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## Review

# SARS-CoV-2 and the central nervous system: Emerging insights into hemorrhage-associated neurological consequences and therapeutic considerations

Joy Mitra<sup>a,\*</sup>, Manohar Kodavati<sup>a</sup>, Vincent E. Provasek<sup>a,g</sup>, K.S. Rao<sup>b</sup>, Sankar Mitra<sup>a</sup>, Dale J. Hamilton<sup>c,d</sup>, Philip J. Horner<sup>a,d</sup>, Farhaan S. Vahidy<sup>e</sup>, Gavin W. Britz<sup>a,d</sup>, Thomas A. Kent<sup>f</sup>, Muralidhar L. Hegde<sup>a,d,\*\*</sup>

<sup>a</sup> Division of DNA Repair Research, Center for Neuroregeneration, Department of Neurosurgery, Houston Methodist Research Institute, Houston, TX 77030, USA

<sup>b</sup> Department of Biotechnology, Koneru Lakshmaiah Education Foundation Deemed to be University, Green Fields, Vaddeswaram, Andhra Pradesh 522502, India

<sup>c</sup> Center for Bioenergetics, Houston Methodist Research Institute, Houston, TX 77030, USA

<sup>d</sup> Weill Cornell Medical College, New York, USA

<sup>e</sup> Center for Outcomes Research, Houston Methodist Research Institute, Houston, TX 77030, USA

<sup>f</sup> Center for Genomics and Precision Medicine, Department of Translational Medical Sciences, Institute of Biosciences and Technology, College of Medicine, Texas A&M Health Science Center, Houston, TX, USA

<sup>g</sup> College of Medicine, Texas A&M University, College Station, TX, USA

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## ABSTRACT

Coronavirus disease 2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) continues to impact our lives by causing widespread illness and death and poses a threat due to the possibility of emerging strains. SARS-CoV-2 targets angiotensin-converting enzyme 2 (ACE2) before entering vital organs of the body, including the brain. Studies have shown systemic inflammation, cellular senescence, and viral toxicity-mediated multi-organ failure occur during infectious periods. However, prognostic investigations suggest that both acute and long-term neurological complications, including predisposition to irreversible neurodegenerative diseases, can be a serious concern for COVID-19 survivors, especially the elderly population. As emerging studies reveal sites of SARS-CoV-2 infection in different parts of the brain, potential causes of chronic lesions including cerebral and deep-brain microbleeds and the likelihood of developing stroke-like pathologies increases, with critical long-term consequences, particularly for individuals with neuropathological and/or age-associated comorbid conditions. Our recent studies linking the blood degradation products to genome instability, leading to cellular senescence and ferroptosis, raise the possibility of similar neurovascular events as a result of SARS-CoV-2 infection. In this review, we discuss the neuropathological consequences of SARS-CoV-2 infection in COVID survivors, focusing on possible hemorrhagic damage in brain cells, its association to aging, and the future directions in developing mechanism-guided therapeutic strategies.

## 1. Introduction

Coronavirus disease 2019 (COVID-19), caused by the zoonotic SARS-CoV-2 infection, has passed a death toll of 5.49 million worldwide, with over 307 million total cases, according to the most recent update on COVID-19 (<https://ourworldindata.org/coronavirus-data>) COVID-19 has profoundly affected people of all ages, sexes, geographical

locations, ethnicities, and religions. Based on the latest statistics of COVID-19 victims, the elderly and individuals with underlying chronic comorbid conditions, such as diabetes, hypertension, respiratory/cardiovascular disorders, and kidney injuries, or following treatment with immunosuppressant medications, are at the highest risk for COVID-19-associated severe complications (Bailey et al., 2021; de Almeida-Pititto et al., 2020; Salazar, 2021; Flythe et al., 2021; Vahidy et al., 2021). As

\* Corresponding author.

\*\* Correspondence to: Division of DNA Repair Research, Center for Neuroregeneration, Department of Neurosurgery, The Houston Methodist Research Institute, Houston, TX 77030, USA.

E-mail addresses: [jmitra@houstonmethodist.org](mailto:jmitra@houstonmethodist.org) (J. Mitra), [mlhegde@houstonmethodist.org](mailto:mlhegde@houstonmethodist.org) (M.L. Hegde).

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we learn more about continuously evolving SARS-CoV-2 viral variants, and their infection routes and long-term implications on human health, it is becoming obvious that viral infection in different brain regions, including deeper neuroanatomical sites, precedes the clinical manifestations of other non-neurological symptoms, such as respiratory distress, cardiac arrest, gastrointestinal discomforts, and kidney injury (Taquet et al., 2021a,b; Prescott, 2021; Nalbandian et al., 2021). Loss of smell and taste in COVID-19 has been linked to neuronal damage in the pre-frontal cortex and olfactory bulb areas, recovery from which takes several months after the initial COVID-19 infection (de Melo et al., 2021; Renaud et al., 2021). Emerging studies have highlighted unique patterns of brain injury involving microhemorrhages and multi-infarcts in the brains of both COVID-19 victims and survivors, using neuroimaging techniques (Fitsiori et al., 2020; Dixon et al., 2020). Notably, the pathological hallmarks identified after SARS-CoV-2 infection overlap with those observed after several fatal neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), and stroke (Yu et al., 2021; Sulzer et al., 2020; Modin et al., 2020). Chronic cardiovascular, neuropathological, and neuropsychiatric disturbances have been observed in the majority of COVID-19 survivors, especially those with comorbid diseases (Han et al., 2021; Nakamura et al., 2021). In this review, we critically discuss the implications of SARS-CoV-2-induced neuropathological events with a focus on the potential mechanistic pathways involved. Finally, based on our recent findings in hemorrhagic stroke pathology, we propose a possible therapeutic strategy to ameliorate chronic neurodegenerative and neuropsychiatric symptoms.

### 1.1. The first known encounter with coronavirus

The first documented appearance of coronavirus occurred in Germany in 1912, when veterinarians were baffled with the symptoms of a heavily swollen belly with febrile temperature in cats. Although medical practitioners were not aware of coronavirus at that time, their observed symptoms were very similar to those of today's coronavirus infections in humans, bronchitis in chickens, and intestinal disease in pigs that kill all newborn piglets. In the late 1960s, researchers first isolated the viral strain from adult patients, who presented with common cold symptoms. Tyrrell and Bynoe (1966) then showed that the isolated viral strain, named B814, could be serially passaged and cause infection when inoculated intranasally in human volunteers (Tyrrell et al., 1966). At about the same time, Hamre and Procknow isolated another strain, named 229E, from the respiratory tracts of medical students with cold symptoms (Hamre and Procknow, 1966). Both strains were sensitive to ether, and required a lipid coat for their virulence, furthermore, these viruses were not related to the known strains of myxo- or paramyxoviruses. While the actual identification of these viral strains was not possible then, McIntosh et al. (1967a,b) reported the discovery of a very similar strain recovered from tracheal organ cultures, which they named "OC", an acronym of organ culture (McIntosh et al., 1967a,b). Almeida and Tyrrell (1967) subsequently showed that electron microscopic structures of B814 and chicken bronchitis virus were very similar (Almeida et al., 1967). Subsequently, several other animal viruses, including infectious bronchitis virus, swine transmissible gastroenteritis virus, swine enteric diarrhea virus, mouse hepatitis virus, and the newly identified swine acute diarrhea syndrome coronavirus, were shown to have similar morphologies (McIntosh et al., 1967a,b; Witte et al., 1968; Lin et al., 2016; Zhou et al., 2018), and this new group was named "coronaviruses", based on the feature that these virus particles were covered with widely spaced, club-shaped surface projections resembling a crown-like structure (Tyrrell et al., 1975), which were further sub-classified. Alpha and beta coronaviruses usually infect mammals, while gamma and delta types infect birds. However, the viruses in some instances can cross-infect mammals (Woo et al., 2012).

### 1.2. The pathogenicity of positive-sense RNA viruses

The majority of the RNA virus sub-types, which infect humans, are zoonotic in nature, indicating that they can cross-infect between vertebrates and humans. Even many of these RNA viruses, not considered zoonotic earlier, might have undergone evolutionary adaptations to be the zoonotic variant (ME et al., 2013). Being one of the fatal zoonotic viruses, the coronavirus exhibits a relatively larger (80–150 nm in diameter) virion size than most other RNA viruses, having approximately 30 kb in the genome (> three times larger than that of HIV and hepatitis C virus and twice that of influenza virus). Importantly, unlike most other RNA viruses, coronaviruses encode RNA-proofreading enzymes, which may explain the lack of activity of the most common antiviral nucleoside analogs (like ribavirin) after coronavirus infection (Eyer et al., 2018; Tong et al., 2020). Additionally, the proofreading activity enables the virus to survive in extreme environments by preventing self-weakening or inactivating mutations (Robson et al., 2020). The critical factor behind the rapid evolution of this deadly virus is its dynamic recombination and swapping large segments of its RNA genome. This mechanism acts as a "double-edged sword" because it produces more contagious novel variants by swapping genomic segments between two distantly related viral species when they are in the same host cell and enables the new variant to avoid the immune defense generated against the original infection. It is worth mentioning in this context, that positive-sense RNA viruses recombine at a much faster rate than negative-sense RNA viruses (Simon-Loriere and Holmes, 2011). Furthermore, efficient genome recombination enables coronaviruses to expand the range of species for crossover infectivity (Oude Munnink et al., 2021; Calvet et al., 2021).

### 1.3. The evolution of SARS-CoV-2

Coronaviruses likely appeared in the biosphere some 10,000–300 million years ago, leading to the generation of dozens of strains through evolution. Some of these strains are highly pathogenic (Graham et al., 2013). Among the seven strains that infect humans, four cause mild upper respiratory tract and common cold symptoms, while the other three strains, namely, severe acute respiratory syndrome coronavirus (SARS-CoV), middle east respiratory syndrome coronavirus (MERS-CoV), and the emerging SARS-CoV-2 cause deadly infections and high mortality. Regarding the origins of coronavirus, bats and rodents have played critical roles as natural reservoirs for viral evolution and spillover to humans. Notably, strains 229E and NL63 associated with common colds, as well as MERS, SARS, and SARS-CoV-2, are hosted by bats, while strains OC43 and HKU1 (associated with mild cold symptoms) are of rodent origin (Su et al., 2016; Forni et al., 2017). It appears interspecies transfer of coronavirus from the bats to humans does not occur directly, rather requires an intermediary vector that transfers the virus to humans. The civet cat, sold in the live animal market of Guangdong Province in China could be such an intermediate vector for SARS-CoV infection in humans (Li et al., 2005; Hu et al., 2017). SARS-related coronaviruses (SARSr-CoV), discovered in the remote bat cave in Yunnan Province in China, were found to have 96% genetic similarity with the human SARS-CoV. These strains have high similarity between the receptor-binding domain (RBD) and hypervariable N-terminal domain (NTD) of the S1 gene (which encodes viral spike protein subunit 1), as well as in the ORF3b and ORF8 (a and b) regions (Hu et al., 2017).

Why outbreaks of coronavirus involving bats as the primary host are so lethal to humans, and yet the bat population remains unaffected is an open question. Studies have shown that bats are known to be immunologically resistant to deadly viruses such as CoV, which are highly virulent for non-volant terrestrial mammals (Schountz et al., 2017). Bats have evolutionarily developed a unique mechanism to control their inflammation-induced DNA damage. Transcriptomics analyses in bat cell lines have shown constitutive expressions of interferon (IFN) alpha-inducing IFN-targeted genes involving an antiviral defense

mechanism (Zhou et al., 2016). Moreover, other studies have shown that dampened NLRP3 and STING-mediated inflammasome activations are keys to their longevity and natural viral reservoir status (Ahn et al., 2019; Xie et al., 2018; Pavlovich et al., 2018). Brook et al. (2020) reported that when invading viruses face constitutive immune activation in bat cells, they become more virulent, while infecting their secondary hosts who have completely different immune systems than their own system (Brook et al., 2020). It is important to note that the receptor-binding domain (RBD) of the S1 protein of SARS-CoV-2 is significantly different in terms of structural features compared to that of its bat counterpart, RaTG13 (Zhang et al., 2020).

As previously mentioned, identification of the intermediate host is critical for controlling viral spillover from bats to humans. By metagenomic analysis of infected pangolin lung samples, Liu et al. (2019) identified the Malayan pangolin as the intermediate host for CoV and Sendai virus (Liu et al., 2019). Subsequently, Zhang et al. found that pangolin CoV had 91.02% and 90.55% genomic similarities with SARS-CoV-2 (COVID-19) and bat CoV RaTG13, respectively (Zhang et al., 2020). Moreover, pangolin CoV and COVID-19 strains have five identical key amino acids in the S1 protein, which binds to the human angiotensin-converting enzyme 2 (ACE2) receptor for viral entry. The most concerning observation were that, unlike pangolin CoV and bat CoV, SARS-CoV-2 retained the S1/S2 furin cleavage site (Zhang et al., 2020). Because the furin enzyme is abundant in the human respiratory tract and other parts of the body, SARS-CoV-2 uses it to jump across species (Andersen et al., 2020). Furin is also required for cleavage-mediated activation of several important proteins in the brain, e.g., brain-derived neurotrophic factor (BDNF) and neurotrophin 3 (NT3), which are essential for neuronal maturation and synaptic plasticity (Seidah et al., 1996; Koshimizu et al., 2009). These findings may suggest the underlying mechanism of SARS-CoV-2 infection in human brain cells. Recent sequence data indicate that the most recent ancestor of SARS-CoV-2 emerged between late November 2019 and early December 2019 (<http://virological.org/t/356>). Therefore, there could be a long unrecognized transmission period when the virus might have transmitted from zoonotic animals to humans and acquired the poly-basic furin cleavage site at S1-S2 junctions (Andersen et al., 2020). This hypothesis is partially supported by the observation that the lineage of the A SARS-CoV HKU1 strain has furin recognition sites and predicted O-linked glycan sites (Chan et al., 2008).

Furthermore, genomic and phylogenetic analyses indicated that the SARS-CoV-2's RBD motif for binding the ACE2 receptor did not originate from RNA recombination. Rather, it may be an ancestral trait shared by bat CoV (Boni et al., 2020). They found that the SARS-CoV-2 lineage might have been segregated from SARS-CoV many centuries ago and from its bat counterpart 40–70 years ago. The divergence dates between SARS-CoV-2 and bat sarbecovirus (RaTG13) were calculated as 1948 (95% highest posterior density (HPD): 1879–1999), 1969 (95% HPD: 1930–2000), and 1982 (95% HPD: 1948–2009). This suggests that the lineage responsible for the COVID-19 pandemic has been present in the species for decades (Boni et al., 2020).

## 2. SARS-CoV-2 infection: ACE2-dependent and -independent pathways

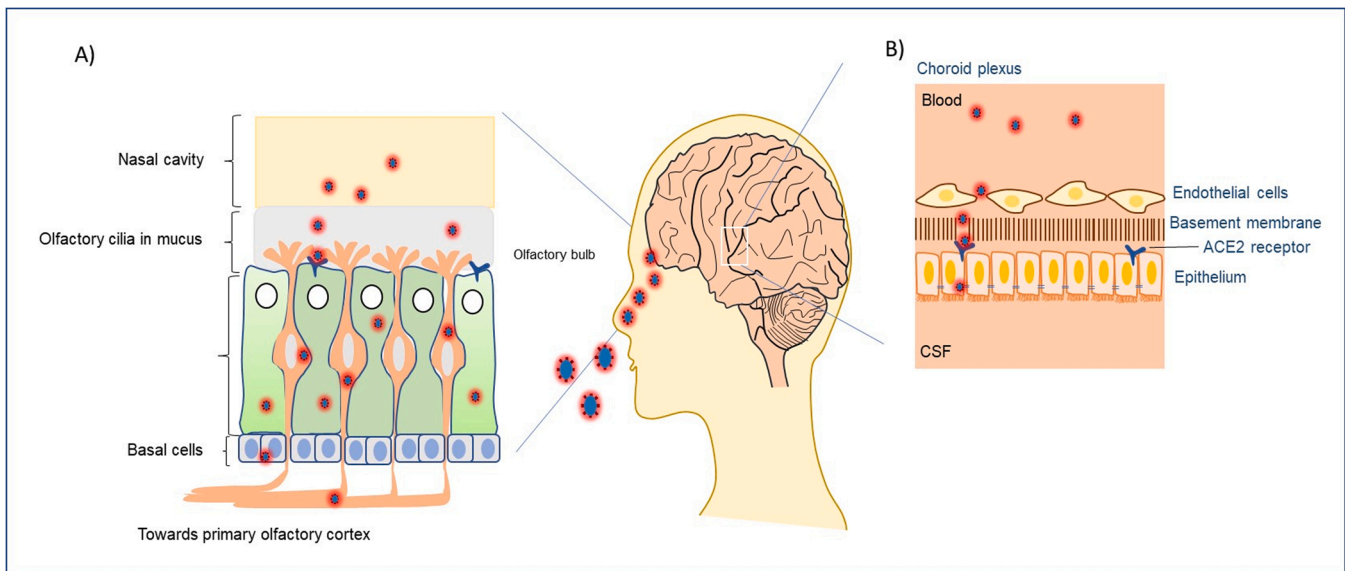
ACE1 and ACE2 are members of the Renin-Angiotensin-Aldosterone System, which regulates the blood pressure and functionality of the body's vital organs. ACE1 converts angiotensin I to angiotensin II, which regulates aldosterone secretion and vasoconstriction-mediated increases in blood pressure. ACE2 confers its beneficial effects by degrading angiotensin I and II to angiotensin 1–9 and angiotensin 1–7, respectively, that are known to counterbalance the deleterious effects of angiotensin II in inducing inflammation (Versmissen et al., 2020). In addition, lower ACE2 expression levels are associated with worse pulmonary and cardiovascular outcomes (Bellomo et al., 2020; Imai et al., 2005) and myocardial inflammation (Oudit et al., 2009). Furthermore,

low ACE2 expression has been correlated with a predisposition toward hypertensive and diabetic disorders, kidney injury, and cardiovascular complications (Lu et al., 2012; Patel et al., 2012; Li et al., 2020a,b). The binding of the SARS-CoV-2 spike protein to ACE2 receptors in the respiratory tract leads to ACE1/ACE2 imbalance, acute increases in blood pressure, acute hypoxia, endothelial dysfunction, and lung injury (Bank et al., 2021).

Furthermore, ACE2 expression is ubiquitous in various cell types related to the respiratory, cardiovascular, urogenital systems, and also in the gastrointestinal tract, central nervous system (CNS), and liver (Hamming et al., 2004). ACE2 is also expressed by circulating leukocytes (Trojanowicz et al., 2017). ACE2 appears to play a central role in the cellular response to various endogenous and exogenous stressors. Intestinal cells express the highest level of ACE2 (Hamming et al., 2004). ACE2 depletion has been linked to a disturbed gut microbiome due to impaired amino acid transport, reduced level of tryptophan in the blood, and activation of intestinal inflammation involving mammalian targets of rapamycin signaling (Hashimoto et al., 2011, 2012; Singer and Camargo, 2011). ACE2 was implicated in the regulation of BDNF expression in cognitive processes, and ACE2 overexpression has been shown to protect AD mice from cognitive decline and amyloid pathology (Evans et al., 2020). Furthermore, ACE2 regulates the level of corticotrophin-releasing hormone at the hypothalamus and serotonin levels during neurogenesis (Klempin et al., 2018; Wang et al., 2018). It has been reported in several studies that the majority of COVID-19 infected patients (~40%) develop neurological symptoms, severe hypoxia, and neuro-inflammation (Mao et al., 2020; Muccioli et al., 2020). Following these reports, studies have characterized how SARS-CoV-2 crosses the blood-brain barrier (BBB) to reach different brain regions (Reynolds and Mahajan, 2021). This study also reported that the main components of the BBB, astrocytes, and brain microvascular endothelial cells, expressed ACE2 receptors that allowed SARS-CoV-2 to bind and alter tight junctions, leading to increased permeability of the BBB and neuro-inflammation.

In this context, it is important to note that nasal epithelial cells, the first contact point of SARS-CoV-2 infection (Fig. 1A), express variable levels of ACE2 receptors depending on the age group. Younger children have consistently lower infection percentages than older children and adults (Castagnoli et al., 2020; Anonymous, 2020). Interestingly, a study of ACE2 levels in children has reported that young children of ages < 10 years had much lower expression of ACE2, when compared to their older counterparts (10–17 years of age), young adults (18–24 years of age), or adults ( $\geq 25$  years of age) (Patel and Verma, 2020). Further case studies in pediatric COVID patients with clear subacute neuropsychiatric symptoms have exhibited the presence of autoantibodies targeting transcription factor 4 (TCF4), antineural as well as anti-SARS-CoV-2 antibodies in their cerebrospinal fluid (CSF) which could be a critical indicator for the immunotherapeutic treatment outcomes (Bartley et al., 2021).

In addition to ACE2, there are several other critical factors, particularly surface serine proteases, that determine viral entry into host cells via membrane fusion between the virion and host cell membranes. This process has been reported for several pandemic viral outbreaks, such as the highly pathogenic avian influenza virus (1918 Spanish flu virus), Sendai virus, and SARS-CoV (Kido et al., 1999, 1992; Kim et al., 2001; Murakami et al., 2001; Okumura et al., 2010). Besides these proteases, transmembrane serine protease 2 (TMPRSS2) and human airway trypsin-like protease (HAT) also serve as critical modulators of viral entry by activating viral surface glycoproteins while binding to ACE2 receptors in human lung airway epithelial cells (Böttcher et al., 2006). Although TMPRSS2 is required following binding of the viral spike protein to the ACE2 receptor, not all airway epithelial cells homogeneously co-express both factors, instead, there is a certain distribution pattern of these two factors in a cell-type dependent manner. Gene expression and immunohistochemical analyses have shown that both nasal and broncho-epithelial type II cells highly co-express ACE2 and



**Fig. 1.** The interaction of SARS-CoV-2 with olfactory cilia for entering the central nervous system (CNS). A) Different layers of cells in the nasal cavity that contain receptors for the very first viral entry into the human host. Some of the olfactory cells express ACE2 receptors that endocytose bound viral particles, before their way to the olfactory bulb in the brain. B) Schematic of the cellular barrier between cerebrospinal fluid and circulating blood in the choroid plexus region. Both endothelial and basement epithelial cells express the ACE2 receptors facilitating the internalization of virions in the brain fluid system.

TMPRSS2, which is key to SARS-CoV-2 pathogenesis (Bertram et al., 2012; Zou et al., 2020; Qi et al., 2020). Importantly, nasal ciliary cells expressing surface ACE2 receptors serve as the primary entry points for SARS-CoV-2, as well as for the early-stage viral replication (Ahn et al., 2021). A previous report found no detectable expression of ACE2 in upper airway passage cells (Hamming et al., 2004). Furthermore, it was reported that approximately 0.8% of type II pneumocytes co-express ACE2 and TMPRSS2 in fibrotic human lung cells, while 0.3% of ethmoidal sinusitis-associated upper respiratory epithelial cells express both ACE2 and TMPRSS2 (Ziegler et al., 2020). Another study using single-cell RNA sequencing reported that TMPRSS2 had a comparatively broader cell type distribution pattern compared with that of ACE2, suggesting that ACE2 could be the limiting factor in regulating viral entry at the early stages of infection (Sungnak et al., 2020). Notably, SARS-CoV-2 was also found to enter TMPRSS2<sup>+</sup> cells using alternative proteases, such as cathepsin B/L, which is expressed in 70–90% of ACE2<sup>+</sup> cells (Sungnak et al., 2020; Hoffmann et al., 2020).

It is still not determined whether low or high ACE2 expression could be beneficial in avoiding COVID-19. From emerging findings, it was suggested that low ACE2 levels in the upper respiratory tract could be beneficial; however, the same phenomena could be detrimental in the case of lower respiratory tract cells, allowing potential risk for severe acute respiratory syndromes and lung injury following COVID-19. It has been observed in several studies involving humans that some diseases can significantly lower ACE2 expression (e.g., type II diabetes (Mizuiru et al., 2008) and hypertension (Koka et al., 2008)), while smoking (Maggi et al., 2021) and inflammatory bowel disease (Garg et al., 2015) can increase ACE2 levels. This raises the question of how individuals with lower ACE2 expression contract COVID-19. A recent finding might be a possible answer to this question. Calver et al. (2021) have reported that the S1 subunit of the SARS-CoV-2 spike protein-bound  $\alpha\beta 3$  and  $\alpha\beta 6$  integrins through their interactions with RGDs, and  $\alpha\beta 3$  levels were upregulated upon SARS-CoV-2 infection (Calver et al., 2021). It has also been shown that TGF $\beta$  increased ACE2 expression following SARS-CoV-2 infection (Nader et al., 2021), suggesting alternative pathways to viral internalization, despite low ACE2 levels in some individuals.

### 3. SARS-CoV-2 genomic mutations and impact on host immunity

Understanding the genetic constitution of SARS-CoV-2 has important clinical significance in developing a therapeutic regimen. Some emerging studies involving next-generation sequencing have made important discoveries in this field. *ORF1a* and *ORF1b* genes together constitute most of the CoV genome. *ORF1a* undergoes canonical translation to produce polyprotein 1a (pp1a). Additionally, programmed frameshift translation in *ORF1a* continuing to the end of *ORF1b* reading frame, yields pp1ab protein (Baranov et al., 2005). Both pp1a and pp1ab then undergo proteolytic cleavage to produce 11 or 15 non-structural proteins (nsps), respectively. *ORF1a*-linked nsps have been shown to regulate viral gene expression, while *ORF1b*-related nsps support viral replications in the host cells (Gulyaeva and Gorbalenya, 2021). One-third of SARS-CoV-2 genome from the 3' end includes important viral structural proteins, such as the S gene encoding spike surface glycoprotein, the E gene for translation of the envelope protein, the M gene for the membrane glycoprotein, and the N gene for the nucleocapsid phosphoprotein, which are essential for viral genome packaging. Spike glycoprotein is composed of two subunits, namely the S1 subunit, which helps anchor the virion to the host-cell surface ACE2 receptor, and the S2 subunit, which mediates viral entry into the host cell by membrane fusion (Miller and Koev, 2000). This 3' end of the genomic region also includes several unnamed open reading frames (ORFs) that are specifically linked to SARS-CoV or its subgenus-associated pathogenesis (Cui et al., 2019). These types of ORFs are termed "accessory" ORFs (Liu et al., 2014). The study of SARS-CoV-2 genomic organization has revealed that ORFs 3a, 6, 7a, 7b, 8, and 9b have strong protein-coding signatures; ORF3c is an alternate-frame gene encoding a novel functional protein, and ORFs 2b, 3d/3d-2, 3b, 9c, and 10 lack any protein-coding sequences (Jungreis et al., 2021). ORF8 consists of ORF8a and ORF8b sub-genomic regions. Mutational analysis of ORF8 suggests its critical role in within-individual fitness but not in person-to-person transmission (Jungreis et al., 2021). Moreover, in vitro studies using a SARS-CoV-2 strain having a 382 nucleotide deletion in ORF8, isolated from a patient in Singapore in March 2020, has shown that the  $\Delta 382$  variant induces very similar host transcriptional responses as wild-type SARS-CoV-2 when transfected in human nasal epithelial cells, suggesting that ORF8 may be dispensable for viral entry and

replication in host cells (Gamage et al., 2020).

Mutational analysis indicated that evolutionary selection pressure of *Sarbecoviruses* could be the prime etiological factor behind the rapid evolution of SARS-CoV-2 proteins. Amino acid changing missense mutations preferentially impacted the non-conserved genomic regions than conserved ones (16.4% vs. 9.4%), reflecting inter- vs. within-strain evolutionary agreement. Considerable deviations from such agreements suggest enhanced or suppressed evolutionary selection, for example, both S1 and nsp3 have exhibited fewer than expected amino acid mutations (S1: 13% observed vs. 17% expected; nsp3: 10% observed vs. 15% expected), despite their extremely high inter-strain variations, representing decelerated evolution, while the dramatically high mutational load on the N gene (21% observed vs. 11% expected) indicates accelerated evolutionary selection toward host adaptation (Jungreis et al., 2021). Analyses of mutations in the N protein have shown that all 29 pathogenic mutations were clustered within the R185–G204 region overlapping the predicted B cell epitope (Grifoni et al., 2020). These adaptations may be associated with the immune escape capacity of the SARS-CoV-2. The RBD harbors multiple mutation hot spots that determine the host range of SARS-CoV-like viruses. For SARS-CoV-2, there are six such amino acids, L455, F486, Q493, S494, N501, and Y505 (Wan et al., 2020). Structure-function studies of the RBD motif of SARS-CoV-2 have shown that it has a higher binding affinity for ACE2 receptors from humans, cats, ferrets, and related species with similar ACE2 receptor sequences (Wrapp et al., 2020; Walls et al., 2020; Letko et al., 2020).

Notably, SARS-CoV-2 has been still undergoing mutational adaptations, resulting in the generation of numerous variants, however, with different virulence properties. Based on the capacity of each variant in causing severe disease and/or death, World Health Organization (WHO) has categorized the most detrimental ones as the variants of concern (VOC), e.g. the delta variant (B.1.617.2), first observed in India. The delta variant of clade 21 A exhibits mutation clusters in ORF1a (D691A, G1125C, M2796L, K2894E, V4102I, etc.), ORF1b (S598G, K774N, D884N, P1095S, P1975L, etc.), ORF3 (S26L, V259L), ORF7a (P45L, V82A, T120I), ORF7b (T40I), ORF8 (D119-, F120-), S (T19R, D138-, P139-, G142D, E156-, F157-, R158G, K417N/T, L452R, T478K, E484K, N501Y, T547I, D614G, V615I/F, P681R, A831V, T95I, P1263L, etc.), N (D63G, L161F, R203M, G215C, D377Y), and M (I82T, S94G, D209Y) (<https://nextstrain.org/ncov/gisaid/global>). Most of the observed mutations in the conserved and highly conserved domains of the spike protein, as well as other viral structural proteins, are likely to provide stronger virulent properties to SARS-CoV-2. More recently, WHO's Technical Advisory Group on Virus Evolution (TAG-VE) has declared the variant B.1.1.529/BA.1 or Omicron (clade 21 K) as the VOC on November 26th, 2021. Although Omicron was found to share common mutations in its spike protein with Beta (B.1.351), Delta, and Gamma (P.1) variants (Garcia-Beltran et al., 2021a,b), genome surveillance and phylogenetic analysis indicate that Omicron has been derived from the Alpha lineage (Garcia-Beltran et al., 2021a,b). Up to 34 missense mutations were detected in the spike protein of Omicron, out of which 15 mutations were within the RBD motif. The majority of these mutations clustered near the N-terminal domain of the spike protein responsible for antibody binding indicates the possible mechanism of escaping the vaccine-mediated neutralization by Omicron (Garcia-Beltran et al., 2021a,b). Omicron pseudovirus harboring mutations like S371L, S373P, T478K, S375F, Q498R, Q493R, and N501Y could bind the host ACE2 receptor 2-fold more efficient than the Delta variant and 4-fold stronger than wildtype pseudovirus. Computational analysis revealed structural reorganization of the spike protein domain from disordered to ordered structure within the RBD region, suggesting a mechanism for stable interaction with host ACE2 receptors (Kumar et al., 2021). Recent investigations on the vaccine (double-dose)-initiated neutralizing antibody response against SARS-CoV-2 indicated undetectable viral neutralization reflecting potent immune escape capacity of the Omicron, however, individuals having booster dose of mRNA vaccines showed

about 4–6 fold less viral load of Omicron than wildtype, suggesting optimal elicitation of polyclonal human neutralizing antibodies can provide substantial resilience to Omicron and future SARS-CoV-2 variants (Garcia-Beltran et al., 2021a,b; Naranbhai et al., 2021; Schmidt et al., 2021).

In addition to gene expression patterns, it is important to understand the architecture of the RNA genome inside the virion to develop antisense RNA-based therapeutic approaches because the RNA structure significantly influences the efficacy of antisense RNA treatment (Patzel et al., 2005; Vickers et al., 2000). SARS-CoV-2 carries the largest RNA genome and the size of the virion is only 80 nm in diameter, it has been challenging to characterize the deeper tertiary genetic architecture (Zhu et al., 2020; Cai et al., 2020). In another study, Cao et al. (2021) were able to reconstruct the genome architecture and identify multiple highly accessible single-stranded regions by exploiting virion RNA in situ conformation sequencing technology, suggesting the possibility for a potential therapeutic platform based on antisense oligos (Cao et al., 2021).

#### 4. SARS-CoV-2 primary entry points in the CNS and diverse neuropathological complications

Emerging studies showed that nasal intramucosal ciliated cells are the primary targets of SARS-CoV-2 entry into the human body. It has been found in nonhuman primates and COVID-19 patients that intramucosal multi-ciliated epithelial cells express SARS-CoV-2 entry-related genes, only in the apical side of this cell type, which may play critical roles in virus internalization, replication, and shedding of active virions in host target organs/tissues (Ahn et al., 2021). Furthermore, Meinhardt et al. (2021) provided substantial evidence that the olfactory trans-mucosal layer, representing the mucosal-neural interface, serves as the gateway for virions to travel to various neuroanatomical regions of the nasopharynx and CNS (Meinhardt et al., 2021).

As we analyze the pathogenic nature of previous SARS-CoV pandemic strains, such as MERS-CoV and SARS-CoV, there is considerable experimental and clinical evidence of the neuro-invasive nature of CoV, resulting in subsequent neuropathological and neuropsychiatric complications (Glass et al., 2004; Li et al., 2016; Netland et al., 2008). Notably, some of the symptoms observed in non-brain parts of the body in COVID-19 patients might be related to SARS-CoV-2 infection in the associated brain regions of these patients, such as in the medulla oblongata, which controls primary respiratory and cardiovascular functions (Meinhardt et al., 2021). Previous studies have suggested that altered psychological status, disinhibition, perseveration, and paranoia could be manifestations of widespread cytokine storm-mediated neuro-inflammation and encephalitis in post-COVID patients (Yousuf et al., 2021; Moriguchi et al., 2020; Wang et al., 2020; Erickson and Banks, 2018). Another study of post-COVID-19 patients indicated that 33% of the discharged patients presented dysexecutive syndromes, including disorientation, motor function deficits, and poor coordination with verbal commands (Helms et al., 2020). Rhea et al. (2021) have reported that the intravenously injected radiolabeled S1 subunit of the spike protein crossed the BBB by adsorptive transcytosis to reach the brain parenchymal regions, in mice. In addition, intranasally administered S1 protein has exhibited the ability to penetrate different brain regions in mice; however, at a rate 10 times lower than the intravenous route. Furthermore, the ACE2 receptor has been found to play roles in S1 uptake in brain and lung tissues, but not in the kidney, spleen, or liver. Conditional immune activation in these mice has revealed the reduced uptake efficiency of the S1 protein in the hippocampus and olfactory bulb (Rhea et al., 2021).

SARS-CoV-2 ancestors and other viruses have shown that their primary routes involved the disruption of the BBB to gain access to the brain. Emerging findings highlighted additional invasion routes for SARS-CoV-2 in the human brain. Choroid plexus cells are critically important in maintaining CSF balance by producing CSF in ependymal

cells lining the ventricles in the brain (Fig. 1B). In addition, this cell type also helps in maintaining the barrier between the blood and CSF (Lun et al., 2015). Notably, neural stem cells at the lateral ventricles are displaced from the ventricular zone to the sub-ventricular zone (SVZ) by ependymal cells (Mirzadeh et al., 2008). Hence, we speculate that SARS-CoV-2 infection in choroid plexus cells may eventually affect the neural stem cell niche in the human brain, leading to long-lasting neuropathological complications. Single-cell transcriptomics analysis revealed that the choroid plexus-CSF barrier was disrupted and choroid plexus cells relayed inflammatory signaling to the parenchymal glia, astrocytes, oligodendrocytes, and microglial cells of the upper cortex in the form of infiltrating T cells and the CCL/CXCL family of chemokines, which can impair cognitive functions (Yang et al., 2021; Baruch et al., 2014). The predominance of SARS-CoV-2 virion-mediated neurotropism in the choroid plexus epithelial cells has also been previously suggested by the results of an in vitro brain organoid study (Jacob et al., 2020). These molecular-level modulations can be correlated with the clinical observations in the post-COVID-19 patient follow-ups because they continue to present symptoms of headache and anosmia even months after their recovery from COVID-19 (Sampaio Rocha-Filho and Voss, 2020; Caronna et al., 2020). Persistent headaches may be attributed to the reduced volumes of CSF due to the damage of choroid plexus cells, while continuing cases of anosmia and hyposmia may be due to loss of the pre-frontal and olfactory bulb neurons. Even brain tissue loss has been suspected in COVID-19 patients (Douaud et al., 2021). Reduction in brain volume could arise from many pathological effects, including stress (Echouffo-Tcheugui et al., 2018); hence, it is possible that patients who contracted COVID-19 experience high degrees of stress at the neuroanatomical level. It has been found that cortical upper layers (layers 2 and 3) are involved in pyramidal excitatory neuronal synaptic signaling to different cognitive regions of the brain, which can be affected by SARS-CoV-2 infection (Yang et al., 2021; Gidon et al., 2020). Moreover, subpopulations of activated microglia and astrocytes in the post-mortem brains of COVID-19 patients resemble the pathological hallmarks of neurodegenerative diseases, such as AD (Sala Frigerio et al., 2019; Keren-Shaul et al., 2017; Mathys et al., 2019). Although there is no conclusive evidence on the interrelations between various neurodegenerative diseases and COVID-19, there are some indications that SARS-CoV-2 infection may increase the risk of most common brain diseases, including accelerated brain aging, PD, AD, amyotrophic lateral sclerosis (ALS), and cerebrovascular disorders. For example, a case report has shown the occurrence of acute hypokinetic-rigid syndrome along with hyposmia in a 58-year-old male patient (Méndez-Guerrero et al., 2020). Apart from observations that advanced stage PD patients have the highest risk for worsening motor dysfunctions, the influence of COVID-19 on the mortality of PD patients remains inconclusive due to significant variations (Fearon and Fasano, 2021). Another case study on two patients with ALS who contracted COVID-19 reported that the patients recovered to their baseline respiratory status, despite having respiratory muscle weakness from ALS (Lee et al., 2021).

Notably, single-cell RNA sequence analysis showed that SARS-CoV-2 infection-induced inflammation could activate several pathways that modulated  $\beta$ -amyloid transportation and aggregation in neuronal cells. In particular, the study has shown upregulation of protein-tyrosine phosphatase 1B (PTP1B) in the COVID-19 patient frontal cortex microglial cluster-associated transcriptome (Yang et al., 2021). PTP1B or PTPN1 activation can indirectly suppress the glycogen synthase kinase 3 $\beta$  signaling pathway, to increase the pathophysiology of amyloidosis and cognitive decline in AD patients (Ricke et al., 2020). Another critical factor related to neuronal processing and trafficking of  $\beta$ -amyloid, low-density lipoprotein receptor-related protein 1B, has been found to increase in the brains of COVID-19 patients (Yang et al., 2021; Cam and Bu, 2006). Receptor interacting serine/threonine kinase 1 (RIPK1) is a critical player in TNFR1 signaling-mediated necroptosis during apoptosis-deficient conditions, which makes RIPK1 a specific therapeutic target for broad-spectrum neurodegenerative, inflammatory and

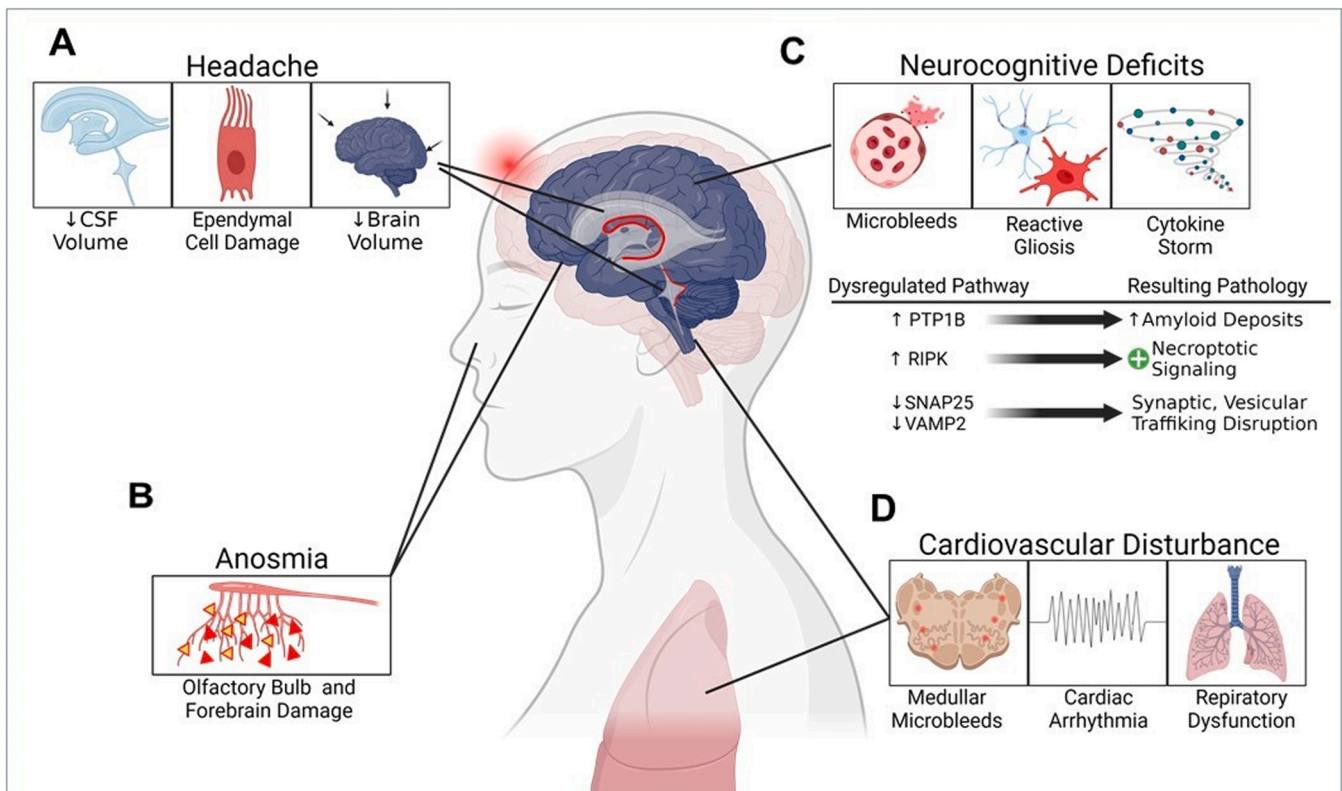
lysosomal storage diseases (Degterev et al., 2019; Wallach et al., 2016). Upregulation of RIPK1 in the brains of COVID-19 patients has suggested possible activation of necrotic pathways (Yang et al., 2021).

Modulation of COVID-19 patient brain gene expression profiles related to synaptic transmission and vesicular trafficking with down-regulation of *SNAP25*, *VAMP2*, and *ATP6VOC* has recently been reported (Yang et al., 2021). A genome-wide association study reported slightly overlapping but unique patterns of neuronal perturbations due to SARS-CoV-2 infections, especially showing strong effects in the glial cell population, indicating the possibility of increased vulnerability to various irreversible neurodegenerative and neuropsychiatric pathologies in long-COVID patients (Yang et al., 2021).

Based on these findings, we speculate that SARS-CoV-2 infection can stimulate the activation of many pathogenic mechanisms that may lead to complex forms of neurocognitive as well as neurodegenerative conditions in COVID-19 survivors (Fig. 2). Further systematic studies in larger cohorts of patients are warranted to delineate the underlying pathomechanisms of possible neurodegenerations during long-lasting COVID.

#### 4.1. "Brain Fog": the impact of COVID-19 on long-term neuropsychiatric sequelae and its association with ageing

Long-term and/or an indefinite period of diverse neuropsychiatric disorders have been reported in non-hospitalized COVID-19 survivors. Most importantly, studies have shown that at least 20–30% of these patients experienced a lingering psychological condition, known as "brain fog," characterized by many cognitive impairments, including memory loss, difficulty in concentrating, forgetting daily activities, difficulty in selecting the right words, taking longer than usual time to complete a regular task, disoriented thought processes, emotional numbness, or poor endurance occasionally accompanied by headaches, insomnia, dysgeusia, and anosmia (Graham et al., 2021; Garrigues et al., 2020). Furthermore, hopelessness, social isolation, insomnia, socio-economic burden, COVID-19 infection, imbalance in daily routines along with pre-existing motor and/or cognitive deficits can significantly affect the emotional and behavioral status, known as "hidden sorrow," of COVID-19 survivors in long-lasting COVID-19 patients (Pinto et al., 2020; Albuquerque et al., 2021). Notably, researchers have reported that COVID-19 survivors who experience "brain fog" or "dysexecutive syndrome" gradually developed multi-organ abnormalities, such as cardiac and hepatic dysfunctions (Nauen et al., 2021). Likely, patients with pre-existing anxiety syndromes and/or hidden grief or trauma may be the most at-risk population for developing "brain fog". A psychiatric study involving both children and young adults has identified the developmental pathways of elevated levels of anxiety and dysregulated worry from childhood to adolescence as a consequence of the COVID-19 pandemic, indicating the importance of detecting vulnerable young populations who are at the risk of developing uncontrolled anxiety and psychological stress (Zeytinoglu et al., 2021). Several reports have also indicated the increased incidences of suicidal behavior, which seems a well-established psychosocial consequence of severe pandemic situations (Banerjee et al., 2021). Increased levels of depression, coping motives, and alcohol consumption due to the COVID-19 pandemic-associated psychological distress have also been reported in an online survey of 833 US residents (McPhee et al., 2020). Retrospective cohort studies and case reports have reported that patients with psychiatric disorders, including schizophrenia, had increased mortality from COVID-19, in the US (Wang et al., 2021; Taquet et al., 2021a,b; Nemani et al., 2021; Palomar-Ciria et al., 2020). Notably, a growing body of evidence has highlighted the critical cross-talk between oxidative stress, neuro-inflammation, and loss of CNS volume in schizophrenia, anxiety, depression, mood disorders, and stress (Müller et al., 2015; Fond et al., 2020; Felger, 2018; Lee and Giuliani, 2019; Ng et al., 2008). These findings reasonably corroborate why patients with pre-existing neuropsychiatric dysfunctions have higher susceptibilities



**Fig. 2.** SARS-CoV-2-associated long-COVID pathogenic mechanisms in the COVID-19 survivors. A) Chronic headaches can be triggered due to the damage of ependymal cells, reduced cerebrospinal fluid (CSF) content, and the resulting shrunken brain volume. B) Viral infection-induced neuronal damage in the olfactory bulb and forebrain areas leads to acute anosmia. C) Initiation of neurocognitive decline resulting from the hemorrhagic microbleed-induced reactive gliosis, neuroimmune activation, and cytokine storms. Several signaling cascades related to synaptic transmission, vesicular trafficking, amyloidogenesis, and necroptotic pathways are dysregulated in this process. D) Similar mechanisms associated with the microbleeds in the deeper brain regions like medullar oblongata lead to cardiac arrhythmia and abnormal respiratory functions.

to COVID-19 mortality. However, further in-depth mechanistic studies are needed to understand the causes, to develop more effective therapeutic strategies.

#### 4.2. Chronic neurological dysfunctions after recovery from COVID-19

Several clinical and observational studies have reported several clinical symptoms that persisted in COVID-19 survivors, even after attaining negative PCR results. The Centers for Disease Control and Prevention (CDC) has listed more than 15 such new or ongoing abnormalities that can last for weeks or even months after the first SARS-CoV-2 infection. Respiratory distress, chronic and migraine headaches, broad-spectrum cognitive deficits, abrupt mood swings, loss of smell, altered taste perceptions, insomnia, musculoskeletal pain, and diarrhea are some of the frequently occurring symptoms in post-COVID-19 patients. Long-COVID also pertains to the new onset of symptoms that are either not fully resolved or were never experienced, after a 30-day recovery period. A meta-analysis reported that the most common sustained symptom was tiredness or fatigue (58%), followed by headaches (44%), attention-deficit/disorders (27%), ageusia (23%), anosmia (21%), memory losses (16%), and anxiety and depression (12–13%) (Lopez-Leon et al., 2021). In addition, chronic systemic inflammation in COVID-19 patients may cause peripheral neuropathy (Bureau et al., 2020). A study on a cohort of 714 COVID-19 patients reported that a significant portion of these patients exhibited severe post-traumatic stress disorder (Bo et al., 2021). Although dementia or long-term memory loss has not been reported yet in COVID-19 survivors, multiple pathomechanistic indications regarding the involvement of amyloidosis, AD, and PD-like pathological hallmarks have suggested

that individuals predisposed to such neurodegenerative conditions may experience an advanced stage of AD-related dementia at an earlier age than expected. Persistence of extended micro-hemorrhagic lesions may also enhance the cellular stress level, along with chronic oxidative damage, leading to long-term motor and cognitive impairments, especially in the aged population. Chronic cardiovascular abnormalities manifested as chest pains in post-COVID-19 patients can be the predominant illness, possibly due to microbleed-associated neuronal damage in the brain stem and medulla oblongata regions (Fig. 2). In summary, post-COVID-19 brain injuries can happen at multi-dimensional levels, which involve complex pathogenic mechanisms.

#### 5. SARS-CoV-2-induced thrombosis, hemolysis, and microbleeds

Emerging studies and case reports have highlighted the high incidences of venous thromboembolic events, disseminated intravascular coagulation, and elevated serum D-dimer levels, which are predictors of blood clotting, as critical factors influencing COVID-19-related mortality. In a retrospective cohort study including 400 hospitalized COVID-19 patients (including 144 critically ill patients) 9.5% of the patients had radiographically confirmed thromboembolic complications (Al-Samkari et al., 2020). Other studies have independently confirmed hyperactivation of blood coagulation pathways, leading to venous thromboembolism and thrombosis in 15–30% of patients who did not respond to the anti-coagulation and anti-prophylactic therapies (Nahum et al., 2020; Lodigiani et al., 2020). It has been reported that patients with lupus and antiphospholipid syndrome, who have circulating antiphospholipid autoantibodies, could be predisposed to severe thrombosis



when they contract COVID-19 (Zuo et al., 2020). This study reported significantly higher levels of anti-phosphatidylserine/prothrombin antibodies in serum samples of COVID-19 patients. Moreover, purified IgG from these patients induced severe venous thrombosis in two different mice models, suggesting that at least half of the COVID-19 patients became positive for extremely pathogenic auto anti-phospholipid antibodies. Meinhardt et al. reported that SARS-CoV-2 infection could lead to micro-thromboembolic events in the CNS involving the brain endothelial cells and the microvasculature (Meinhardt et al., 2021). Dixon et al. (2020) found that clinical characteristics of cerebral microhemorrhages in COVID-19 patients were correlated with the patterns of microbleeds in non-COVID patients with severe neuropathological conditions (Dixon et al., 2020). They showed that microbleeds had predilections for the brainstem, cortical white matter, and corpus callosum of patients. Another neuroimaging study by Fitsiori et al. (2020) also reported these unusual patterns of microbleeds, especially in the corpus callosum, as well as in the subcortical and para-hippocampal regions, middle cerebellar peduncles, and internal capsule in moderate to critically ill COVID-19 patients (Fig. 3) (Fitsiori et al., 2020).

5.1. Ageing factor in post-COVID-19 recovery: potential involvement of ferroptosis and cellular senescence pathways

Biological aging is a known key contributor to most progressive degenerative diseases, including neurodegeneration. The prevalence of stroke is also more than 70% in individuals aged above 65 years. This is of particular importance because COVID-associated death and microhemorrhagic lesions have been found to comprise three-quarters of the COVID-related death in subjects of more than 65 years of age in the United States as well as globally, according to the CDC's recent updates, while the death ratio comes to 1 in 1400 people aged less than 65 years, suggesting that chronological aging is also a crucial contributor to patient fatality. Several studies have consistently reported significantly high risks of ischemic/hemorrhagic stroke-like events, mostly cryptogenic in nature, and hypoxia, acute necrotizing hemorrhagic

encephalopathy, and acute cerebrovascular adverse events, possibly due to hypercoagulability as the leading causes of high mortality in COVID-19 patients (Yaghi et al., 2020; Kvernland et al., 2021; Dhamoon et al., 2021; Margos et al., 2021; Katz et al., 2020; Bridwell et al., 2020). Studies have also reported cerebral microbleeds as a clinicopathological sign for long-term neurodegenerative conditions, which are relevant in the context of the long-lasting COVID scenario among COVID-19 survivors. Traumatic microbleeds can be detected up to 5 years from their origins, using neuroimaging (Rizk et al., 2020). Microbleeds are also common in the elderly population, indicating that it is a predictor of brain aging (Fisher et al., 2010; Sumbria et al., 2018). Hence, the formation of high numbers of microbleeds in COVID-19 patients may suggest accelerated brain aging in long-COVID patients. Moreover, microbleeds have been pathologically linked to neurodegeneration, cognitive impairment, and dementia (Akoudad et al., 2016; Sepehry et al., 2016).

Increasing evidence of cerebral microbleeds and hemosiderin deposits, in both cardiovascular and neurodegenerative disorders, suggests the utilization of microbleed size and location as biomarkers for the diagnoses and prognoses of these patients, especially in case of stroke (Pétrault et al., 2019). Further evidence exhibits SARS-CoV-2-induced microhemorrhages and intracerebral endotheliitis in the brainstem, deep brain gray and white matter areas, cerebellum, and neocortex (Kirschenbaum et al., 2021). Because the brainstem includes the medulla oblongata, which regulates cardiovascular functions of the body, microhemorrhages in the brainstem can induce long-term cardiovascular dysfunctions, which have been widely observed in COVID-19 survivors as symptoms of long-lasting COVID. Together, these findings may provide the basis for investigating motor and cognitive deficits in COVID-19 patients' post-mortem brain samples as well as from follow-up studies of COVID survivors.

Previously, we showed the biodegradation of hemoglobin into multiple toxic by-products, including hemin, as the primary contributing factor in eryptosis and ferroptosis (Derry et al., 2020). We further provided evidence that hemin can cause direct DNA double-strand breaks

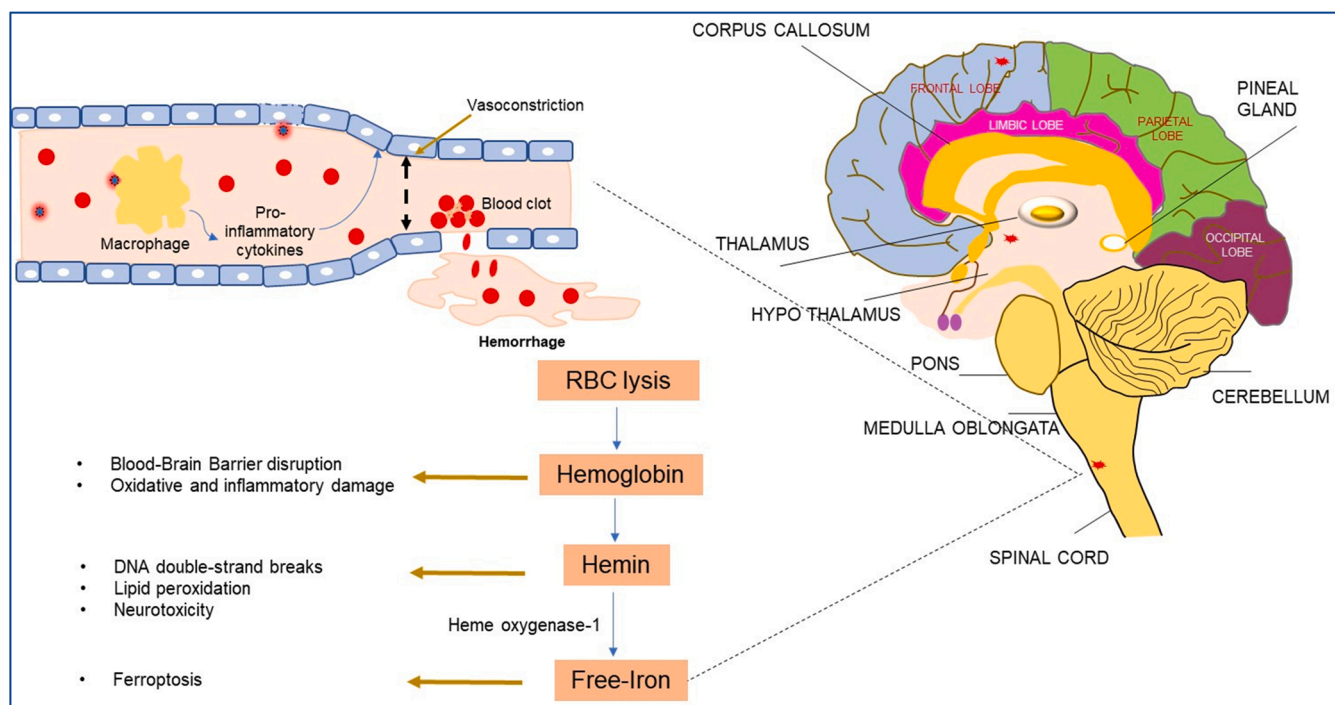
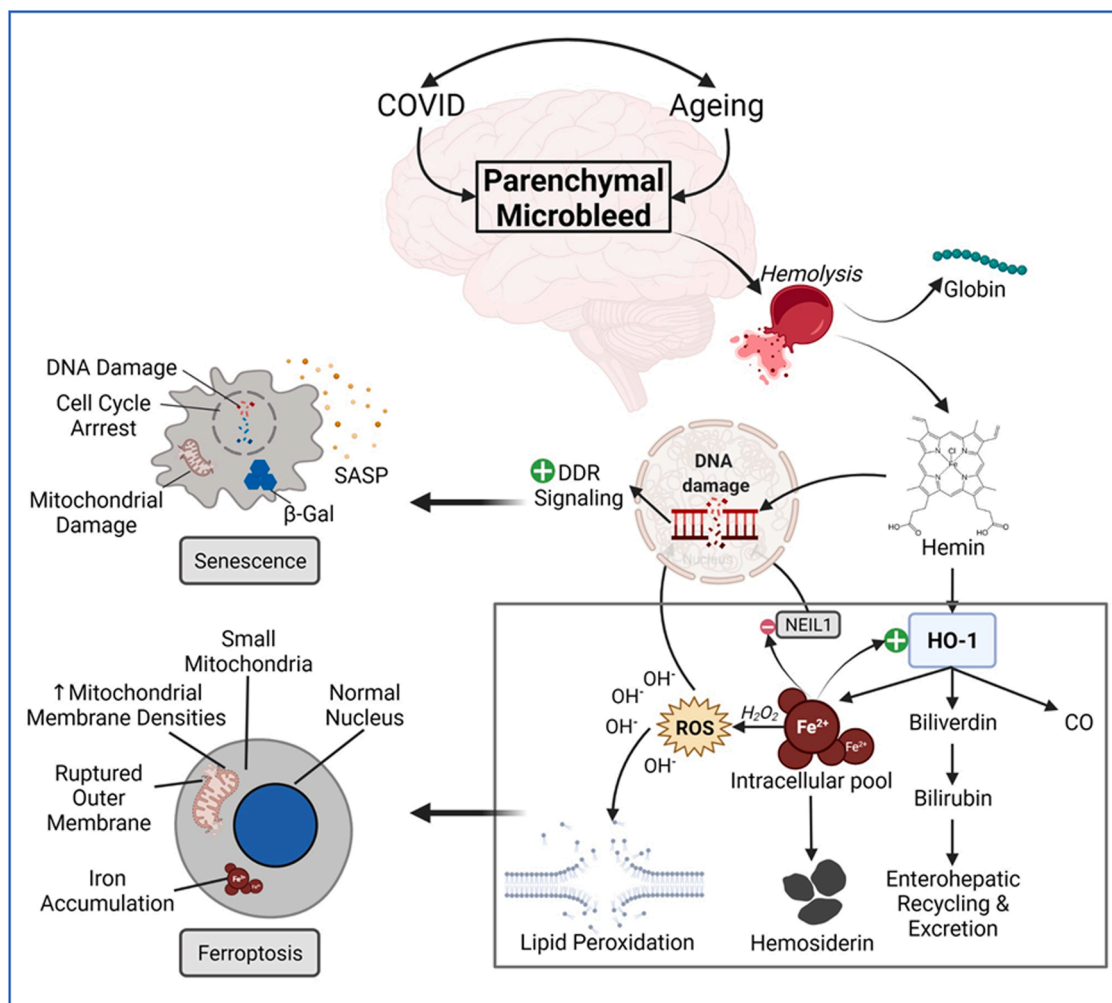


Fig. 3. SARS-CoV-2 infection-induced microbleeds in the brain and its potential consequences. A) Mechanism of virion recognition by endothelial ACE2 receptors, which in turn induce activation of a cytokine storm, leading to vessel rupture and downstream genotoxic and cytotoxic effects. B) Illustration of different brain regions in the sagittal section, indicating the formation of microbleeds as red spots in certain locations.

(DSBs) in the genome, the most lethal form of genome damage, in both endothelial and neuronal cells (Dharmalingam et al., 2020). We found that acute exposure to hemin induced cellular senescence or senescence-like states as an early response, possibly due to widespread genome damage together with acute oxidative stress and inflammation. While unresolved and/or persistent senescence is pathological, in this instance, we proposed that hemin-induced early senescence protected the cells from iron toxicity, which acutely increases during further degradation of hemin to bile salts. Deregulation of this tightly regulated hemin detoxification pathway could cause iron-mediated ferroptosis and cell death. Thus, several molecular factors orchestrate the hemin degradation mechanism, leading to the production of free iron, which then can induce both oxidative stress and iron-mediated ferroptosis (Seiwert et al., 2020). In this context, upregulation of heme oxygenase-1 (HO-1) gene expression in response to hemin exposure is protective against several diseases related to hemolysis and oxidative stress (Karatazaferi et al., 2019; Martín et al., 2019). However, hemin-induced HO-1 expression could not prevent SARS-CoV-2 infection, using an in vitro cell model (Maestro et al., 2021). Furthermore, observation of viral infection-induced multi-infarcts and microhemorrhages in distinct brain regions in the form of hemosiderin deposits, which primarily act as an

iron storage complex in combination with partially digested lysosomes and ferritins, has been correlated with the upregulation of ferritin light and heavy chain proteins in the CNS of COVID-19 patients (Yang et al., 2021), suggesting iron overloading in these affected brain regions.

Ferroptosis was first discovered in 2012 as a nonapoptotic iron-mediated cell death mechanism (Dixon et al., 2012). In its simplified form as shown in Fig. 4, the chemical basis of ferroptosis is the induction of reactive oxygen species (ROS) through the participation of pro-oxidant iron in a redox mechanism via the Fenton reaction. The pathological hallmark of such oxidative stress is the disruption of lipid membranes, either by direct attack from ROS under the downregulated condition of glutathione peroxidase 4 (GPx4)-associated antioxidant defense (known as canonical ferroptosis) (Li et al., 2020a,b; Hadian and Stockwell, 2020) or by overloading of the intracellular iron (II) pool in combination with hyperactivation of HO-1 (called non-canonical ferroptosis) (Hassannia et al., 2018). Furthermore, lipid peroxidation can be induced by enzymes like non-heme iron dioxygenase and lipoyxygenase (Kagan et al., 2017; Haeggström and Funk, 2011) or by free radicals (Gaschler and Stockwell, 2017). Elevated levels of malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE) and reduced expression of GPx4 serve as markers for ferroptosis (Ayala et al., 2014).



**Fig. 4.** Pathomechanistic implications of ferroptosis in age-related neuronal damage in the long COVID-19 survivors. Microbleeds are frequently detected in the aged brain in neuroimaging examinations. However, COVID-19 drastically increases the number of these microhemorrhagic lesions in the brain parenchyma. Following the hemolysis, hemoglobin disintegrates into globin and hemin parts. The schematic of ferroptosis illustrates how hemin sequentially undergoes biodegradation to form the pro-oxidant free iron ions, which in turn get engaged in Fenton's reaction to produce reactive oxygen species (ROS), resulting in the oxidative stress-induced genome damage as well as membrane disruption via lipid peroxidation mechanism, and ultimately cell death via ferroptosis. Since acutely overloaded intracellular iron (III) ions can inactivate oxidative DNA damage repair proteins like NEIL1, unrepaired DNA damage persistently sends out damage response signals, leading to cellular senescence. The key cellular hallmarks of a senescent and ferroptotic cell are indicated in the respective illustrations.

Cerebral hemorrhage-derived hemin exposure can induce the expression of Toll-like receptor 4 (TLR4) signaling, which in turn activates pro-inflammatory factors, like IL-6 and phosphorylated STAT3. Upregulation of these factors has been correlated with progressive cognitive impairment in hemorrhagic stroke survivors (Derry et al., 2020; Xiong et al., 2016). Moreover, studies have shown the effects of cytokine storms in inducing a senescent stage, along with the accumulation of oxidative DNA damage (Ren et al., 2009). The persistent senescent stage can in turn lead to continuing inflammatory signal activation (Stojanović et al., 2020). Such chronic inflammation has been found to induce telomere dysfunction, leading to irreversible cellular aging (Jurk et al., 2014). We and others have reported that induction of DNA damage response (DDR) signaling induced a senescence-like state (Dharmalingam et al., 2020; Kang et al., 2015), and an increase in the activity of the transcription factor, GATA4, which maintains cross-talk between the DDR and autophagy to cause senescence and inflammation in a p53-independent and NF- $\kappa$ B-dependent manner, and further activating downstream secretory factors (cytokines, chemokines, proteases, nucleases, and growth factors), collectively called the senescence-associated secretory phenotype (SASP), related to cell death (Kang et al., 2015). Elevated GATA4 level is a potential biomarker of cellular senescence in the aging brain. In this context, several studies have suggested that the deleterious effects of pre-existing senescent cells and chronic inflammation in elderly people who contracted COVID-19, could be a potential factor responsible for the intensive responses to pathogen-associated molecular pattern (PAMP) factors and high mortality in patients > 65 years of age (Nehme et al., 2020; Yanez et al., 2020; Perez-Saez et al., 2021; Ho et al., 2020). Consistent with this possibility, a preclinical study has reported that selective elimination of senescent cells by senolytic agents, like fisetin, after exposure to SARS-CoV-2 S1 protein reduced mortality to 50% and overall inflammation in aged mice, suggesting that fundamental aging mechanisms may be the potential therapeutic target to improve the resilience of the elderly population (Camell et al., 2021). However, this study did not consider the effect of viral spike protein on the brain endothelium and resulting microhemorrhages, which have been frequently observed in COVID-19 patients, irrespective of the age group. Excessive free iron can also induce stress granule formation and sequestration of structurally disordered domains containing pathogenic factors related to various neurodegenerative diseases, psychomotor dysfunctions, and increased dopamine levels in the basal ganglia (Chiueh, 2001; Baradaran-Heravi et al., 2020; Zhu et al., 2016; Kim et al., 2018; Bartels et al., 2019; Ma et al., 2021; Becerril-Ortega et al., 2014). It has also been reported that iron overload inhibited the enzymatic capacity of proteins, like NEIL1, that are involved in genome maintenance in response to oxidative stress (Hegde et al., 2010). Taken together, these findings suggest that managing the free iron overload, resulting from hemin breakdown, in and surrounding the SARS-CoV-2-induced microbleeds/multi-infarct areas, could be used to save affected neuronal and non-neuronal cells by carefully balancing the ferroptosis-senescence axis. Our previous findings suggested that hemin exposure induced oxidative stress and genome damage in an organelle-selective manner, e.g., hemin exposure showed immediate oxidative stress in the mitochondria, followed by the cytosol, and finally in the nucleus (Dharmalingam et al., 2020). Because iron is an essential and critical factor for overall human health, nonspecific chelation of iron may give rise to undesirable adverse events, further worsening complications. We have found that treatment with a dual function nanozyme (PEGylated carbon-nanoparticle conjugated with antioxidant scavenger and iron chelator deferoxamine) reverted neuronal senescence and prevented cells from ferroptosis at the same time, if treated within 1 h of hemin exposure, further suggesting that inflammation is the ultimate and universal pathogenic factor in determining the fate of the cells (Dharmalingam et al., 2020). This finding is consistent with a previous report that chronic inflammation may cause irreversible damage to telomeres (Jurk et al., 2014). Another important parameter is the appropriate stoichiometric combination of

the antioxidant and iron chelator, such as the combination of PEGylated antioxidant nanoparticles and deferoxamine, to exert synergistic effects on recovery of senescent parameters, reduction of oxidative stress, and increased cell viability in the affected cell populations (Dharmalingam et al., 2020).

## 6. Summary and future directions

In conclusion, SARS-CoV-2 infection-induced microhemorrhages in crucial brain regions have the potential to accelerate brain aging in COVID-19 survivors and can also lead to complex and irreversible neurodegenerative conditions, a risk factor for both cognitive and motor functions. Loss of neuronal cells in COVID-19 patient-affected brain areas may be attributed to a combination of senescence and ferroptosis along with acute inflammation-induced oxidative stress-mediated cell death. But the crosstalk between these phenomena needs further exploration. Notably, coagulopathy is found to be major risk factor associated with death or long-term physical disabilities in most COVID-19 patients, which requires individualized treatment strategies based on the patient's comorbid conditions. Combinatorial therapies involving antioxidant and target-specific iron chelators could be a potential strategy for ameliorating acute neuroinflammation and neuronal loss, a topic for future investigation. In this context, our nanozyme formulation has demonstrated promising therapeutic potential in *in vitro* and animal studies. Currently, there are only a handful of medications and ongoing clinical trials to ameliorate post-stroke long-term neuropathological conditions. Some of the Federal Drug Administration (FDA) approved drugs acting as the inhibitor of the coagulation factor Xa are apixaban (clinical trial: NCT03907046), dabigatran (Pradaxa®), and rivaroxaban (Xarelto®) (Chen et al., 2020). Because persistently high levels of inflammatory biomarkers in the blood have been detected in the recovery stage of COVID patients (Ali et al., 2021), it will be important to determine whether such chronic inflammations can induce stress granule formation in the brain, as it often does under other stress response conditions (Herman et al., 2019). Statins, minocycline, and melatonin are the most commonly administered anti-inflammatory drugs used to treat the neuroinflammation in the CNS (Kaelber et al., 2016). Under the influence of predisposed or comorbid pathological conditions, blood-degraded hemin and its toxic by-products can result in the pathogenic protein-RNA aggregate formation, leading to proteinopathy-associated neurodegenerative diseases. As mentioned earlier, proteinopathy-related neurocognitive decline or impairment can act as the predominant risk exposure to dementia. Clinically, cholinesterase inhibitors are primarily used to treat mild to moderate dementia conditions (Battle et al., 2021), FDA has recently approved a monoclonal antibody therapy (MAB), Aduhelm (BLA: 761178), that can induce targeted clearance of toxic protein aggregates in preventing neuronal death in Alzheimer's and related dementias. Thus, further mechanistic investigation of the fate and implications of microhemorrhages in the brains of COVID-19 survivors is urgently needed to better strategize the patient-specific therapeutic combination in treating COVID-19-induced long-term neurological and/or neuropsychiatric disorders. Furthermore, careful medical and clinical follow-ups should be performed to diagnose early symptoms of neuropathological, neuropsychiatric, and/or cardiovascular dysfunctions to prevent patients from developing irreversible motor/cognitive impairments and cardiovascular disorders.

## Conflict of interest

The authors declare that the study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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