus into the CNS, leading to manifestation of associated symptoms (Fig. 1D).

As the pandemic progresses, new variants of SARS-CoV-2 have been reported. Recently, additional lineages such as B.1.1.7 (or alpha variant) in the United Kingdom, B.1.351 (or beta variant) in South Africa, and P.1 (or gamma variant) in Brazil have been described based on mutations at various genes [87–89]. At the time of writing, the B.1.617 lineage, first discovered in India [90–94], divided into the three sublineages B.1.617.1 (or kappa variant), B.1.617.2 (or delta variant), and B.1.617.3, which have fallen into the international spotlight (particularly the B.1.617.2 sublineage), has increased potential to evade antibody and overall immune action, posing an increased potential for infecting individuals already vaccinated against the initial SARS-CoV-2 strain [95]. According to the Centers for Disease Control and Prevention (CDC), in the two-week period between August 8, 2021, and August 14, 2021, the B.1.617.2 strain accounted for approximately 86.1% of reported COVID-19 cases in the United States, elevated from 2.4% of cases in the period between May 9, 2021, and May 15, 2021 [96].

The B.1.1.7, B.1.351, and P.1 variants have been characterized by the presence of a N501Y mutation in the S protein, as well as an additional E484K mutation observed in B.1.351 and P.1 [87–89]. These mutations have resulted in an increased rate of viral transmission among these variants, with the B.1.1.7 strain having a reported increase of 35-45% in prevalence [89,97–98]. The B.1.617.2 variant has been particularly characterized by several mutations in the S protein [95].

The B.1.1.7 and B.1.351 variants have also been demonstrated to bind to ACE2 with somewhere between a twofold to fivefold increase in binding affinity than the initial SARS-CoV-2 strain with concerns being raised regarding the ability of neutralizing antibodies to bind to these new variants [99–100]. The B.1.617.2 variant contains mutations in the receptor binding domain (RBD) which may facilitate viral binding through the shifting of a nonpolar amino acid to a positively charged residue and from a polar to a positively charged amino acid, respectively [95]. Studies have suggested that these L452R and E484Q mutations may increase interaction between the S protein and ACE2 and, as such, increase infectivity of the virus [101–103].

However, no data have been published to date regarding these variants' affinities for the NRP1, despite evidence of it being a co-receptor for SARS-CoV-2 [104]. Cleavage of the Spike protein by furin results in generation of an S1 domain with a polybasic Pro-Arg-Arg-Ala-Arg carboxyl-terminal sequence (681-PRRAR-685). This polybasic peptide conforms to the C-end rule (CendR) motif, which can bind to NRP1. Sequence comparison of the B.1.1.7 variant to the original lineage A strain revealed that the Spike CendR peptide sequence 681-PRRAR-685 involved in NRP1 binding had a proline to histidine change at position 681 (P681H) (Fig. 2A). When comparing the B.1.617.2 variant, a proline to arginine change was observed at the same position (P681R) (Fig. 2A).

Excited by this finding, we evaluated the effect of the P681H point mutation using protein structure modeling. Protein Data Bank (PDB) structure with accession code 7JJC was used as a basis to show the interaction between the NRP-1-b1 domain and the Lineage A SARS-CoV-2 CendR peptide (Fig. 2B). The impact of this mutation can be seen in Figs. 2C-2E, where the interactions of the variant and wild-type CendR peptides with NRP1 can be observed. We found that this mutation resulted in a shortening in the distance between this histidine residue and the interacting surface residues of NRP1 by 2 Å, from 16 Å between the proline and NRP1 in the original lineage A strain to 14 Å between histidine and NRP1 in lineage B.1.1.7 (Table 1), suggesting a tight interaction of the B.1.1.7 Spike protein for NRP1, which may result in increased penetration of the virus into the CNS. We also assessed this phenomenon in the B.1.617.2 (delta) Spike, where arginine conversely increased the distance from NRP1 at about 17 Å, a 1 Å gain in distance from the original lineage A parental SARS-CoV-2 strain (Table 1). Further detailed epidemiological and protein–protein interaction studies are required to address this hypothesis.

Several studies examining the Spike P681R mutation present in the B.1.617.2 delta variant have reported an increased susceptibility of SARS-CoV-2 to furin cleavage and increased fusogenicity [90,105–108]. These gain-of-function traits may facilitate increased viral

Table 1. Distances between amino acid residue 681 on SARS-CoV-2 spike protein and NRP1.

	NRP1 Residue	PRO-681	HIS-681	ARG-681
1	GLY-318	15.5	15.3	19.2
2	TYR-297	10.3	8.7	13
3	GLU-319	14.5	14.4	17.8
4	LYS-351	15.9	12.4	15.5
5	THR-349	14.3	11.5	14
6	GLU-348	14.2	12.3	14.2
7	TRP-301	15.4	14.3	17
8	THR-316	17.2	15.9	19.7
9	ILE-415	21.4	19.7	24
10	THR-353	16.1	13.3	17.1
11	SER-346	17.9	15.6	18.2
12	ASP-320	17.1	15	19.9
13	GLY-414	19.9	17.4	21.6
Average		16.13077	14.29231	17.78462

entry of the virus into neurons and astrocytes via NRP1.

Sequence comparison shows that circulating SARS-CoV-2 strains have a four amino acid insertion in the S protein PRRA cleavage site relative to the most closely related Bat-2019 strain isolated from *Rhinolophus sinicus* (accession number QWN56232). The molecular and evolutionary mechanisms underlying this observation are yet to be elucidated. However, the potential mechanism for this may be the existence of a stretch of nucleotides with substantial similarity upstream and downstream to the twelve inserted nucleotides that encode the PRRA cleavage site (Fig. 2A), which may have enabled the replication–transcription complex to convert from one RNA genome template to another—resulting in the insertion of the twelve nucleotides coding for the four polybasic amino acids containing the furin cleavage site into the SARS-CoV-2 genome [109]. Further investigations are needed to define the functional significance of the mutations in this basic cleavage site and SARS-CoV-2 neurovirulence.

Pandemic potential RNA viruses

We identified Zika virus (ZIKV) and Nipah virus (NiV) as two pandemic-potential viruses. Given the history surrounding these viruses, we define pandemic-potential viruses as viruses with the ability to adapt and evolve to cause widespread infection globally.

Zika Virus (ZIKV)

Zika virus (ZIKV) is a positive-sense, single-stranded RNA virus that is a member of the family *Flaviviridae* [110–111]. The ZIKV genome is translated into one single polyprotein 3423 amino acids in length [112]. The genome encodes a capsid protein, membrane protein, and an envelope protein—generally reminiscent of coronavirus structures—along with seven nonstructural proteins [112]. However, unlike coronaviruses, ZIKV does not have pronounced spike proteins. Instead, surface glycoproteins encoded by a precursor premembrane gene undergo complex conformational changes that fully expose the envelope protein, which allows the virus to actively bind cells via the AXL, DC-SIGN, Tyro3, and TIM-1 proteins [112–114].

In adults, infection with ZIKV has been attributed to incidence of neurological complications, such as Guillan–Barré syndrome and a 'Zika-like syndrome', associated with incidence of a low-grade fever, myalgia, rash, and conjunctivitis [115–116]. Perhaps the most notable complication resulting from ZIKV infection is the incidence of microcephaly in babies born from infected mothers. Evidence of ZIKV causing CNS malformations in neonates, such as microcephaly, fetal cerebral malformations, polymalformative syndromes, brainstem dysfunction, or the inability to swallow, was found upon investigation of suspected cases in French Polynesia and Brazil [117].

ZIKV is thought to infect endothelial cells in the BBB, resulting in penetration of the BBB without significant increase in BBB permeability [118–122]. Particularly, ZIKV has been shown to infect primary human brain microvascular endothelial cells (HBMECs), allowing for passage through the BBB without directly inducing damage (Fig. 1C) [120–121]. However, experiments conducted in 3D cultures and *in vivo* models have shown that inflammatory response from the organism, particularly the release of TNF-α or IFN response, or activation of the Hippo signaling pathway can induce disruption of the BBB during the course of ZIKV infection [119–120,123–124].

Nipah Virus (NiV)

Nipah virus (NiV) is a negative-sense, single-stranded RNA virus of the family *Paramyxoviridae* in the genus *Henipavirus* [125]. The NiV genome encodes of six structural proteins: nucleoprotein (N), phosphoprotein (P), matrix protein (M), fusion protein (F), attachment glycoprotein (G), and the large protein or RNA polymerase protein (L) [126]. NiV is classified as a BSL-4 pathogen due to its high pathogenicity and lack of effective treatments or vaccines [127].

NiV has been associated with systemic infection in the heart, kidney, lungs, and brain [128]. This is due to the viral entry receptors ephrin-B2 and ephrin-B3 expressed on a variety of cell types found in these

organs [129]. Endothelial cells are a major target by NiV though the cause of viral entry to the CNS is currently unknown [130]. The most notable complications attributed to NiV include fever, headache, and drowsiness, followed by disorientation and mental confusion [130]. During the early stages of the infections, respiratory issues have been observed [130].

NiV can be detected in bronchiolar epithelial cells in most human cases [131]. There is little literature available regarding NiV entry to the CNS and its proliferation throughout the host, though most studies seem to indicate that specific leukocyte populations allow infected cells to cross the BBB, facilitating NiV entry into the CNS [128]. NiV was found to infect neurons and microglial cells that express CD68 in nonhuman primates [132]. As such, it has been hypothesized that the BBB can be breached by direct NiV virus infection of lymphocytes and monocytes, utilizing the Trojan horse mechanism of BBB entry [128]. The direct infection of the endothelium of the BBB by NiV has been substantiated by a study by Wong *et al.* [133].

Human Immunodeficiency Virus-1 (HIV-1)

HIV-1 (family *Retroviridae*) is composed of two copies of noncovalently linked, unspliced, positive-sense, single-stranded RNA of about 9700 nucleotides in length, enclosed by a conical capsid composed of the viral protein p24 [134–135]. The HIV-1 genome encodes a small number of viral proteins, which facilitate infection of host cells [136]. The HIV-1 genome encodes for polyproteins which are cleaved and processed to produce several structural proteins: Gag, Pol, and gp160 polyproteins—as well as proteins necessary for RNA synthesis and transport, which can be both global and specialized to certain tissue types [137–139]. The HIV-1 genome consists of a series of stem-loop structures connected by small linkers, with the V3 loop responsible for viral genome transcription and replication inside host immune cells [140–141]. Given the ability of HIV-1 to generate a provirus containing a DNA genome upon infection of a human cell, we consider HIV-1 to share characteristics with DNA and RNA viruses [142]. This virus is particularly useful to study due to the comprehensive characterization of its ability to invade the BBB over decades of research.

Infection with HIV-1 has been closely associated with HIV encephalitis and neurobehavioral impairment [143]. HIV-1 infection has also been attributed to neurocognitive dysfunction including decreased attention and concentration, information processing, memory, learning and psychomotor speed, motor slowing, incoordination, and tremors [143]. A consequence of this chronic disease is viral proteins causing inflammatory response within the CNS [144]. Evidence of HIV-1 causing CNS malformations can manifest as structural and functional damage within the CNS and BBB [145]. HIV-1 has been shown to infect astrocytes, though this remains a slightly controversial perspective, as well as microglial cells, which serve as reservoirs for the virus in the CNS [146].

HIV infection results in alterations in the BBB integrity, tight junction protein expression, and also invades the CNS via the Trojan horse mechanism [147–149]. Early studies on the effects of HIV-1 within the brain revealed elevations in markers for vascular permeability and morphologic abnormalities consistent with dysfunction of the BBB [137–139]. HIV-1 infection increases monocyte transmigration across cultured endothelial cells and signaling in human brain endothelial cells [150–152]. Many of these alterations can, either directly or indirectly, cause damage to the BBB and create increased leakiness of the barrier, allowing for further entry of infected cells into the CNS [145].

Potential of neuroimaging in informing neurological symptoms

Neuroimaging of patients with ZIKV and NiV shows signatures similar to those of encephalitis white matter lesions visible as hyperintensities on T2-weighted magnetic resonance images (MRI) in addition to the spinal cord and the retina in case of NiV [153–155]. Compared with ZIKV and NiV, the neurobehavioral characteristics of HIV-1 have been extensively studied from the point of view of structural brain morphometry, functional brain imaging, and diffusion imaging as the symptoms may range from dementia, neuroinflammation, and general neuropathy [155–158].

On the other hand, neuroimaging findings on the effects of SARS-CoV-2 have been sparse and largely comprise observational case studies with limited experimental control. Furthermore, the imaging modalities are typically restricted to MRI in a clinical setting and thus may not include advanced imaging protocols. Here, we briefly summarize salient neuroimaging findings and suggest future avenues for the role of neuroimaging in diagnosing neurobehavioral sequelae of COVID-19. Recent reports indicate heterogeneity of symptom dimensions including neuropsychological dysfunction, neuropathogenesis, cerebral microhemorrhages, encephalopathies including leukoencephalopathy, cerebrovascular disease, as well as acute or subacute infarcts [159–165].

Clarifying these non-specific changes, as well as unraveling the broad-spectrum neuroimaging associations

with downstream disease symptomology, is a challenging task. In addition to existing clinical imaging modalities, new cutting-edge research protocols will need to be applied to separate subtypes of COVID-19-related etiologies. Structural MRI including susceptibility weighted imaging (SWI) can help identify lesions in subcortical and deep white matter structures [162]. Going further, gray matter volumes from high-resolution structural MRI in the cortex can be studied at the regional level [160] using brain morphometry approaches such as deformation-based morphometry including voxel or volumetric tensor-based morphometry [165]. Global observed signal hyperintensities on fluid-attenuated inversion recovery (FLAIR) [166] can be used to identify deep cortical gray matter regions, such as the medial temporal lobe which can be further segmented into the hippocampus and the amygdala. Then, three-dimensional shape analysis can further map precisely localized changes involving the gray matter subcortical structures [167]. Cortical thickness analysis can also reveal abnormalities in gray matter sulci and gyri in regions such as the cingulate, frontal and prefrontal cortex, and olfactory cortex, which have been previously implicated in COVID-19 [160]. High-resolution diffusion-weighted imaging (DWI) can be performed to detect microstructural damage in the CNS using regional white matter volumes or by using diffusion parameters such as fractional anisotropy (FA), axial (AD), mean (MD), and radial (RD) diffusivities. Diffusion indices such as FA, AD, MD, RD matter intensities can be further combined with cortical gray matter measures to yield superficial white matter, a new measure that has been studied in the context of anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis, recently implicated in a case report of an adult COVID-19 patient, but also in a toddler [168–170]. It should be also noted that the severity of encephalopathy was also correlated with a higher probability of death [164].

Fig. 3 shows T2-weighted MR images for a healthy control of age 44 years and subjects who were diagnosed with COVID-19 of ages 30, and 60 years, and who also exhibited neuropsychiatric symptoms. The 30-year-old subject showed decreased mood, moderate anxiety, chronic and exertional fatigue, and brain fog with a Montreal Cognitive Assessment (MoCA) score of 15. The 60-year-old subject additionally showed severe symptoms of depression, insomnia, and a global cognitive decline with performance at dementia level and a MoCA of 15. All three subjects underwent MR scanning using a 32-channel head coil on a 3T Siemens MAGNETOM PRISMA (Siemens, Munich, Germany) scanner at the UCLA Ahmanson Lovelace Brain Mapping Center. The subject data acquisition was approved by the institutional review board (IRB) at UCLA. Specifically, the parameters of the T2-weighted image comprised a repetition time (TR = 3200 ms), echo time (TE = 564 ms), field of view = $256 \times 256\,mm^2$, and an isotropic voxel resolution of $0.8 \times 0.8 \times 0.8\,mm^3$. Based on visual inspection of the scans, compared with the healthy control subject, we observed white matter hyperintensities of varying sparsity in the corona radiata adjacent to the right lateral ventricles for both the COVID-19 subjects. The 60-year-old subject having severe symptoms showed a large number of white matter hyperintensities in the cingulum, the thalamic radiation, as well as the corpus callosum. These data suggest the appropriateness and applicability of including image-based approaches to monitor integrity of the BBB in patients with COVID-19.

Finally, the psychiatric consequences of long COVID-19, including depression, bipolar disorder, obsessive compulsive disorder, as well as psychosis, will need a multifaceted neuroimaging battery of protocols [171]. This will involve sophisticated brain connectivity analyses that will help to map out specific circuits implicated in neuropsychiatric disorders [172–174].

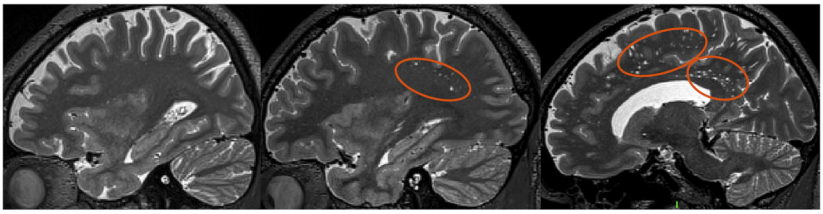

Fig. 3. Magnetic Resonance (MR) Neuroimaging of Control and COVID-19 Patients. Sagittal views of T2-weighted MR images showing white matter hyperintensities in a healthy control (44 years) and subjects with COVID-19 (30 and 60 years) who also showed neuropsychiatric symptoms including anxiety, and brain fog. The 60-year-old subject additionally exhibited severe long haul COVID-19 symptoms including depression and insomnia and performed at the level of dementia.

Table 2. A Summary of the information presented.

Virus Name	Family	Genome sense and size	Intermediate host	Major organ(s) affected	Cell type(s) infected	Cellular receptor(s)	Possible mechanism of neurological infection
SARS-CoV	*Coronaviridae*	Positive; 30kb	Masked palm civet	Respiratory tract	Epithelial cells, macrophages, T lymphocytes, Dendritic cells	ACE2	Trojan horse mechanism
MERS-CoV	*Coronaviridae*	Positive; 30 kb	Dromedary camel	Respiratory tract	Epithelial cells, T lymphocytes, Monocytes, Macrophages, Dendritic cells	DPP4	None known
SARS-CoV-2	*Coronaviridae*	Positive; 30 kb	Unknown	Respiratory tract, heart, brain, liver, kidney, gastrointestinal tract	Epithelial cells, cardiomyocytes	ACE2, NRP1, Lectins	Potentially Trojan horse mechanism and/or infection of brain endothelial cells
HIV-1	*Retroviridae*	Positive; 9.2-9.6 kb	Chimpanzee	Immune cells	CD4+ T lymphocytes, macrophages, dendritic cells	CD4	Trojan horse mechanism
NiV	*Paramyxoviridae*	Negative; 18 kb	Fruit bats, flying foxes, and domestic pigs	Heart, kidney, lungs, brain	Epithelial cells, neurons, mononuclear leukocytes	Ephrin-B2, Ephrin-B3	Trojan horse mechanism
ZIKV	*Flaviviridae*	Positive; 10.8 kb	*Aedes* mosquitoes	Brain	Glial cells, astrocytes	AXL, DC-SIGN, Tyro3, TIM-1	Infection of brain endothelial cells

Conclusions

We have discussed the potential mechanisms by which various RNA viruses are able to breach the BBB and summarized recent evidence of mechanisms by which SARS-CoV-2 is able to invade the CNS. Of note, HIV, NiV, and SARS have conclusively been shown to take advantage of a Trojan horse mechanism by which infected leukocytes ferry the virus across the BBB. Conversely, ZIKV infects brain endothelial cells, which in turn shed the virus into the brain.

With regard to SARS-CoV-2, current evidence supports the hypothesis that the virus may able to infect brain endothelial cells and pericytes to gain access to CNS. From this, we conclude that SARS-CoV-2 could exploit two mechanisms to invade the CNS, namely the so-called Trojan horse mechanism as well as infected brain endothelial cells. This would explain why one of the hallmarks of early SARS-CoV-2 infection is anosmia and ageusia, which manifest as a result of viral entry into the CNS and PNS. Table 2 recapitulates the key features of each virus discussed herein, presenting genomic information, disease information, and epidemiological data [44,110,111,175–183]. Based on these considerations, the examination of SARS-CoV-2 infection in animal models focusing on immune cell populations, as well as brain endothelial cell populations using functional neuroimaging technologies appear to be promising areas of future research.

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