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REVIEW

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Neuromodulatory effects of SARS-CoV2 infection: Possible therapeutic targets

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ABSTRACT

Introduction:: Although SARS-CoV-2 primarily manifests in the form of respiratory symptoms, emerging evidence suggests that the disease is associated with numerous neurological complications, such as stroke and Guillain–Barre syndrome. Hence, further research is necessary to seek possible therapeutic targets in the CNS for effective management of these complications.

Areas covered:: This review examines the neurological complications associated with SARS-CoV-2 infections and the possible routes of infection. It progresses to illuminate the possible therapeutic targets for effective management of these neuromodulatory effects and the repurposing of drugs that could serve this purpose. To this end, literature from the year 1998–2021 was derived from PubMed.

Expert opinion:: The neurological manifestations associated with COVID-19 may be related to poor prognosis and higher comorbidity. Identification of the key molecular targets in the brain that are potential indicators of the observed neuropathology, such as inflammatory mediators and chromatin modifiers, is key. The repurposing of existing drugs to target potential candidates could reduce the mortality attributed to these associated neurological complications.

1. Introduction

It has been more than a year after the first report of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [1]. In December 2019, a new pneumonia-like disease originated in Wuhan, China. The disease was found to be caused by an influenza-like virus, the novel coronavirus (nCoV). The condition was later named Corona Virus Disease-2019 (COVID-19) in February 2020 by the World Health Organization (WHO). The sudden and rapid outburst of COVID-19 raises a major concern in the scientific community for immunization and therapies. The nCoV infection is quite similar to the disease caused by severe acute respiratory syndrome coronavirus (SARS-CoV) in 2003, which affected most of the Asian countries. Therefore, the novel coronavirus was later renamed as 'SARS-CoV-2' by the International Committee on Taxonomy of Viruses (ICTV) [2]. This novel beta coronavirus is a single-stranded positive-sense RNA, and belongs to the family Coronaviridae, having a characteristic crown-like spike protein making the virus envelope. The virus spread rate is very high and can be transmitted through contact [3].

Two previously known human coronaviruses which caused serious lung infections were SARS-CoV (severe acute respiratory syndrome or 'SARS') outbreak in 2002 and MERS-CoV (Middle East respiratory syndrome or 'MERS') outbreak in 2012 [4]. Like, SARS and MERS, the novel coronavirus has also been classified as a zoonotic disease. Since the disease spread globally, it was declared a global pandemic by WHO, currently, the worldwide cases reached more than 160 million, and affected socio-economic, and medical status worldwide (https://www.worldometers.info/coronavirus on20.05.2021). This disease is a highly contagious respiratory syndrome that rapidly spread to almost every country after its origin in China. It was earlier considered as an upper respiratory tract disease but later found to involve and severely affect multiple organs such as the intestine, liver, heart, kidney, and the nervous system [5].

Moreover, SARS-CoV and MERS-CoV's neuroinvasive potential, which are near related to SARS-CoV-2, has also been reported earlier. A study showed that approximately 50% of all the inspected coronavirus cases carried the human coronavirus RNA genome in the central nervous system [6]. A few months after the disease outbreak, the studies reported a pronounced involvement of the Central Nervous System (CNS). Later, CNS hemorrhage was reported as a deadly complication in COVID-19 patients below the age of 65 years [7]. Further, there are worldwide reports of COVID-19 affecting both the peripheral and central nervous systems [8–11]. Considering the fact that neurological complications associated with the coronavirus disease can further complicate the recovery and treatment of the patient, it becomes

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Article highlights

- SARS-CoV-2 has the potential to invade the central nervous system and cause neuromodulatory effects.
- The cytokine storm and associated immunological responses are the main culprits behind the SARS-CoV-2 associated neuropathology.
- Several molecules and regulatory pathways such as c-jun signaling, histone deacetylases, ubiquitin proteosome system, cyclophilin, exportins and estrogen receptors can be explored as potential therapeutic targets.
- Drugs known to modulate the activities of the possible therapeutic targets in the CNS can be repurposed for timely and cost-effective management of the neurological complications associated with SARS-CoV-2 infection.

This box summarizes key points contained in the article.

essential to understand the molecular basis of the neurological comorbidities that arise in COVID-19 patients and to discover potential therapeutic targets associated with these neurological manifestations for improving the clinical conditions of the patients. In this respect, the review discusses the basic structure, pathogenesis and mechanism of SARS-CoV-2 infection, followed by a discussion on its entry into the brain. We further discuss the various potential therapeutic targets associated with SARS-CoV-2 mediated neuromodulators and the importance of drug repurposing for tackling neurological complications and offer new therapeutic opportunities. To this end, we performed a PubMed search using the following search terms with various combinations: SARS-CoV, SARS-Cov-2, MERS, coronavirus, neurological complications, brain network, drug repurposing, COVID-19, neurons. The relevant literature published from the year 1998 to 2021 was taken into consideration.

2. Structure of SARS-CoV-2

SARS-CoV-2 is a virus that contains a positive-sense single-stranded RNA (ssRNA). The ssRNA is present along with nucleoproteins and is packaged into a capsid which is made up of matrix protein [12]. The genome of SARS-CoV-2 consists of at least six open reading frames (ORFs), out of which ORF 10 and 11 present near the 3′ terminus codes for the four main structural proteins [13,14]. The structure of the genome is defined by many key features, such as a unique N-terminal which is located within the spike protein. The genes that code for the major structural proteins are arranged in 5′ to 3′ order as spike (S), membrane (M), envelope (E), and nucleocapsid (N) (Figure 1). The typical number of ORFs present in its genome is six, however, it can vary. Out of this, ORF1a and ORF1b produce two polypeptides pp1a, and pp1ab, and are separated from each other through a frameshift. The polypeptides thus formed by these 2 ORFs are further processed by chymotrypsin-like protease (3CLpro) or main protease (Mpro) and one or two papain-like proteases into 16 nsps, and all these enzymes are coded by the virus itself. The single guide RNAs (sgRNAs) of CoVs are responsible for translating the structural and accessory proteins, out of this the 4 main structural proteins are S, M, E, and N proteins which are encoded by ORFs 10, 11 on the one-third of the genome near the 3′-terminus and some of the accessory proteins are HE protein, 3a/b protein, and 4a/b protein [13,14]. The mature proteins formed by the virus are essential for its replication and genome maintenance [13].
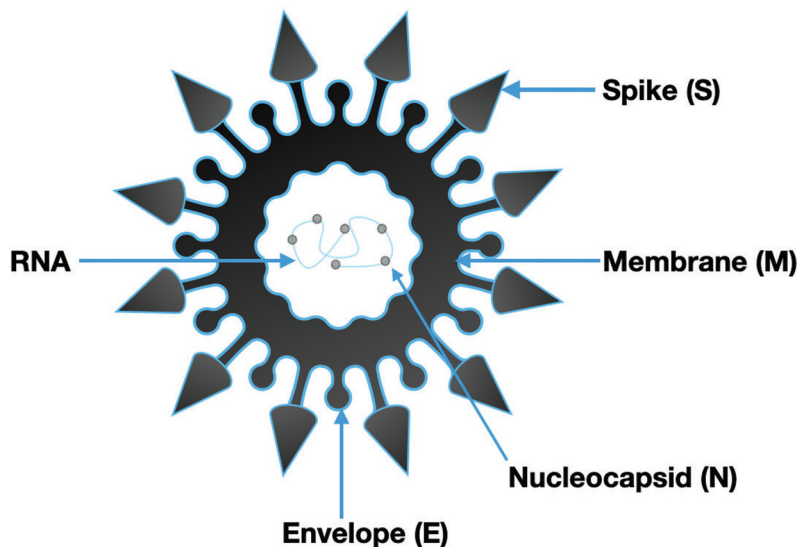

Figure 1. Schematic diagram of the structural features of SARS-CoV-2 and its primary structural proteins. The figure shows the overall structure of the SARS-COV-2. It is a single-stranded RNA virus consisting of four main structural proteins. The nucleocapsid (N) protein forms the capsid of the genome and then genome is further packed by an envelope consisting of spike (S) and membrane (M) glycoproteins, and envelope (E) protein. The S protein protrudes out from the surface and mediates viral entry into the host cell. The M protein is a transmembrane protein that helps facilitate the assembly of the virus particles. The E protein is the smallest structural protein that plays a role in virus assembly, pathogenesis and release.

In the membrane, there are three to four viral proteins present and M glycoprotein is the most abundant of them and it spans the membrane bilayer thrice, leaving a short NH2-terminal domain outside the virus and a long COOH terminus (cytoplasmic domain) inside the virion [12]. S protein is another viral protein that is responsible for inducing antibody formation and it is a type I membrane glycoprotein forming the peplomers. The intracellular formation of virus particles occurs through the M protein and does not require S protein. Studies have shown that the coronavirus, if grown in the presence of tunicamycin, produces a noninfectious virus particle that is spike less and only contains M protein but not S protein [12–15].

3. Mechanism of SARS-CoV2 entry into the CNS

The primary cellular receptor of SARS-CoV-2 is angiotensin converting enzyme-2

(ACE2), mainly expressed by alveolar cells, enterocytes, vascular endothelium cells, and smooth muscle cells. ACE2 is also robustly expressed in neuronal and glial cells, hence the virus is capable of showing neurotropism and infecting the brain [16–18]. A study reveals the SARS-CoV-2 entry in CNS through the neural–mucosal interface in the olfactory mucosa. Mice expressing human ACE2 evidenced the SARS-CoV-2 entry in the brain through intranasal infection. Further, it exploits the neuroanatomical connections, such as endothelial lining and nervous tissue, involving the subtle olfactory and sensory nerve endings to reach the brain [19].

It has also been suggested that a potent cytokine storm is sufficient to alter the permeability of the blood–brain barrier (BBB) and facilitate the entry of SARS-CoV-2 inside the brain. However, SARS-CoV-2 primarily enters the brain cells through interaction with the cellular receptor ACE2 and the binding geared up by transmembrane protease serine 2 (TMPRSS2). A study revealed the spatial and cell-type expression of ACE2 receptors in brain neurons, astrocytes and oligodendrocytes and showed that ACE2 expression was higher in substantia nigra, ventricles, middle temporal gyrus, olfactory bulb, and posterior cingulate cortex [20]. Moreover, ACE2 was found to be expressed on both cell surface and the cytoplasm of neuronal cell cultures [18,21]. The cells such as astrocytes having a low expression of ACE2 protein were instead found to express an alternative receptor for SARS-CoV-2 binding i.e. dipeptidyl peptidase 4 (DPP4). SARS-CoV-2 alternatively used human DPP4 protein to infect developing astrocytes in cortical tissues [22]. SARS-CoV-2 binds to the ACE2 receptor with very strong affinity through Receptor Binding Domain (RBD) of 220 residues [23]. A punctual mutation in RBD of SARS-CoV-2 corresponding to SARS-CoV favors an energetically favorable change for interaction with human ACE2 [24]. SARS-CoV-2 infection is initiated by the interplay of its transmembrane S glycoprotein with the host-cell receptor, which induces endocytosis by facilitating the union of the viral envelope with the plasma membrane of a host cell. S glycoproteins make homotrimers typically projected from the virus surface guiding the link to host receptors which

are composed of two functional subunits (S1-S2) [25]. The S1 subunit has a critical RBD which interacts with its cognate host cell receptor while the S2 subunit promotes the cell membrane fusion. S2 subunit mediated virus host cell fusion and entry encompass two tandem domains, heptad repeat 1 (HR1) and heptad repeat 2 (HR2) which networks to form a six-helical bundle (6-HB), thus bringing the viral and cell membranes into close vicinity for fusion [26]. Since SARS-CoV-2 has evolved with the upgraded binding affinity for HR1 and HR2 domains, it has accelerated the progression of virus membrane fusion and resulted in enhanced viral contagion or transmission [23,27]. SARS-CoV and SARS-CoV-2 exhibit similar routes to interact with the host cell and utilize ACE2 a metallopeptidase located on the host cell and mediate viral entry. ACE2 is expressed on the major viral target ciliated lung epithelial cells where its catalytic domain binds to SARS-S with high affinity [24].

Interestingly, SARS-CoV-2 showed a nearly 10–20 fold relatively high binding affinity to ACE2, compared to other SARS CoVs due to the presence of FURIN cleavage site, which is generally lacking in SARS-CoV [24,28]. In SARS-CoV-2, the presence of functional polybasic (FURIN) cleavage site at the interface between S1–S2 subunits of S glycoprotein, plays an essential role in defining the viral infection and host type. FURIN mediated pre-cleavage at the S1/S2 site in infected cells following proteolytic action of host cellular TMPRSS2 ensures the adequate processing and activation of S protein ultimately resulting in the discharge of the viral RNA genome into the cytoplasm [24,25].

Once inside the cell, released viral RNA in the cytoplasm works as messenger RNA and utilizes host cell ribosome machinery to translate necessary proteins which are the requisite of assemblage for the active and viable virus. Initially, the translation of polyproteins pp1a and pp1ab takes place by genomic RNA template whereas, further cleavage between these two polyproteins leads to the formation of non-structural proteins (nsps) [29]. Subsequently, nsps mediate the rearrangement of cellular membrane results in the construction of double-membrane vesicles (DMVs) in which replicase-transcriptase complex (RTC) are anchored and assemble by RNA-dependent RNA polymerase (RdRp) and helicase comprising subunits [30]. Next, the viral replicate uses a full-length positive strand of genomic RNA (gRNA) as a template for the synthesis of a full-length anti-sense genome, which further serves as a template for the production of new gRNA. Likewise, polymerase switches template to synthesize 5′ nested set of negative sense subgenomic RNA (sgRNA) and 3′ nested set positive sense sgRNA by discontinuous transcription. This sgRNA further encodes viral structural and accessory proteins following subsequent particle assemblage in the Endoplasmic reticulum-Golgi intermediate complex (ERGIC) orchestrated by the M protein. During particle assembly homotypic interaction of M protein and its subsequent interaction with S, N, and E proteins mediate viral morphogenesis, recruitment of structural component to assembly location, and induces membrane curvature [31]. After the particle assembly, mature virions are delivered in smooth-walled vesicles and exported out of the cell through exocytosis to infect newer cells [30].

4. Neurological complications associated with SARS-CoV2 infection

The entry of SARS-CoV2 in the brain can cause both specific and nonspecific neurological symptoms. Some of the earliest reported neurological complications were nonspecific symptoms, such as headache and dizziness. Later on, the list of neurological complications associated with SARS-CoV2 infection grew rapidly.

So far, there are multiple observations on CNS pathological changes associate with COVID-19: cerebrovascular injury comprising diffuse cerebral ischemia, microhaemorrhages, hemorrhagic strokes, microangiopathy of white matter, thrombosis, meningitis, acute myelination, and encephalopathy (Figure 2). Hypercoagulopathy is also a matter of concern after viral infection as in a case report presented by Fadi Al Saiegh et al. patients detected with ischemic stroke. However, there were no viral particles detected in cerebrospinal fluid (CSF) [32]. In such cases, anticoagulant therapy with the administration of small-molecule heparin was found to turn down the mortality in COVID-19 patients [33]. Also, microscopic examinations have revealed a neuronal loss in various brain parts like the hippocampus, cerebral cortex, and cerebellar Purkinje cell layer [34]. The virus-infected astrocytes and microglial cells activate neuroinflammation by releasing various cytokines and stress factors, such as tumor necrosis factor alpha (TNFα), interleukin 6 (IL-6) and reactive oxygen species (ROS). Covid-19 pathogenesis is characterized by a cytokine storm in which there is a high level of circulating pro-inflammatory cytokines such as IL-6, IL-8, IL-2, IL-7, IL-10, IL-1RA, TNF-α, G-CSF (granulocyte-colony stimulating factor), FGF (fibroblast growth factor), interferon-γ-inducible protein (IP10), MCP-1 (monocyte chemoattractant protein), macrophage inflammatory protein, VEGF (vascular endothelial growth factor) and also C reactive protein [35,36]. Most of these cytokine profiles rise with the progression and severity of disease. The release of these cytokines is associated with hyperactivation of the innate immune system, which can cause damage to the CNS either directly via cytopathic effects or indirectly by the activation of inflammatory cells [37]. The systemic inflammatory response provoked by SARS-CoV-2 infection causes the breakdown of the blood–brain barrier (BBB). Thereby, causing high BBB permeability resulted in peripheral cytokines to enter into the CNS. Thereby, an extensive inflammatory response arises in brain, particularly in the olfactory bulbs and medulla oblongata [38]. Since medulla oblongata is central to respiratory system regulation and rhythm generation, inflammation to this brain architecture may result in respiratory failure in COVID-19 patients [39].

Moreover, out of these pro-inflammatory cytokines, IL-1 is an important pro-inflammatory cytokine that stimulates the mast cells leading to the generation of pro-inflammatory mediators, such as chemokines, histamine, tryptase and cytokines such as IL-6. The release of histamine by mast cells can further cause the macrophages to release IL-1 which again activates the mast cells, thus aggravating the inflammatory response [40–42] p.19,. Preclinical data from neurotropic viral infections suggest that IL-6 plays a key role in facilitating tissue damage, promotes virus persistence and leads to chronic demyelination. At the same time, in response to the neuroinfection, there is also a release of anti-inflammatory cytokines such as IL-10 and IL-Ra [43]. Thus, it is the fine balance between the levels of pro- and anti-inflammatory cytokines that determines the extent of damage to the CNS.

The typical neurological symptoms observed in SARS-CoV-2 infected patients are headache, dizziness, nausea, and vomiting; however, severe patients indicated acute cerebrovascular
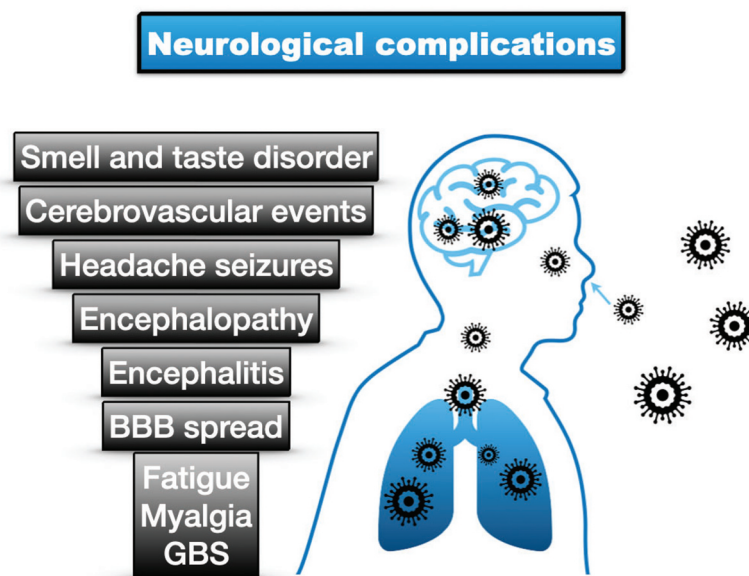

Figure 2. Neurological complications during SARS-CoV-2 infection. The SARS-COV-2 virus gains entry into the CNS via retrograde axonal transport through the olfactory nerve and bulb or upon fenestration of the blood brain barrier due to pathological changes associated with the infection. Following the entry of SARS-CoV-2 in the brain, several neurological and pathological changes takes place. The range of neurological complications that arise as a result of infection can be either acute such as headaches, smell and taste disorders, fatigue or it can lead to severe neurological complications such as encephalopathy, encaphilitis, chronic seizures, GBS and cerebrovascular events such as stroke and intracranial hemorrhage. (GBS: Guillain–Barre syndrome; BBB: blood-brain barrier).

diseases and compromised consciousness [8]. A study conducted by Carlos Manuel et al. on COVID-19 patients witnessed seizures in less than 1% of cases without any history of epilepsy except only one patient. This study involving the largest no. of patients (more than 800) showed that almost 58% of COVID-19 patients evolved at least one neurologic indication. The first stage of neurological symptoms was predominantly anosmia and dysgeusia, markers of early infection and onset within 4–9 days of disease. The second and third stages of severe patients included encephalopathy, myopathy, and autoimmune disease [10].

It has been further observed that neutrophil infiltration and generation of neutrophil extracellular traps (NET) cause thrombosis in the lungs, kidneys, heart, liver, and brain [44]. NETs are basically DNA-based complexes that are released by neutrophils which trap and deactivate viruses. This is a matter of concern, since NETs are thrombogenic and cause severe coagulopathy in the brain and other organs [45,46].

It has been observed that most infected patients display a wide inflammatory response, upsetting both white and gray matter, regardless of the disease course. This reaction has been found to be more pronounced in the medulla oblongata and olfactory bulb, characterized by activation and huddling of microglia, astrogliosis, and perivascular cuffing of T cells with the presence of neutrophilic plugs [38].

The increased lung edema (observed by lung opacity on chest image) and alveolar downfall lead to intrapulmonary shunting leading to declining oxygen, thereby creating hypoxia. The hypoxic condition accompanied by the enhanced anaerobic metabolism and lactic acid accumulation in the brain cells results in cerebral edema, diminished blood flow, and augmented intracranial pressure [47]. The disease is further associated with thrombolytic events, arrhythmic complications, cardiac manifestations, coagulopathies and thromboembolic complications. Such complications can give rise to several cerebrovascular events, such as acute ischemic stroke, cerebral venous sinus thrombosis and intracranial hemorrhage. One of the main mechanisms linked to these pathologies is the dysregulation of the renin-angiotensin system as the virus binds to ACE2 and depletion of this receptor can lead to endothelial dysfunction, vasoconstriction, hypertension ultimately leading to cerebrovascular events, such as stroke and hemorrhage [48]. Hepatic failure and anomalies following SARS-CoV-2 are often reported and the hepatic injuries caused due to the infection manifests into hepatic encephalopathy. Encephalopathy occurs due to hepatic overactivation observed in the disease which is associated with a marked increase in acute phase protein, which further induces the production of C-reactive protein potentiating systemic inflammation along with hyperammonaemia occurring as a result of hepatic injury [49,50].

Interestingly, a recent study has shown that SARS-CoV-2 can also infect and replicate in neurospheres and brain organoids originating from induced pluripotent stem cells (iPSCs). The organoids were positively stained for neuronal markers, such as TUJ1 (a marker for neuronal cells), PAX6 (radial glial cell marker), and Nestin (proliferating neural progenitor cell marker). Moreover, the authors confirmed the presence of ACE2 receptors, TMPRSS2, FURIN, and Cathepsin L in brain cells which are required for infection with SARS-CoV-2 [51]. This further widens the knowledge of the available routes for viral entry.

Considering the increasing evidence pointing to the neurological complications arising due to COVID-19 infection, the chronic neurological sequelae of the disease are increasingly becoming a cause of concern. The reason for this concern stems from the fact that the previously known neurotropic respiratory viruses have resulted in chronic brain pathologies. Studies have confirmed that the flu-pandemic of 1918 led to several neurological complications in the affected individuals at a later stage of life, including psychosis, encephalitis, lethargica and sleep disorders. The influenza epidemics have also been linked to other neurological disorders such as Parkinson's disease and schizophrenia. Herpes simplex virus 1 infection has also been known to be associated with Alzheimer's and cognitive decline. Thus, the research conducted so far for these viruses provides a way to gain an insight into the long-term neurological effects that can develop in people who recover from the COVID-19 disease. More importantly, the evidence accumulated from coronavirus pandemics in 2002 and 2012 has shown that one in five recovered individuals had impaired memory, depression, anxiety, sleep disorders, fatigue and insomnia. Thus, the long-term neurological sequelae associated with SARS-COV-2 cannot be ignored and for this purpose, the current research is being extended to assess the impact of the infection later in life. To further contribute to the research an international consortium has been formed to better understand the biology of the virus that can cause Alzheimer's and other dementias [52]. Also, a prospective study conducted by Frontera et. al. has found that about 90% of the COVID-19 patients who had neurological symptoms at the time of infection developed anxiety, depression, sleep problems, fatigue and high rates of cognitive impairment, 6 months after being discharged [53]. Thus, it is essential to carry out research not only to understand how the virus directly impacts the CNS but also to project the impact of the infection on the global burden of neurological disorders in the coming years.

5. Novel therapeutic targets for SARS-CoV-2 associated neuronal complications

5.1. Cyclophilin A

Cyclophillins (Cyps) are a class of conserved intracellular proteins that belong to the PPIase family and there are seven main types of Cyps that are found in humans, namely CypA, CypB, CypC, CypD, CypE, Cyp40, and Cypp. Out of these CypA is the one that is the most dominant protein and is associated with viral infections such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and, hepatitis C virus (HCV) [54,55]. It has been observed that CypA is responsible for mediating cytokine release from microglia and astroglia and hence, it becomes important to assess its levels in the brains of COVID 19 patients and develop strategies to inhibit it [56]. Further, several studies have shown that CypA inhibition plays an effective role in inhibiting the replication of diverse coronaviruses [56,57]. A recent study by Sofitc et al. has also shown

that inhibition of CyPA by Alisporivir reduced the SARS-CoV2 RNA production in-vitro and it further inhibited a post-entry step in viral replication [58]. All of this makes CypA an interesting therapeutic target to tackle neurological complications.

5.2. Ubiquitin/proteosome system

The Ubiquitin/proteosome system (UPS) is a key system that plays a role in the maintenance of protein homeostasis and regulation of protein degradation. UPS is known to play an important role in normal brain development, as well as for regulating the proper functioning of both pre- and postsynaptic compartments of neurons [59]. Studies have suggested that ubiquitin and ubiquitin-related pathways are often exploited by the coronaviruses for their survival and a recent study has also shown pathological effects like tauopathies and neuronal cell death occurring in patients infected with SARS-CoV2. Further, recent studies employing bioinformatics tools and network analysis have shown that SARS-CoV2 infected host cells do have a ubiquitin modified proteome and the UPS protein module is highly linked to the neurological complications that are commonly seen in SARS-CoV2 infected patients [60,61].

5.3. Estrogen receptors

The existing data suggest that SARS-CoV2 infection has been associated with a greater mortality rate in males as compared to females. One reason for this difference is attributed to the differential levels of estrogen present in the sexes. It is known that estrogen in low concentrations stimulates the immune system and blocks viral replication and recent studies have shown the link between estrogen and ACE2 levels [62]. Interestingly, a study that suggests the hypothalamus as one of the hubs for SARS-CoV2 infection also showed a possible link between estrogen receptor alpha, metabolism, and viral susceptibility [63]. Further, a brain network analysis has also found out ESR1 is one of the hub genes linked with SARS-CoV-2 [61].

5.4. Histone deacetylases

Histone deacetylases (HDACs) are known to regulate the expression of genes by catalyzing the removal of acetyl both from histone and non-histone substrates. It is further known that the majority of the HDAC classes are widely expressed in the different areas of the brain and their levels play an important role in regulating neural functioning [64]. A bioinformatics study has revealed that HDACs play a pivotal role in modulating the pathogenesis of SARS-CoV-2 [65]. Curiously, network analysis has revealed that HDAC1 and SIRT 7 are some key genes that can be linked with brain injury linked to SARS-CoV-2 infection. This study further suggests HDAC1 as one of the most targetable genes due to its interactions with various drugs that can be used for treatment purposes [61]. Since HDAC inhibitors (HDACi) are readily available in the market and are already being used in the treatment of several neuronal diseases, exploiting HDACs as therapeutic targets in SARS-CoV-2 neuromodulation can prove to be a time-saving and effective strategy.

5.5. JUN protein

JUN protein is expressed in several regions of the brain and it is observed that following any kind of synaptic insult there is an increase in the expression of this protein [66]. It has been shown through several studies that c-jun is activated in viral infections and in the case of SARS-CoV it is revealed that nsp1 has the ability to decrease the expression of c-jun, thus implying the importance of JUN protein levels in case of SARS-CoV2 infection. Now, the importance of JUN protein as a therapeutic target for SARS-CoV2 mediated neuromodulation comes into light after JUN was revealed as the central hub protein with connection to several host proteins that interact with SARS-CoV2 [61]. Also, considering its role in inflammation it is another target that should be further studied for its therapeutic potential.

5.6. Exportin-1

Exportin-1 (XPO-1) is the major carrier protein that regulates the entry and exit of most of the proteins through the nucleus. It has been shown that XPO-1 plays a role in neurodegeneration and neuroinflammation and hence, it emerges as an important molecule whose altered levels in the brain can cause neurological complications in SARS-CoV-2 disease [67]. The importance of considering this molecule as a therapeutic target is further highlighted by the evidence provided by the studies stating that it is involved in exporting the viral proteins from the nucleus to the cytoplasm and it interacts with about 119 host proteins modulated by SARS-CoV-2 [61,68].

6. Drug repurposing for managing neurological complications associated with COVID-19

Repurposing of drugs is a valuable strategy as it can help in accelerating the identification of drug candidates in a time- and cost-effective manner as the safety profiles are already known. Considering the novel therapeutic targets of SARS-CoV2 mediated neuromodulation proposed in the previous section of this review, drug repurposing can be used to target the proposed key genes and hence, can help to reduce the comorbidities arising due to neurological manifestations of the virus (Figure 3).

Considering the proposed role of cyclophilins in epilepsy, cyclophilin inhibitors can be used as candidate drugs for managing neurological complications. Amongst the various cyclophilin inhibitors present, cyclosporin A (CsA) has been shown to inhibit the replication of hCoV-229E and there are several studies that have suggested that CsA has the ability to inhibit the replication of almost all types of coronaviruses. However, it is also essential to consider that the immunosuppressive properties of CsA can lead to several adverse side effects during the antiviral therapy, and hence, it is advised to use the analogues such as Alisporivir, NIM811, SCY-635, sangliferins, and STG-175 that are non-immunosuppressive in nature [69].

There are several drugs that are used to inhibit proteosome activity on a routine basis in tumor pathologies and since UPS has shown to play a role in neurological complications associated with COVID-19 infection, we can repurpose these drugs to manage the complications. There are several proteosome
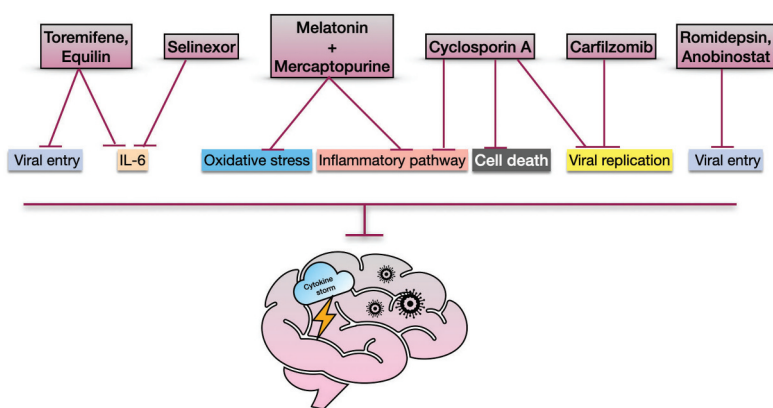
Figure 3. Potential repurposing of drugs for managing neuronal complications The various drugs which can be repurposed for managing neuropathology associated with SARS-COV-2 infection are shown in the figure. The entry of the virus can be inhibited by using selective estrogen receptor modulators such as Toremifene, equilin, or HDAC inhibitors like romidepsin, and anobinostat. Cyclosporin A which is a cyclophilin inhibitor and carfilzomib which is a proteosome inhibitor can effectively inhibit viral replication in the neurons. Further, the inflammatory pathways can be supressed by use of serlinexor, toremifene, equilin, and combination of melatonin and mercaptopurine. This combination can also be employed to reduce oxidative stress in the brain. Overall, the effect of these drugs is to reduce the cytokine storm and the viral load in the CNS which will help to manage the COVID-19 associated neurological complications.

inhibitors that can be tested such as MG132, Lactacistin, Carfilzomib, Ixazomib [70]. Further, Carfilzomib has already emerged as a candidate for the treatment of COVID-19 using computational drug repurposing [71].

A network analysis has revealed that ESR1 shows interactions with several of the FDA approved drugs such as fulvestran, tamoxifen, raloxifene, estradiol, and ethinylestradiol. Another study has shown that Selective estrogen receptor modulators (SERMs) utilize the non-classical pathways associated with estrogen receptors to broadly inhibit viral replication [61]. Out of the several SERMs predicted through network analysis, toremifene and equilin emerge to be potential repurposed drugs [68].

A study conducted by Liu et al. has shown that romidepsin which is an HDACi has the ability to effectively block the viral entry. Following this, the group conducted more research and discovered that other HDACi such as anobinostat, givinostat hydrochloride monohydrate, CAY10603, and sirtinol were also able to inhibit spike/ACE2 mediated viral entry [72]. Further, trapoxin B, trichostatin A, and vorinostat have also been shown to interact with HDAC1 in diseased brain-SARS-CoV-2 network analysis [61].

Since c-jun signaling has shown to play an important role in neurological manifestations of SARS-CoV-2, inhibition of c-jun can serve as effective treatment. For this purpose, a network analysis reported that melatonin and mercaptopurine can be used as combinatorial drug therapy to inhibit this signaling pathway [68].

Previous studies have revealed that XPO1 inhibition can be used as an effective antiviral therapy, and recent clinical studies using Selinexor which is an XPO1 inhibitor for COVID-19 therapy are also in progress [73]. Thus, more XPO1 inhibitors can be considered for SARS-CoV2 mediated neuromodulation drug repurposing. Some of the candidates could be Verdinexor and guanosine triphosphate. Out of these two, guanosine triphosphate has already been shown to be an effective candidate for drug repurposing by docking experiments carried out by Kumar et al. and Verdinexor has been proven to be effective against influenza and other viruses [61,74–76].

7. Conclusion

In this review, we discussed the ability of SARS-CoV2 to invade the central nervous system and cause neurological symptoms, a fact that is well known but little considered. Sars-COV-2 has the ability to enter the CNS and cause several adverse effects, and managing these

neurological complications offer the potential to reduce mortalities due to comorbidities, and hence, this subject warrants greater research. The evidence presented in the paper shows that there is a link between several molecules being altered by the viral entry and neurological pathology observed upon SARS-CoV-2 infection. These therapeutic targets not only open the possibilities for gaining a better understanding of the mechanisms of SARS-CoV-2 mediated neuromodulation but also present opportunities to repurpose the existing drugs (Figure 4). Hence, this will increase the current understanding of neurological aspects of the SARS-CoV2 infection and also expand the possibilities of management of COVID-19.

8. Expert opinion

The studies conducted so far provide evidence that coronaviruses do have an ability to invade the CNS and cause neuromodulation, however, research is more or less limited to animal models. This fact is particularly relevant for SARS-CoV-2 as the information of its ability to cause neurological complications in humans is very limited. Thus, there is a need to address the basic questions concerning the neuromodulatory properties of SARS-CoV2 utilizing in-vitro as well as in-vivo approaches. More importantly, considering the devastating health consequences of the ongoing pandemic, clinical research should be conducted on an urgent basis. Even though, there are a lot of studies that have well established the neuroinvasive potential of the virus, several questions still remain unanswered, such as whether the neurological complications observed during the acute phase of the disease can lead to long-lasting impacts such as cognitive impairment or chronic epilepsy or not. Further, there is also uncertainty regarding the ability of SARS-CoV2 to establish latent infections which can trigger neurological disorders in the future. These gaps in the research arise due
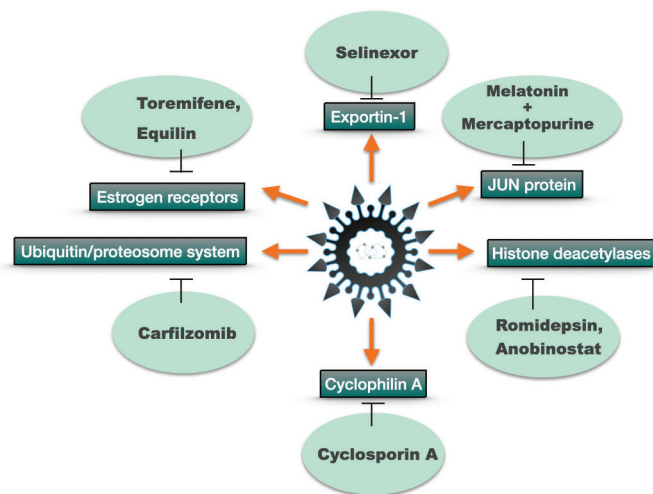
Figure 4. Potential therapeutic targets of SARS-CoV2 mediated neuromodulation The given figure shows the various neuromodulatory targets of SARS-CoV2 and their regulation by repurposable drugs for the effective management of neurological complications. Toremifene and equilin which belong to the category of SERMs have the ability to inhibit the estrogen receptors by utilizing the classical pathways and help inhibit the viral replication. Carfilzomib can inhibit the Ubiquitin proteosome system which is often exploited by SARS-CoV-2 and a modified ubiquitin proteome contributes to the neurological complications observed in the disease. Cyclophilin A which is associated with the cytokine storm observed in the disease as it mediates the glial cytokine release can be inhibited by the use of cyclosporin A. Romidepsin and anobinostat acts as histone deacetylase inhibitors as several HDACs are known to play an important role in the pathogenesis of the disease by regulating the expression of several histone and non-histone proteins. Lastly, a combination of melatonin and mercaptopurine can be used to inhibit the c-jun signaling which is activated upon SARS-CoV-2 contributing to the pathogenesis of the disease as the signaling mediates the effect of several other host proteins known to interact with viral proteins. (SERMs: Selective estrogen receptor modulators).

to the rapid development of the disease and the limited understanding of the biology of the new virus. In such a scenario, to accelerate clinical research previous public health emergencies and evidence from neurotropic respiratory viruses that led to earlier pandemics can be used as indirect evidence and can set a future direction for the ongoing research [52]. Also, systematic reviews employing a comprehensive set of sources can help evaluate the efficacy of research on new treatments. Currently, the ongoing clinical trials are aimed at developing novel therapeutics, preventing the disease, understanding the immune response of the affected individuals and the epidemiology of the disease. These clinical trials have been launched keeping in mind the need for speed and scale and involves enrolling patients in a single randomized trial. One such clinical trial launched by WHO and its partners is Solidarity, under which mortality trials of remdesivir, hydroxychloroquine, lopinavir, and interferon beta-1a showed that these repurposed drugs had little or no effect on the hospitalized patients and thus, these findings refuted the earlier hopes associated with these drugs [77]. The clinical trials conducted to test the efficacy of monoclonal antibodies to prevent COVID-19 infection provided promising results as the research showed that a combination of Bamlanivimab and etesevimab reduces viral load and accelerated recovery [78,79]. The inpatient treatment with the anti-coronavirus immunoglobulin trial that began in 2020, is testing the efficacy of anti-coronavirus hyperimmune intravenous immunoglobulin to augment the natural antibody response [80]. Besides this several clinical trials are also taking place to examine the immune response in hospitalized patients to identify predictors of clinical outcomes and provide recommendations to identify novel targets. A clinical trial conducted by the National institute of neurological disorders and stroke tests the neurological functioning of people who have recovered from COVID-19 but are still experiencing the symptoms, thus such

a clinical trial is expected to provide a better insight into the long-term neurological manifestations of SARS-CoV-2 infection [81].

Another concerning fact is the ongoing mutation in the virus. Indian SARS-CoV-2 Consortium on Genomics (INSACOG) a group consisting of 10 National Laboratories under the Ministry of Health and Family Welfare, India has revealed a total of 771 variants, which includes the B.1.1.7 lineage from the United Kingdom (UK), B.1.351 lineage from South Africa, and P.1 lineage from Brazil [82,83]. N440K is another variant that has been shown to be associated with immune escape. 501Y. V2 is a new variant found in South Africa; however, there is still uncertainty with the severity of the infection caused by this variant. Compared to the existing list of variants (Table 1), the amount of knowledge gained about the neuropathological consequences caused by different strains is limited in nature [82–84]. Thus, looking at the current scenario, it becomes imperative to identify signs and symptoms suggesting brainstem impairment in COVID-19 patients, better characterize the molecular

Table 1. The table summarizes the vaccine efficacy, disease severity, transmissibility, and viral neutralization results of B.1.1.7, 501Y.V2, P.1, and N440K variants of SARS-CoV-The specific mutations in the S gene receptor binding domain are also indicated against each variant.

Name of variant	Mutations	Concern
B.1.1.7	N501Y	Increased transmissibility, Increased severity
501Y.V2	N501Y, E484K, K417N	Increased transmissibility, Increased severity, Reduced Antibody binding and immune protection
P.1	N501Y, E484K	Increased transmissibility, Increased severity, Possible reduction of vaccine effectiveness
N440K	N440K	Increased severity

targets in the CNS that are modulated by SARS-CoV-2 infection, and rationally use the existing drugs to prevent or dampen the neurological complications in COVID-19 patients.

As discussed in the review, there are several therapeutic targets that can be exploited for managing the neurological complications associated with SARS-CoV-2 infection, and to better understand the mechanism of CNS infection. Further, there are several drugs that can be repurposed to therapeutically target the proposed pathways and molecules. However, there are several scientific and regulatory challenges that need to be overcome in order to successfully implement this strategy. There is a need to carefully plan the preclinical and clinical trials, evaluate the benefits of using a drug and also the potential side effects. Computational drug-repurposing approaches can be used to speed up the process, as these will highlight the drugs with the capacity to manage the neurological complications in COVID-19 patients but it is important to consider that the current knowledge about SARS-CoV-2 mediated neurological effects is still limited and hence, the value of basic research cannot be ignored.

Abbreviations

3CLpro	Chymotrypsin-like protease
6-HB	Six-helical bundle
ACE2	Angiotensin-converting enzyme 2
BBB	Blood-brain barrier
CNS	Central Nervous System
COVID-19	Corona Virus Disease-2019
CsA	Cyclosporin A
CYps	Cyclophillins
DMVs	Double-membrane vesicles
DPP4	Dipeptidyl peptidase 4
ERGIC	Endoplasmic reticulum-Golgi intermediate complex
ESR1	Estrogen Receptor 1
FDA	Food and Drug Administration
gRNA	Genomic RNA
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDACi	HDAC inhibitor
HDACs	Histone deacetylases
HIV	Human immunodeficiency virus
HR1	Heptad repeat 1
HR2	Heptad repeat 2
ICTV	International Committee on Taxonomy of Viruses
IL-6	Interleukin 6
iPSCs	Induced pluripotent stem cells
MERS-CoV	Middle East respiratory syndrome coronavirus
Mpro	Main protease
nCoV	Novel coronavirus
NET	Neutrophil extracellular traps
Nsps	Non-structural proteins
ORFs	Open reading frames
RBD	Receptor Binding Domain
RdRp	RNA-dependent RNA polymerase
RNA	Ribonucleic acid
ROS	Reactive oxygen species
RTC	Replicase-transcriptase complex
SARS-CoV	Severe acute respiratory syndrome coronavirus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SERMs	Selective estrogen receptor modulators
sgRNAs	Single guide RNAs
SIRT 7	Sirtuin7
ssRNA	Single stranded RNA
TMPRSS2	Transmembrane protease serine 2
TNFα	Tumor necrosis factor alpha
UPS	Ubiquitin/proteosome system
WHO	World health organisation
XPO-1	Exportin-1

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Coronavirus disease (COVID-19) update [Internet]. [cited 2021 May 25]. Available from: https://www.who.int/bangladesh/emergencies/coronavirus-disease-(covid-19)-update.
2. Liu Y-C, Kuo R-L, Shih S-R. COVID-19: the first documented coronavirus pandemic in history. Biomed J. 2020;43(4):328–333.
3. Cascella M, Rajnik M, Aleem A, et al. Features, Evaluation, and Treatment of Coronavirus (COVID-19). StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 [cited 2021 May 26]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK554776/.
4. From SARS and MERS to COVID-19: a brief summary and comparison of severe acute respiratory infections caused by three highly pathogenic human coronaviruses | respiratory Research | full Text [Internet]. [cited 2021 May 26]. Available from: https://respiratory-research.biomedcentral.com/articles/10.1186/s12931-020-01479-w.
5. Zaim S, Chong JH, Sankaranarayanan V, et al. COVID-19 and Multiorgan Response. Current Problems in Cardiology. Mosby Inc.; 2020;45 (8):100618. DOI: 10.1016/j.cpcardiol.2020.100618.
6. Arbour N, Day R, Newcombe J, et al. Neuroinvasion by Human Respiratory Coronaviruses. J Virol. 2000;74(19):8913–8921.
7. von Weyhern CH, Kaufmann I, Neff F, et al. The Lancet. In: Richard horton, Early evidence of pronounced brain involvement in fatal COVID-19 outcomes. Lancet Publishing Group, 2020. e109.
8. Mao L, Jin H, Wang M, et al. Neurologic Manifestations of Hospitalized Patients with Coronavirus Disease 2019 in Wuhan, China. JAMA Neurol. 2020;77(6):683–690.
9. Varatharaj A, Thomas N, Ellul MA, et al., Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study. Lancet Psychiatry. 7(10): 875–882. 2020.
    •The article provides clinical evidence for neurological complicationsassociated with COVID-19.

10. Romero-Sánchez CM, Díaz-Maroto I, Fernández-Díaz E, et al. Neurologic manifestations in hospitalized patients with COVID-19: the ALBACOVID registry. Neurology. 2020;95(8):e1060–e1070.

11. DeKosky ST, Kochanek PM, Valadka AB, et al. Blood Biomarkers for Detection of Brain Injury in COVID-19 Patients. J Neurotrauma. 2020;43:1–43.

12. de Haan CAM, Kuo L, Masters PS, et al. Coronavirus Particle Assembly: primary Structure Requirements of the Membrane Protein. J Virol. 1998;72(8):6838–6850.

13. Genomic characterization of a newly discovered coronavirus associated with acute respiratory distress syndrome in humans - PubMed [Internet]. [cited 2021 Apr 7]. Available from: https://pubmed.ncbi.nlm.nih.gov/23170002/.

14. Evaluation of modified vaccinia virus Ankara based recombinant SARS vaccine in ferrets - PubMed [Internet]. [cited 2021 Apr 7]. Available from: https://pubmed.ncbi.nlm.nih.gov/15755610/.

15. Coronavirus Genomics and Bioinformatics Analysis [Internet]. [cited 2021 Apr 7]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3185738/.

16. Hamming I, Timens W, Bulthuis MLC, et al. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004;203(2):631–637.

17. Li G, He X, Zhang L, et al. Assessing ACE2 expression patterns in lung tissues in the pathogenesis of COVID-19. J Autoimmun. 2020;112:102463.

18. Xu J, Lazartigues E. Expression of ACE2 in Human Neurons Supports the Neuro-Invasive Potential of COVID-19 Virus. In: Juan M. Saavedra, Cellular and Molecular Neurobiology. 2020. p. 1.

19. Meinhardt J, Radke J, Dittmayer C, et al. Olfactory transmucosal SARS-CoV-2 invasion as a port of central nervous system entry in individuals with COVID-19. In: Nature: Neuroscience. 2020.

20. Chen R, Wang K, Yu J, Howard D, French L, Chen Z, Wen C, Xu Z. The Spatial and Cell-Type Distribution of SARS-CoV-2 Receptor ACE2 in the Human and Mouse Brains. Front Neurol. 2021 Jan 20;11:573095.10.3389/fneur.2020.573095

21. Gheblawi M, Wang K, Viveiros A, et al. Circulation Research. In: Angiotensin-Converting Enzyme 2: SARS-CoV-2 Receptor and Regulator of the Renin-Angiotensin System: celebrating the 20th Anniversary of the Discovery of ACE2. Lippincott Williams and Wilkins, Lippincott Williams & Wilkins Company, 2020. 1456–1474.

22. Andrews MG, Mukhtar T, Eze UC, Simoneau CR, Perez Y, Mostajo-Radji MA, Wang S, Velmeshev D, Salma J, Kumar GR, Pollen AA, Crouch EE, Ott M, Kriegstein AR. Tropism of SARS-CoV-2 for Developing Human Cortical Astrocytes. bioRxiv [Preprint]. 2021. DOI:10.1101/2021.01.17.427024

23. Arbeitman CR, Auge G, Blaustein M, et al. Structural and functional comparison of SARS-CoV-2-spike receptor binding domain produced in Pichia pastoris and mammalian cells. Sci Rep. 2020;10:1–18.

24. Ortega JT, Serrano ML, Pujol FH, et al. Role of changes in SARS-CoV-2 spike protein in the interaction with the human ACE2 receptor: an in silico analysis. EXCLI J. 2020;19:410–417.

25. Walls AC, Park Y-J, Tortorici MA, et al. Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. Cell. 2020;181(2):281–292.e6.

26. Xia S, Liu M, Wang C, et al. Inhibition of SARS-CoV-2 (previously 2019-nCoV) infection by a highly potent pan-coronavirus fusion inhibitor targeting its spike protein that harbors a high capacity to mediate membrane fusion. Cell Res. 2020;30(4):343–355.

27. Shang J, Wan Y, Luo C, Ye G, Geng Q, Auerbach A, Li F. Cell entry mechanisms of SARS-CoV-2. Proc Natl Acad Sci U S A. 2020 May 26;117(21):11727–11734. DOI:10.1073/pnas.2003138117

28. Lukassen S, Chua RL, Trefzer T, Kahn NC, Schneider MA, Muley T, Winter H, Meister M, Veith C, Boots AW, Hennig BP, Kreuter M, Conrad C, Eils R. SARS-CoV-2 receptor ACE2 and TMPRSS2 are primarily expressed in bronchial transient secretory cells. EMBO J. 2020 May 18;39(10):e105114. DOI:10.15252/embj.20105114

29. Astuti I. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): an overview of viral structure and host response. Diabetes Metab Syndrome. 2020;14(4):407–412.

30. Sola I, Almazán F, Zúñiga S, Enjuanes L. Continuous and Discontinuous RNA Synthesis in Coronaviruses. Annu Rev Virol. 2015 Nov;2(1):265–88. DOI:10.1146/annurev-virology-100114-055218

31. Schoeman D, Fielding BC. Coronavirus envelope protein: current knowledge. Virol J. 2019 May 27;16(1):69. DOI:10.1186/s12985-019-1182-0

32. Al Saiegh F, Ghosh R, Leibold A, et al. Status of SARS-CoV-2 in cerebrospinal fluid of patients with COVID-19 and stroke. J Neurol Neurosurg Psychiatry. 2020;91(8):846–848.

33. Tang N, Bai H, Chen X, et al. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020;18(5):1094–1099.

34. Mehta S, Bhandari S, Mehta S. Brain autopsies in fatal COVID-19 and postulated pathophysiology: more puzzling than a Rubik's cube. J Clin Pathol. 2020 Sep 9:jclinpath-2020-206967. DOI:10.1136/jclinpath-2020-206967. Epub ahead of print

35. Ragab D, Salah Eldin H, Taeimah M, et al. The COVID-19 Cytokine Storm; What We Know So Far. Front Immunol. 2020;11:1446.

36. Tang Y, Liu J, Zhang D, et al. Cytokine Storm in COVID-19: the Current Evidence and Treatment Strategies, Front Immunol, Internet]. 2020;11. 10.3389/fimmu.2020.01708.

37. Thepmankorn P, Bach J, Lasfar A, et al. Cytokine storm induced by SARS-CoV-2 infection: the spectrum of its neurological manifestations. Cytokine. 2021;138:155404.
   • **The article describes the association of cytokine storm with neurological complications.**

38. Schurink B, Roos E, Radonic T, et al. Viral presence and immuno-pathology in patients with lethal COVID-19: a prospective autopsy cohort study. Lancet Microbe. 2020;1(7):e290–e299.

39. Chamberlin NL. Functional organization of the parabrachial complex and intertrigeminal region in the control of breathing. Respir Physiol Neurobiol. 2004;143(2–3):115–125.

40. Conti P, Caraffa A, Gallenga CE, et al. Coronavirus-19 (SARS-CoV-2) induces acute severe lung inflammation via IL-1 causing cytokine storm in COVID-19: a promising inhibitory strategy. J Biol Regul Homeost Agents. 2020;34:1971–1975.

41. Mast cells contribute to coronavirus-induced inflammation: new anti-inflammatory strategy. [Internet]. Biolife - Scientific Publisher. 2020 [cited 2021 Jul 5]. Available from: https://www.biolifesas.org/biolife/2020/02/04/mast-cells-contribute-to-coronavirus-induced-inflammation-new-anti-inflammatory-strategy/.

42. Pignataro G, Cataldi M, Taglialatela M. Neurological risks and benefits of cytokine-based treatments in coronavirus disease 2019: from preclinical to clinical evidence. Br J Pharmacol. 2021. 10.1111/bph.15397
   •• **It is an extensive review that covers the evidences from preclinical and clinical studies regarding the neurological effects of the drugs targeting cytokine-mediated inflammation.**

43. Zhao Y, Qin L, Zhang P, et al. Longitudinal COVID-19 profiling associates IL-1RA and IL-10 with disease severity and RANTES with mild disease. JCI Insight. 2020;5(13):e139834.

44. Churink B, Roos E, Radonic T, et al. Viral presence and immuno-pathology in patients with lethal COVID-19: a prospective autopsy cohort study. The Lancet Microbe. 2020;1:e290–e299.

45. Jenne CN, Kubes P. Virus-Induced NETs – critical Component of Host Defense or Pathogenic Mediator? PLoS Pathog. 2015;11(1):1–4.

46. Hidalgo A. A NET-thrombosis axis in COVID-19. Blood. 2020;136(10):1118–1119.

47. Dhont S, Derom E, Van Braeckel E, et al. Respiratory Research. In: Robert Bals, The pathophysiology of "happy" hypoxemia in COVID-19. BioMed Central Ltd, 2020. 198.

48. Sharifian-Dorche M, Huot P, Osherov M, et al. Neurological complications of coronavirus infection; a comparative review and lessons

learned during the COVID-19 pandemic. J Neurol Sci. 2020;417:117085.

49. Liver injury in COVID-19: management and challenges - The Lancet Gastroenterology & Hepatology [Internet]. [cited 2021 Jul 5]. Available from: https://www.thelancet.com/journals/langas/article/PIIS2468-1253(20)30057-1/fulltext.

50. Bobermin LD, Quincozes-Santos A. COVID-19 and hyperammonemia: potential interplay between liver and brain dysfunctions. Brain Behav Immun Health. 2021;14:100257.

51. Zhang B-Z, Chu H, Han S, et al. SARS-CoV-2 infects human neural progenitor cells and brain organoids. Cell Res. 2020;30(10):928–931.

52. Erausquin GA, De, Snyder H, Carrillo M, et al. The chronic neuropsychiatric sequelae of COVID-19: the need for a prospective study of viral impact on brain functioning. Alzheimers Dement. 2021;17 (6):1056–1065.

53. Frontera JA, Yang D, Lewis A, et al. A prospective study of long-term outcomes among hospitalized COVID-19 patients with and without neurological complications. J Neurol Sci. Internet]. 2021;426. Available from:. https://www.jns-journal.com/article/S0022-510X(21)00180-5/abstract

•• **One of the first prospective studies to assess the long term neurological outcomes of COVID-19 infection.**

54. Wang P, Heitman J. The cyclophilins. Genome Biol. 2005;6(7):226.

55. Cyclophilin inhibition as potential therapy for liver diseases - ScienceDirect [Internet]. [cited 2021 May 21]. Available from: https://www.sciencedirect.com/science/article/pii/S0168827814004772.

56. Tribouillard-Tanvier D, Carroll JA, Moore RA, et al. Role of Cyclophilin A from Brains of Prion-infected Mice in Stimulation of Cytokine Release by Microglia and Astroglia in Vitro. J Biol Chem. 2012;287(7):4628–4639.

57. De Wilde AH, Zevenhoven-Dobbe JC, van der Meer Y, et al. Cyclosporin A inhibits the replication of diverse coronaviruses. J Gen Virol. 2011;92(11):2542–2548.

58. Inhibition of SARS-CoV-2 Infection by the Cyclophilin Inhibitor Alisporivir (Debio 025) | antimicrobial Agents and Chemotherapy [Internet]. [cited 2021 May 21]. Available from: https://aac.asm.org/content/64/7/e00876-20.

59. Rao G, Croft B, Teng C, et al. Ubiquitin-Proteasome System in Neurodegenerative Disorders. J Drug Metab Toxicol. [Internet]. 2015;6. Available from:. ;. : https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6370320/

60. Zhang H, Zheng H, Zhu J, et al. Ubiquitin-Modified Proteome of SARS-CoV-2-Infected Host Cells Reveals Insights into Virus–Host Interaction and Pathogenesis. J Proteome Res. 2021;20(5):2224–2239.

61. Prasad K, AlOmar SY, Alqahtani SAM, et al. Brain Disease Network Analysis to Elucidate the Neurological Manifestations of COVID-19. Mol Neurobiol. 58(5): 1875–1893. 2021.

•• **A systemic approach has been employed by the authors to study the genetic association between COVID-19 and various brain disorders which provides a molecular insight into the neurological manifestations of the disease.**

62. Stilhano RS, Costa AJ, Nishino MS, et al. SARS-CoV-2 and the possible connection to ERs, ACE2, and RAGE: focus on susceptibility factors. FASEB J. Internet]. 2020; 10.1096/fj.202001394RR

63. Nampoothiri S, Sauve F, Ternier G, et al. The hypothalamus as a hub for SARS-CoV-2 brain infection and pathogenesis. bioRxiv. 2020;2020.06.08.139329.

64. Kumar S, Attrish D, Srivastava A, et al. Non-histone substrates of histone deacetylases as potential therapeutic targets in epilepsy. Expert Opin Ther Targets. 2021;25(1):75–85.

65. Teodori L, Sestili P, Madiai V, et al. MicroRNAs Bioinformatics Analyses Identifying HDAC Pathway as a Putative Target for Existing Anti-COVID-19 Therapeutics. Front Pharmacol. Internet]. 2020;11. Available from. ;. https://www.frontiersin.org/articles/10.3389/fphar.2020.582003/full

• **The study provides a network based approach to rapidly discover the drugs that can be repurposed for coronavirus treatment.**

66. Herdegen T, Waetzig V. AP-1 proteins in the adult brain: facts and fiction about effectors of neuroprotection and neurodegeneration. Oncogene. 2001;20(19):2424–2437.

67. Tajiri N, Peña IDL, Acosta SA, et al. A Nuclear Attack on Traumatic Brain Injury: sequestration of Cell Death in the Nucleus. CNS Neurosci Ther. 2016;22(4):306–315.

68. Zhou Y, Hou Y, Shen J, et al. Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2. Cell Discov. 2020;6(1):1–18.

69. Liu C, von Brunn A, Zhu D. Cyclophilin A and CD147: novel therapeutic targets for the treatment of COVID-19. Med Drug Discover. 2020;7:100056.

70. Lindner HA, Fotouhi-Ardakani N, Lytvyn V, et al. The papain-like protease from the severe acute respiratory syndrome coronavirus is a deubiquitinating enzyme. J Virol. 2005 Dec;79(24):15199–208. DOI:10.1128/JVI.79.24.15199-15208.2005

71. Wang J. Fast Identification of Possible Drug Treatment of Coronavirus Disease -19 (COVID-19) Through Computational Drug Repurposing Study. ChemRxiv J Chem Inf Model. 2020 Feb 21. DOI: 10.26434/chemrxiv.11875446.

72. Liu K, Zou R, Cui W, et al. Clinical HDAC Inhibitors Are Effective Drugs to Prevent the Entry of SARS-CoV2. ACS Pharmacol Transl Sci. 2020;3(6):1361–1370.

73. Uddin M, Zonder JA, Azmi AS. Exportin 1 inhibition as antiviral therapy. Drug Discov Today. 2020;25(10):1775–1781.

74. Perwitasari O, Johnson S, Yan X, et al. Verdinexor, a Novel Selective Inhibitor of Nuclear Export, Reduces Influenza A Virus Replication In Vitro and In Vivo. J Virol. 2014;88(17):10228–10243.

75. Widman DG, Gornisiewicz S, Shacham S, et al. In vitro toxicity and efficacy of verdinexor, an exportin 1 inhibitor, on opportunistic viruses affecting immunocompromised individuals. PLOS ONE. 2018;13(10):e0200043.

76. Kumar A, Saxena AK, Lee GG, et al. Rational Drug Design and Docking of the RNA Dependent RNA Polymerase Domain of NCoV. In: Kumar A, Saxena AK, Lee GG, et al. editors. Novel Coronavirus 2019: in-silico Vaccine Design and Drug Discovery [Internet]. Singapore:Springer; 2020:37–46. Available from 10.1007/978-981-15-7918-9_5

77. Consortium WST. Repurposed Antiviral Drugs for Covid-19 — interim WHO Solidarity Trial Results. N Engl J Med. [Internet]. 2020 Available from]. https://www.nejm.org/doi/full/10.1056/NEJMoa2023184

78. Gottlieb RL, Nirula A, Chen P, et al. Effect of Bamlanivimab as Monotherapy or in Combination With Etesevimab on Viral Load in Patients With Mild to Moderate COVID-19: a Randomized Clinical Trial. JAMA. 2021;325(7):632–644.

79. Chen P, Nirula A, Heller B, et al. SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19. N Engl J Med. 2021;384 (3):229–237.

80. Inpatient Treatment of COVID-19 With Anti-Coronavirus Immunoglobulin (ITAC) - Full Text View - ClinicalTrials.gov [Internet]. [cited 2021 Jul 5]. Available from: https://clinicaltrials.gov/ct2/show/NCT04546581.

81. National Institute of Neurological Disorders and Stroke (NINDS). An Observational Study of Neurologic Function After COVID-19 Infection [Internet]. clinicaltrials.gov 2021 [cited 2021 Jul 1]. Report No.: NCT04564287. Available from: https://clinicaltrials.gov/ct2/show/NCT04564287.

82. Science Brief: emerging SARS-CoV-2 Variants. CDC [Internet]. [cited 2021 Apr 7]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/scientific-brief-emerging-variants.html.

83. WHO. SARS-CoV-2 Variants [Internet]. [cited 2021 Apr 7]. Available from: https://www.who.int/csr/don/31-december-2020-sars-cov2-variants/en/.

84. Wanner M The emergence of SARS-CoV-2 variants sparks concern [Internet]. The Jackson Laboratory. [cited 2021 May 26]. Available from: https://www.jax.org/news-and-insights/2021/february/new-coronavirus-variants-spark-concerns.