Role of neuroinflammation mediated potential alterations in adult neurogenesis as a factor for neuropsychiatric symptoms in Post-Acute COVID-19 syndrome—A narrative review

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ABSTRACT

Persistence of symptoms beyond the initial 3 to 4 weeks after infection is defined as post-acute COVID-19 syndrome (PACS). A wide range of neuropsychiatric symptoms like anxiety, depression, post-traumatic stress disorder, sleep disorders and cognitive disturbances have been observed in PACS. The review was conducted based on PRISMA-S guidelines for literature search strategy for systematic reviews. A cytokine storm in COVID-19 may cause a breach in the blood brain barrier leading to cytokine and SARS-CoV-2 entry into the brain. This triggers an immune response in the brain by activating microglia, astrocytes, and other immune cells leading to neuroinflammation. Various inflammatory biomarkers like inflammatory cytokines, chemokines, acute phase proteins and adhesion molecules have been implicated in psychiatric disorders and play a major role in the precipitation of neuropsychiatric symptoms. Impaired adult neurogenesis has been linked with a variety of disorders like depression, anxiety, cognitive decline, and dementia. Persistence of neuroinflammation was observed in COVID-19 survivors 3 months after recovery. Chronic neuroinflammation alters adult neurogenesis with pro-inflammatory...
cytokines suppressing anti-inflammatory cytokines and chemokines favouring adult neurogenesis. Based on the prevalence of neuropsychiatric symptoms/disorders in PACS, there is more possibility for a potential impairment in adult neurogenesis in COVID-19 survivors. This narrative review aims to discuss the various neuroinflammatory processes during PACS and its effect on adult neurogenesis.

Subjects  Anatomy and Physiology, Immunology, Neurology, Psychiatry and Psychology, COVID-19
Keywords  Post-acute COVID-19 syndrome, Neuroinflammation, COVID-19, SARS-CoV-2, Neurogenesis, Cytokine storm, Astrocyte, Microglia

INTRODUCTION
The first case of COVID-19 caused by SARS-COV-2 virus was reported in Wuhan, China on 31st December 2019 and since then the disease has spread to 228 countries throughout the globe (Worldometer, 2022). The incubation period of the SARS-COV-2 virus ranges between 5.1 and 11.5 days with most people developing symptoms after 14 days of active monitoring or quarantine (Lauer et al., 2020). The severity of this disease has a wide range with symptoms like fever, cold, cough, breathing difficulty, pneumonia, other body systems failure and even death has been noted in very severe cases of COVID-19 (WHO, 2022). People with younger age mostly act as asymptomatic carriers whilst the older age group is the most vulnerable group with high severity and mortality (Nuzzo et al., 2021). People with older age (greater than 60 years), pregnancy, chronic pulmonary disease conditions, diabetes and hypertension, cardiovascular diseases and health care workers are high-risk groups for COVID-19 (Ceriello, Stoian & Rizzo, 2020; Huang et al., 2020; WHO, 2022; Wiersinga et al., 2020; Zhou et al., 2020).

Acute COVID-19 has been defined as the period that extends from the onset of symptoms to 3 to 4 weeks. Any symptoms persisting beyond this period are categorized as post-acute COVID-19, where the SARS-COV-2 virus is not detectable (Nalbandian et al., 2021). Similar patterns of persistence of symptoms have been noted previously during the SARS epidemic and MERS outbreak (Ahmed et al., 2020; Hui et al., 2005). A thorough understanding of this phenomenon is vital for the prognosis of the patients as well as to equip healthcare settings to aid in diagnosis and treatment. The post-acute COVID-19 syndrome (PACS) involves multiple organ systems (Nalbandian et al., 2021) and the pathophysiology is held to be different from that of acute COVID-19 (Dixit et al., 2021). Garg et al. (2020) state that PACS is the persistence of symptoms which is sought to be linked with residual inflammation from the convalescent phase of viral replication, organ damage, extended ventilation, or idiopathic (nonspecific) effects of hospitalization. PACS is observed not only in those who had severe forms of COVID-19 but also in outpatients (Montani et al., 2022).

Neuropsychiatric symptoms during the acute stage as well as post-acute COVID-19 are not uncommon ranging from cognitive impairment, delirium, mood changes, and extreme fatigue (Rubin, 2020; Woo et al., 2020). Incidences of dementia, anxiety, and insomnia were noted even after 3 months post-infection (Czeisler et al., 2020). Various studies that
assessed the neuropsychiatric symptoms, 14 days to 6 months following acute COVID-19, noted a higher prevalence of symptoms of insomnia, anxiety, depression, and PTSD (Montani et al., 2022). There is conflicting evidence concerning the association between disorders. Several studies showed the relation between the two while several others could not replicate this result (Montani et al., 2022). Though the etiology for such long-lasting effects on the neuropsychiatric facet is still being studied and ever evolving, a few intricate mechanisms have been postulated in the literature. Some of them include biological and environmental factors (Nakamura et al., 2021), virus-induced autoimmunity (Achar & Ghosh, 2020), coagulopathy leading to multi-organ system failure (Achar & Ghosh, 2020), and direct viral infiltration into the nervous system through ACE2 receptor (Gupta et al., 2021; Saikarthik, Saraswathi & Al-Atram, 2021). In an interesting study by Yapici-Eser et al. (2021), it was proposed that SARS-COV-2 proteins mainly the non-structural protein group (NSP) and spike protein mimic various growth factors, such as FGF (1, 2, 4 types), VEGF2, GDNF, IGF, etc. It was hypothesized that such protein mimicking interactions could potentially be associated with neuropsychiatric disorders and variation in risk factors could trigger different pathways presenting with different phenotypes of the disease (Yapici-Eser et al., 2021).

Rationale for the study
Several mechanisms have been proposed previously in the etiology of neuropsychiatric disorders. However, the neuropsychiatric symptoms in PACS and their impact is believed to have long-term consequences which is not much explored. Neuroinflammation has been known to affect cognition, behaviour by means of disrupted BBB, neurotransmission and also by means of impaired neurogenesis (Klein et al., 2021). This narrative review reviews the available literature to address the possible mechanism of COVID-19-induced neuroinflammation as a cause for the various neuropsychiatric symptoms and also to explore the plausible association of impaired neurogenesis in PACS. This timely summary of recent developments would provide a definitive path to researchers, to better understand the pathophysiological basis which would aid in managing the neuropsychiatric symptoms during PACS.

Survey methodology
This study used the narrative review method along with PRISMA-S, which is an extension of PRISMA guidelines for reporting literature search strategies in systematic reviews (Rethlefsen et al., 2021). Due to the scarcity of studies on the effect of COVID-19 on adult neurogenesis, as well as lack of homogeneity in the already published literature, a narrative review style was chosen (Harvey, Schofield & Williden, 2018). Electronic searches were made in databases such as Pubmed, Cochrane, Scopus, Web of Science, Google scholar, and ResearchGate as well as preprint databases such as medRxiv and Research Square. General Google searches were done to report the latest number of COVID-19 cases globally. Being a narrative review, multiple combinations of words were used as search strategies. Some of the words that were used included “SARS-CoV-2”, “COVID-19”, “adult neurogenesis”, “adult hippocampal neurogenesis”, “neuroinflammation”, “hippocampus”,
“neuropsychiatric symptoms”, “neuropsychiatric disorders”, “Post-Acute COVID-19 syndrome”, “long COVID-19”, etc. A combination of these words were also used, for example, “neuroinflammation and COVID-19”, “neurogenesis and SARS-CoV-2”. In addition, author names and a list of references were used for search of related references. The last search in the above-mentioned databases was made on 15.06.2022. After reading the abstracts those articles that did not match the requirements of this narrative review were excluded. Articles and preprints in the English language in both clinical and pre-clinical studies were included in this narrative review. Any duplication of articles was removed using the EndNote reference manager (Version 20).

RESULTS

Neuropsychiatric symptoms/disorders in PACS

Survivors of earlier infections caused by other coronaviruses like MERS and SARS presented with an increased risk of neuropsychiatric disorders like anxiety, depression, and PTSD (Hopkins et al., 1999; Rogers et al., 2020). Cognitive decline, decreased mental processing speed, and impairment in memory, attention, and concentration were observed in SARS survivors 1 year after the onset of the disease (Hopkins et al., 1999). A comprehensive systematic review by Rogers et al. (2020) found that out of the 20 neurological and neuropsychiatric complications of COVID-19 that were studied, non-specific symptoms like headache (20.7% (16.1–26.1%)) and anosmia (43.1% (35.2–51.3%)) and core psychiatric disorders of depression (23% (11.8–40.2%)) and anxiety (15.9% (5.6–37.7%)) were found to be highly prevalent. The non-specific symptoms like anosmia, dysgeusia, weakness, and fatigue were the most common, occurring in more than 30% of the patients (Rogers et al., 2020). Many of these complications are capable of becoming a chronic condition and many of the symptoms in PACS could be a continuation of those from the acute phase of the disease (Carfì, Bernabei & Landi, 2020). Survivors of critical illness after discharge from the hospital were found to have a higher prevalence of neuropsychiatric disorders like depression, anxiety, and PTSD (Nikayin et al., 2016; Parker et al., 2015; Rabiee et al., 2016). Most of the neuropsychiatric symptoms of COVID-19 were found to be common in patients with milder forms of the disease (Rogers et al., 2020). Thus, the neuropsychiatric symptoms/disorders are observed in survivors of COVID-19 irrespective of the disease severity which can become chronic.

SARS-CoV-2 entry into the brain

SARS-CoV-2 is a beta coronavirus, a positive sense single stranded RNA virus. Its surface is enveloped with crown-like spikes like other coronaviruses. The spike protein which is responsible for host specificity and tissue tropism is a type-1 glycoprotein. It includes two subunits, S1 for host receptor binding and S2 for the fusion of viral and host cell membrane (Gallagher & Buchmeier, 2001). The cell receptor through which SARS-CoV-2 binds to the host is the ACE2 receptor. The S1 subunit binds with the ACE2 receptor followed by the fusion of S1 to the cell membrane which is mediated by S2. Priming/cleavage of the S1 and S2 subunits is performed by TMPRSS2, a serine protease that is a member of the Hepsin/TMPRSS subfamily (Hoffmann et al., 2020).
SARS-CoV-2-associated central nerve system (CNS) disease has complex and varied pathogenesis. The propensity of the virus to enter the CNS is widely studied. There are three possible routes of viral entry into CNS viz. transmucosal invasion, hematogenous spread, and retrograde neuronal dissemination (Pezzini & Padovani, 2020). SARS-CoV-2 can cross the neural-mucosal interface by infecting the olfactory neurons or diffuse through the channels that are formed by the ensheathing cells of olfactory mucosa and enter the CNS. The virus then may travel along the olfactory tract and reach different areas of the brain connected to it by axonal transport, trans-synaptic transport, or microfusion (Meinhardt et al., 2021; Van Riel, Verdiel & Kuiken, 2015). SARS-CoV-2 can breach the peripheral nerve terminals and can reach the CNS through the trans-synaptic route. It can invade peripheral chemoreceptors and cranial nerves and reach the brain stem (Li, Bai & Hashikawa, 2020). SARS-CoV-2 can also likely enter CNS through gut-brain axis via the enteric nerves (Esposito et al., 2020; Shi et al., 2021). In the hematogenous spread, the virus disseminates the circulation and may breach the blood-brain barrier or blood-CSF barrier to enter the brain or through circumventricular organs that lack blood brain barrier (BBB) (Pezzini & Padovani, 2020). In the Trojan horse mechanism, virus-infected leucocytes may cross the BBB to enter CNS (Desforges et al., 2020) (Fig. 1).

**Immune response in COVID-19**

A cytokine storm is currently considered to be the trademark attribute of the pathogenesis of COVID-19. It is a destructive systemic hyperinflammatory response. It involves autocrine and paracrine activation of various immune cells such as mast cells, macrophages, leucocytes, and endothelial cells which causes increased levels of chemokines and pro-inflammatory cytokines like interleukin-6 (IL-6), IL-1β, IL-8, tissue necrosis factor-alpha (TNF-α), chemokine (C-C-motif) ligand 2 (CCL2), CCL5, IL-17, IL-18, IL-33, CXCL-10, interferon-γ (IFN-γ), and granulocyte-colony stimulating factor (G-CSF) (Azkur et al., 2020; Kempuraj et al., 2020; Li et al., 2020; Nile et al., 2020). SARS-CoV-2 infection activates both immediate and late immune responses in the body. SARS-CoV-2 being a novel coronavirus, there is no prior exposure for the human immune system to this virus and hence it is the innate immune system that acts as the first line of defence (Serrano-Castro et al., 2020). The precise mechanism of immune response to SARS-CoV-2...
is not yet fully understood. SARS-CoV-2 which enters the body gets attacked by innate immune cells and the severity of the disease will depend on the capacity of the innate immune system to ward off the virus (Zhu et al., 2020). Coronaviruses are capable of facilitating innate immune suppression and inhibiting adaptive immunity (Oh et al., 2016). Mast cells, macrophages/monocytes, natural killer cells, neutrophils, T lymphocytes, and resident tissue endothelial and epithelial cells are the innate immune cells that get activated by SARS-CoV-2 and are responsible for the cytokine storm in lungs (Azkur et al., 2020; Kempuraj et al., 2020; Kritas et al., 2020). From the initial infection and lysis of the cells (mostly pneumocytes), DAMPs (damage-associated molecular patterns) and PAMPs (pathogen-associated molecular patterns) are produced which activate the innate immune system. DAMPs include cellular contents released from dying cells and proteins released following tissue injury like heat shock protein, heparin sulphate, hyaluronan fragments and PAMPs (pathogen-associated molecular patterns) include oxidized phospholipids and viral RNAs (Imai et al., 2008; Kuipers et al., 2011). These activated immune cells release various pro-inflammatory cytokines, chemokines, proteases, and histamine which help the immune system to fight off the viral infection by recruiting and activating other innate and adaptive immune cells and antiviral gene expression programs (Vardhana & Wolchok, 2020). However, excess activation of these immune cells causes a worsening of the inflammatory response and an increase in the disease severity (Kempuraj et al., 2020). Lymphopenia induced by cytokine storm impairs the adaptive immune system to produce anti-viral antibodies which is critical in the clearance of the virus (Manjili et al., 2020). Cytokine storm and sustained systemic inflammatory response cause acute respiratory distress syndrome (ARDS), multiple organ failure, and death in COVID-19 patients (Li et al., 2020).

An increase in pro-inflammatory Th17 cells and lymphopenia associated with decreased CD4+ T cells, CD8+ T cells, and natural killer cells, and increased cytokine levels (IL-6, IL-10, and TNF-α) were observed in COVID-19 patients (Pedersen & Ho, 2020). The cytokine levels increased during the disease process and declined during the recovery period. Increased levels of IL-6 correlate with mortality and the need for ventilator support (Vardhana & Wolchok, 2020). Patients who are clinically deteriorating were found to present with progressive depletion of lymphocytes while the clinical recovery was preceded by a recovery in lymphocyte count (Chen et al., 2020). The increased levels of IL-6 can further upregulate the cytokine storm in COVID-19 patients. Thus, lymphopenia and the level of cytokine storm are considered to be the markers for COVID-19 which helps to assess and predict disease severity and mortality in COVID-19 patients (Debuc & Smadja, 2021; Kempuraj et al., 2020).

**Neurovascular unit and neuroinflammation**

Inflammation is the early tissue response to an insult or injury or pathogenic invasion. Neuroinflammation is the inflammatory process in the central nervous system (CNS), which is primarily due to the activation of astrocytes and microglial cells. Astrocytes develop from radial glial cells in due course of neuronal differentiation (Barry & McDermott, 2005) whereas microglia are developed from erythroid-myeloid progenitor...
Microglial cells, the blood-brain barrier (BBB), neurons and the extracellular matrix forms the neurovascular unit (NVU) \cite{DelZoppo2010}. The blood-brain barrier varies across each part of the CNS primarily depending on factors such as requirements of the brain region and the diameter of the blood vessel \cite{Rhea&Banks2019}. The NVU responds to an insult/injury which can lead to disruption of BBB, infiltration of leucocytes, release of inflammatory factors, and activation of microglia & astrocytes \cite{Mraasko&Veltkamp2014}. Recent studies have shown that microglia and astrocytes exist in a continuum of two extremes as two different phenotypes. Thus, both these cells have pro-inflammatory and anti-inflammatory phenotypes which depend on the signals received by these cells \cite{Jha,Lee&Suk2016}.

The extracellular and intracellular signals influence the phenotype of microglia. The pro-inflammatory phenotype of microglia (M1) has been known to increase the level of tumor necrosis factor (TNF), IL-1\(\beta\) (interleukin 1 beta), IL-6, and IFN-\(\gamma\). The release of these inflammatory mediators causes neurotoxicity (by excitotoxicity), neurodegenerative diseases (increased immune activation), and cytotoxicity (release of reactive oxygen species) \cite{Block, Zecca & Hong, 2007; Jha, Lee & Suk, 2016; Smith et al., 2012}. On the other hand, the anti-inflammatory phenotype (M2) causes a release of transforming growth factor (TGF), IL-10, IL-13, and IL-4 which provides neuroprotection, a release of trophic factors, and resolution of neuroinflammation \cite{Jha, Lee & Suk, 2016; Orihuela, McPherson & Harry, 2016; Wang et al., 2015}. Conditions such as hypoxia or ischemia cause activation of astrocytes called “reactive astrocytes” which has a distinct morphology \cite{Faulkner et al., 2004}. These astrocytes release a wide variety of pro-inflammatory and anti-inflammatory cytokines, and chemokines \cite{John, Lee & Brosnan, 2003}. Similar to microglia, astrocytes also exist in two phenotypic forms viz. Pro-inflammatory astrocyte (A1) and anti-inflammatory astrocyte (A2) which has diverse effects on the NVU \cite{Fan & Huo, 2021}. A1 phenotype secretes pro-inflammatory cytokines such as TNF-\(\alpha\), IL-1\(\beta\), IL-6, nitric acid, ROS, and glutamate. The A2 phenotype produces neurotrophic factors, thrombospondins, and IL-10 which act as anti-inflammatory mediators (neuroprotective) \cite{Fan & Huo, 2021; Jha, Lee & Suk, 2016}.

**Neuroinflammation in COVID-19**

The cytokine storm in COVID-19 causes disruption of blood-brain barrier and intracranial cytokine storm \cite{Coperchini et al., 2020; Serrano-Castro et al., 2020}. Through the disrupted blood-brain barrier, the infiltration of immune cells, and inflammatory cytokines into the brain occurs. This is also one of the pathways of entry of SARS-CoV-2 into the brain. All these activate glial cells, endothelial cells, neurons, mast cells, and other immune cells which trigger neuroinflammatory processes \cite{Coperchini et al., 2020; Kempuraj et al., 2020; Serrano-Castro et al., 2020}. SARS-CoV-2 can also enter the cerebral circulation from systemic circulation and attach to ACE2 which is abundant in foot processes of astrocytes, microglia, pericytes, and endothelial cells which are the main cellular element of the blood-brain barrier \cite{Hernández et al., 2021}. This process is aided by the sluggish blood flow in cerebral microcirculation, resulting in the disruption of BBB. This in turn will facilitate the entry of SARS-CoV-2 into neurons and glial cells where it
can infect and replicate and cause neuroinflammation and neurodegeneration. Thus, SARS-CoV-2 can not only exacerbate pre-existing neuroinflammatory and neurodegenerative conditions but also cause neuroinflammatory and neurodegenerative disorders (Baig et al., 2020).

Another possible mechanism by which the pathologic changes in COVID-19 can cause neuroinflammation could be due to a potential dysregulation of renin angiotensin system (RAS). As mentioned earlier, ACE2 plays a major role in the regulation of RAS. There are two arms/axis in RAS, one is the pro-inflammatory and pro-fibrotic arm, and the other is the anti-inflammatory and anti-fibrotic arm. A variety of proteins and enzymes are involved in the RAS. Angiotensinogen is the precursor that gets converted to Angiotensin-I (Ang-I) by renin. Angiotensin-converting enzyme (ACE) converts Ang-I to Angiotensin-II which acts via AT1 (primary mediator) and AT2 receptors to cause vasoconstriction, increase in vascular permeability, inflammation, angiogenesis, thrombosis, and fibrosis. This arm (ACE/Ang-II/AT1) is the pro-inflammatory and pro-fibrotic arm. ACE2 on the other hand inactivates Ang-II by converting it to its antagonistic peptide, Ang (1-7) which binds with Mas receptors and causes vasodilation, and anti-apoptotic, anti-proliferative, anti-inflammatory effects, and attenuates the signal cascade produced by Ang-II. This arm (ACE2/Ang (1-7)/Mas receptor) is the anti-inflammatory and anti-fibrotic arm (Rice et al., 2004). It is also believed to exhibit anxiolytic and antidepressant effects (de Melo & Almeida-Santos, 2020). A balance in the ACE/ACE2 ratio is critical to maintain an equilibrium between the two arms of RAS. An imbalance in the ACE/ACE2 ratio was implicated in various pathological conditions including Alzheimer’s disease, pulmonary hypertension, cardiovascular, and renal pathology (Bernardi et al., 2012; Kehoe et al., 2016; Lavrentyev & Malik, 2009; Yuan et al., 2015). SARS-CoV-2 induced downregulation of ACE2 depletes the key component of the protective arm of RAS which could result in an unrestrained activation of the deleterious pro-inflammatory and pro-fibrotic arm of RAS. Dysregulation of RAS in the brain is linked with neuroinflammation (Labandeira-Garcia et al., 2017; Rodriguez-Perez et al., 2016). Overactivation of RAS by augmentation of local AT1 receptors was found to exacerbate neuroinflammation (Grammatopoulos et al., 2007; Rodriguez-Pallares et al., 2008; Villar-Cheda et al., 2012).

**SARS-COV-2, astrocytes, and microglial interaction**

Microglia is a vital innate component of the CNS and astrocytes act as mediators for the SARS-COV-2 infection. Microglia provides anti-viral responses in mild cases and produces neurotoxic effects in severe cases of COVID-19. An increase of pro-inflammatory cytokines caused by both these glial cells can amplify the neuroinflammation and lead to impairment in neurological functions in COVID-19 patients (Vargas et al., 2020). Further, cellular cross-talks between astrocyte, microglia, and endothelial cells are implicated in maintaining the cytokine microenvironment in COVID-19 patients (Matias, Morgado & Gomes, 2019; Vargas et al., 2020). Owing to the important functions of both astrocyte and microglia in homeostasis and during viral episodes, it is highly possible for the involvement of these cells in the post-acute phase of SARS-COV-2 infection.
Adult neurogenesis

There are several contradictory pieces of evidence on adult neurogenesis in humans mainly spurred by the lack of direct evidence from live human subjects (Berger, Lee & Thuret, 2020).

The formation of new neurons in the adult brain from neural stem cells and neural progenitor stem cells is called neurogenesis. During embryonic development, it is involved in the formation of the brain, and in the adult brain, it persists in certain areas of specialized microenvironment called the neurogenic niche. The neurogenic niche plays a crucial role in the maintenance and regulation of neural stem cell proliferation and contains various trophic factors, hormones, vasculature, and glial cells that enhance neurogenesis (Mu, Lee & Gage, 2010). New neurons are generated by the neurogenic niche throughout adult life in response to both physiological and pathological stimuli (Fan & Pang, 2017). Neurogenesis involves the generation of new neurons, glial cells, oligodendrocytes, and astrocytes. It is a complex process that includes cellular proliferation, differentiation, survival, and integration. There are numerous intrinsic and extrinsic factors that regulate neurogenesis in an integrated manner. The events in neurogenesis occur in two phases, the early phase of proliferation, fate commitment, and cellular migration and the late phase of development of synaptic circuitry and survival of the neurons (Pathania, Yan & Bordey, 2010). The subventricular zone (SVZ) of lateral ventricles and the subgranular zone (SGZ) of the dentate gyrus of the hippocampus are the two sites of adult neurogenesis (Toda et al., 2019).

The stem cells in the subgranular zones get differentiated into neural progenitor cells which become immature neurons and then mature neurons. However, only 15–30% of immature neurons survive the maturation process. The survived mature neurons become granule cells whose axons form the mossy fibers extending to the hilus and CA3 region and their dendrites in the molecular layer receive connections from the entorhinal cortex. Over a period of several weeks, they show increased synaptic plasticity and become indistinguishable from other older granule cells (Kempermann, Song & Gage, 2015). Newborn neurons at the subventricular zone migrate to the striatum and they differentiate to form striatal interneurons and in rodents, they migrate along the rostral migratory stream (RMS) and differentiate to form interneurons of the olfactory bulb (Shohayeb et al., 2018). Neurogenesis in the hippocampus is a unique form of brain plasticity that plays a crucial role in memory, learning, pattern separation, and cognitive flexibility.

Dysregulation of adult neurogenesis in the hippocampus is associated with psychiatric symptoms and cognitive decline in psychiatric and neurological disorders (Toda et al., 2019). In addition to the role of neurogenesis in physiological conditions, the newly generated neurons also move to sites of brain injury and form the endogenous repair system (Apple, Fonseca & Kokovay, 2017). It has been found that apart from SGZ and SVZ, certain areas of the adult brain like the neocortex, tegmentum, substantia nigra, amygdala, brainstem, and spinal cord also retain some neurogenic potential. However, more explorations are needed to confirm this and elucidate the functional significance (Fan & Pang, 2017) (Fig. 2).
Why adult neurogenesis is important in relation to COVID-19 and PACS?

Research studying adult neurogenesis in COVID-19 and COVID-19 survivors is scarce. However, extrapolation of the results of some recent studies allows for a speculation that adult neurogenesis can have a role to play in the neuropsychiatric symptoms/disorders in COVID-19 and PACS.

Firstly, neuropsychiatric disorders like depression, anxiety, and PTSD are found to be prevalent in COVID-19 survivors (Rogers et al., 2020; Tu et al., 2021). Recent studies postulate a potentially increased risk of developing and/or worsening existing neurodegenerative disorders like Alzheimer’s disease and Parkinson’s disease in COVID-19 patients (Brundin, Nath & Beckham, 2020; Ciaccio et al., 2021; Leta et al., 2021; Sulzer et al., 2020). One of the common features of these neuropsychiatric conditions is that they correlate well with cognitive deficits, mood dysregulation, and a reduction in hippocampal volume and they display impaired adult neurogenesis (DeCarolis & Eisch, 2010).

Secondly, brain imaging studies revealed a negative correlation between hippocampal grey matter volume and loss of memory, and severity of post-traumatic stress syndrome (PTSS) in COVID-19 survivors (Lu et al., 2020; Tu et al., 2021). Memory acquisition depends on newborn neurons and a decrease in adult hippocampal neurogenesis is implicated in the impairment of acquisition of memory (Misane et al., 2013; Recinto et al., 2012). Though the studies found an increase in gray matter volume in COVID-19 survivors 3 months and 1 year after their recovery, it could be attributed to the ongoing nature of the traumatic event of the pandemic with elevated levels of stress and anxiety and a compensatory response (Lu et al., 2020; Tu et al., 2021).
Thirdly, anosmia is a key feature of acute COVID-19 and is also observed in PACS (Araújo, Arata & Figueiredo, 2021; Aziz et al., 2021). Recent brain imaging studies show dysfunction, abnormalities, and atrophy of the olfactory bulb in COVID-19 patients and patients suffering from PACS who presented with anosmia (Chiu et al., 2021; Galougahi et al., 2020; Kandemirli et al., 2021). Neurogenesis in the olfactory epithelium and olfactory bulb is essential for the sense of smell and anosmia is associated with impaired adult olfactory neurogenesis (Boesveldt et al., 2017; Lledo & Valley, 2016). In addition, anosmia is an important pre-motor symptom of Parkinson’s disease which appears to have no direct association with the neurodegenerative process of substantia nigra but seems to be related to impaired adult neurogenesis (Marxreiter, Regensburger & Winkler, 2013; Winner, Kohl & Gage, 2011). COVID-19 is theorized to cause defects in the dopamine system, loss of dopaminergic neurons, and an exacerbation of clinical features of Parkinson’s disease (Brundin, Nath & Beckham, 2020; Sulzer et al., 2020).

Finally, the role of ACE2 in adult neurogenesis in COVID-19 gives a much more vital perspective on the discussion at hand. ACE2 is a surface membrane protein that acts as an obligatory receptor for SARS-CoV-2 and facilitates its entry into the host cell (Hoffmann et al., 2020). In addition to serving as a receptor for SARS-CoV and SARS-CoV-2 virus, ACE2 also acts as a negative regulator of the renin-angiotensin system (RAS) and facilitates amino acid transport in the intestine (Gheblawi et al., 2020; Hoffmann et al., 2020). Various experiments conducted on rodent models give insight into the sites of ACE2 expression. ACE2 is expressed mainly in the lungs, intestine, brain, liver, heart, kidney, and testes. In the brain, it is expressed in neurons, oligodendrocytes, and astrocytes and the sites of ACE2 expression in the brain include ventricles, hippocampus, hypothalamus, substantia nigra, middle temporal gyrus, pontine nuclei viz. pre-Bötzinger complex and nucleus of tractus solitarius and in the olfactory bulb (Gheblawi et al., 2020). More importantly, ACE2 is highly expressed in the key components of the blood-brain barrier viz. astrocytes, astrocytic foot processes, pericytes, and endothelial cells (Hernández et al., 2021).

A recent study conducted using human induced pluripotent stem cells (iPSC) derived neural cells found ACE2 expression in young neurons and human-induced pluripotent stem cell-derived neural progenitor cells (Kase & Okano, 2020). The tissues and organs that are the major target sites for SARS-CoV-2 are those which has higher expression of ACE2 (Pagliaro & Penna, 2020). Similar to SARS-CoV, binding of SARS-CoV-2 with ACE2 causes downregulation of ACE2 (Datta et al., 2020; Seltzer, 2020; Tang et al., 2021; Triana et al., 2021). This downregulation of ACE2 will cause dysregulation of RAS and other complications in addition to its direct effects. Out of the many physiological functions of ACE2, its neuroprotective role is of prime importance to this discussion. Pre-clinical experiments conducted in animal models show the diverse neuroprotective function of ACE2. In an Alzheimer’s disease rodent model, Diminazene, an ACE2 activator was found to increase CREB, BDNF, and nicotinic receptors while reducing apoptotic and inflammatory proteins which all play a major role in adult neurogenesis (Kamel et al., 2018). In transgenic mice, neurotoxic amyloid protein Aβ43 is converted to a neuroprotective form Aβ40 by ACE2 (Liu et al., 2014). ACE2 deficient mice exhibited
impaired memory and learning, and abolition of exercise-induced adult hippocampal neurogenesis (Klempin et al., 2018; Wang et al., 2016).

ACE2 is involved in the intestinal neutral amino acid transport via the neutral amino acid transporter BoAT1. ACE2/BoAT1 complex regulates the gut microbiota composition and function. ACE2 knock-out animals presented with impaired gut microbiota composition (Hashimoto et al., 2012). SARS-CoV-2 entry into the enteric host cells leads to ACE2 shedding by S priming which may lead to gut microbiota dysbiosis (He et al., 2020; Viana, Nunes & Reis, 2020). There is an increase in interest among the researchers regarding a potential link between gut microbiota and the development of neuropsychiatric disorders linked to impaired adult neurogenesis like anxiety and depression (Peirce & Alviña, 2019). Prolonged antibiotic treatment-induced depletion of gut microbiota in adult mice caused an impairment in adult neurogenesis and cognitive function (Möhle et al., 2016). Thus, gut microbiota dysbiosis could be another way through which ACE2 downregulation by SARS-CoV-2 may lead to impaired adult neurogenesis.

ACE2 is involved in the intestinal absorption of tryptophan, the precursor of serotonin which plays a major role in adult neurogenesis and is implicated in psychiatric illness like anxiety and depression. Downregulation of ACE2 reduces serotonin levels in brain thereby affecting adult neurogenesis (Klempin et al., 2013).

Hence, based on the above-mentioned factors, COVID-19 may have a potential impact on adult neurogenesis which could be implicated in the neuropsychiatric symptoms/disorders in COVID-19 survivors. The current review is speculative and relied on thorough literature review discusses the possible implication of potentially impaired adult neurogenesis in neuropsychiatric symptoms/disorders in PACS with emphasis on the role of neuroinflammation.

**Neuroinflammation and hippocampus in PACS**

It has been elucidated recently that prolonged inflammation caused by a release of pro-inflammatory cytokines can cause some neurological deficits and cognitive dysfunction during the post-acute phase of COVID-19 (Maltezou, Pavli & Tsakris, 2021). Recent studies point towards the persistence of neuroinflammation in patients 3 months after recovery from COVID-19 which emphasize the link to the neuropsychiatric sequelae of COVID-19 in PACS (Goldberg et al., 2021; Lu et al., 2020). A recent study by Serrano-Castro et al. (2022) found that the chemokine and growth factor profile of COVID-19 patients, 3 months after discharge depicted a persistent neuroinflammatory state.

Researchers across the globe use different small and large animal models to study COVID-19 and PACS regarding host response, transmission, pathogenesis, and therapeutic strategies. The World Health Organization (WHO) has assembled WHO-COM (WHO COVID-19 modelling), an international panel to develop and study new animal models for COVID-19 research. Readers can refer to the review by Muñoz-Fontela et al. (2020) for information regarding animal models used in COVID-19 research. Various viral infections were found to affect hippocampal functioning including neurogenesis, protein and neurotrophin expression, neuron morphology and function (Bobermin et al., 2020; Francesca et al., 2006; Hosseini et al., 2018; Li Puma et al., 2019; von
Rüden et al., 2012). SARS-CoV virus-infected C57/BL6 mice model showed that viral RNA and the live virus could be isolated from the brain of infected mice which was mainly localized in the hippocampus (Glass et al., 2004). A recent study by Klein et al. (2021) found that SARS-CoV-2 infected hamsters and a post-mortem study of brains of patients deceased from COVID-19 showed disruption in BBB, activation of microglia and, increased expression of brain-derived IL-1β and IL-6 in the hippocampus and lower medulla. The study also concluded that the persistence of neurological problems as noted in PACS could be mediated due to neuroinflammation affecting neural vasculature, neurotransmission and neurogenesis (Klein et al., 2021).

Neuroimaging studies in live patients (Chiveri et al., 2021; Moriguchi et al., 2020) and post-mortem brain studies (Fabbri et al., 2021; Solomon et al., 2020; Thakur et al., 2021) have shown neuropathogenic changes in the hippocampus caused by SARS-CoV-2 infection. Given the implication of hippocampal pathology in various neuropsychiatric disorders, SARS-CoV-2 mediated neuropathogenic changes in the hippocampus could be attributed to neuropsychiatric disorders like depression in PACS (Nestler et al., 2002; Roddy & O’Keane, 2019; Roddy et al., 2019). SARS-CoV-2 induced potential impaired adult hippocampal neurogenesis could very well be one of the underlying cellular mechanisms behind neuropsychiatric symptoms/disorders in COVID-19 survivors. Future studies to elucidate the role of SARS-CoV-2-induced neuroinflammation and a possible impairment in adult neurogenesis in the development of neuropsychiatric disorders are much needed.

**Putative role of neuroinflammation in potentially impaired adult neurogenesis in PACS**

Earlier studies have shown that the hippocampus is highly susceptible to the effects of neuroinflammation (Barrientos et al., 2015; Hueston et al., 2018). The expression of IL-1β, a pro-inflammatory cytokine that is an important mediator of neuroinflammation, and its receptor are at high levels in the hippocampus (Ban et al., 1991; Parnet et al., 1994). Acute exposure to IL-1β disrupts adult hippocampal neurogenesis and contributes to cognitive and memory impairments in stress-related psychiatric disorders (McPherson, Aoyama & Harry, 2011; Ryan et al., 2013). Chronic exposure to IL-1β causes impairment in adult hippocampal neurogenesis which affects hippocampal-dependent processes like pattern separation (Hueston et al., 2018). There are different mechanisms by which neuroinflammation affects adult neurogenesis as discussed below (Fig. 3).

**Glial cells**

In normal physiological conditions, the neuroglial pathways and network operate to maintain neuronal health and circuitry. In the case of chronic inflammatory conditions, there occurs an imbalance in the cytokines in the microenvironment which activates neurodegenerative pathways (Yap et al., 2021; Zhang, Zhang & You, 2018). One of the ubiquitous element of neuroinflammation is the activation of astrocytes and microglia (Glass et al., 2010; Tjalkens, Popichak & Kirkley, 2017). They affect neurogenesis by the secretion of inflammatory mediators.
Figure 3  Putative mechanism depicting the effect of neuroinflammation on adult neurogenesis during PACS. The entry of SARS-COV-2 virus into the brain triggers the release of proinflammatory cytokines which may potentially affect the hippocampal neurogenesis. This could be possibly hypothesized as the reason for the various neuropsychiatric symptoms that are present during PACS.

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**Microglia**

Microglia secrete the growth factors, brain-derived neurotrophic factors (BDNF) and insulin-like growth factors (IGF-1) which play a key role in adult hippocampal neurogenesis (Nakajima et al., 2001; Suh et al., 2013). Experimental evidence shows that these factors are expressed in the regions of SGZ and hippocampus during adulthood, though found to be decreased initially after birth (Dyer et al., 2016; García-Segura et al., 1991; Mori, Shimizu & Hayashi, 2004). Inhibition of neural progenitor cell proliferation and reduction in the thickness of granule cells was noted in BDNF receptor, TrkB knockout mouse (Galvão, Garcia-Verdugo & Alvarez-Buylla, 2008). IGF-1 promotes neural precursor cell (NPC) proliferation, differentiation as well as survival probably by anti-apoptotic effects (Åberg et al., 2003). It was found that voluntary exercise increased neurogenesis by increasing the proportion of microglia that expresses BDNF and IGF-1 (Kohman et al., 2012; Littlefield et al., 2015). Short-term signaling of these neurotrophic factors viz., BDNF, and IGF, mediates cellular plasticity needed for learning and memory, whereas long-term signalling leads to neurogenesis (Duman, 2004).

Microglia are similar to macrophages and are primarily responsible for maintaining brain homeostasis and response to injury (Block, Zecca & Hong, 2007). Activated microglia become ameboid-shaped and express ACE2 and transmembrane protease serine subtype 2 (TMPRSS2) (Singh, Bansal & Feschotte, 2020). A recent study has shown that microglia are directly infected by the SARS-COV-2 virus and can cause self-apoptosis, thereby causing a reduction in the number of microglia which leads to further infiltration of the virus (Jeong et al., 2022). Secondly, infection with SARS-COV-2 significantly increased the level of TNF-α and IL-6, suggesting that activated microglia lead to neuroinflammation (Jeong et al., 2022). A Post-mortem study of brains of patients deceased from COVID-19 showed neuropathological signs of microglial activation (Matschke et al., 2020). A study by Huang et al. (2020) showed that plasma levels of pro-inflammatory markers including different types of IL, FGF, IFN-γ, TNF-α, and VEGF were increased in severe COVID-19 patients who needed admission to intensive care unit. It could be hypothesized that the release of these inflammatory cytokines by activated microglia could lead to the breakage of BBB precipitating various neurological signs and deficits in COVID-19 infected patients (Vargas et al., 2020). Very recently, a “two-hit” hypothesis of activation of microglia has been proposed, which could explain the vulnerability of certain groups (aging, co-morbidity, poor diet) for severe COVID-19 infection and prolonged sickness behavior (Bouayed & Bohn, 2021).

**Astrocytes**

In 2002, Song, Stevens & Gage (2002) discovered that in adult rats, astrocytes promote neural precursor cell differentiation to neurons in the hippocampus but not in the spinal cord. BDNF, fibroblast growth factor 2 (FGF-2), glial cell-derived neurotrophic factors (GDNF) and vascular endothelial growth factors (VEGF) are the neurogenic growth factors secreted by astrocytes (Araki, Ikegaya & Koyama, 2021). Astrocytic BDNF acts on the post synaptic cells of the hippocampus and stimulates neurogenesis. Such activity was found to alleviate anxiety-like symptoms in experimental mice (Quesseveur et al., 2013).
Acute stress potentiates hippocampal neurogenesis that was mediated through astrocyte secreted FGF-2 and neutralizing FGF-2 prevented the proliferation of NPCs in cultures (Kirby et al., 2013). Dexmedetomidine was found to mediate neurogenesis in Dentate gyrus (DG), by upregulating the expression of GDNF derived from astrocytes, neural cell adhesion molecule (NCAM) and cAMP response element-binding protein (CREB) by improving astrogenesis (Zhang et al., 2019). In a recent study, it was found that enhanced VEGF promoted neurogenesis by transdifferentiation of astrocytes to neurons and such effects were abolished after treatment with Flurocitrate which is an astrocyte inhibitor in the striatum of the ischemic stroke model (Shen et al., 2016).

Owing to the importance of astrocytes in the formation of BBB, it could be postulated that infection of astrocytes with SARS-COV-2 virus could compromise the integrity of BBB (DeOre et al., 2021). Previously, compromise in BBB, and neuroinflammation have been implicated in various neurodegenerative and neuropsychiatric disorders caused due to several types of Viral infections (Palus et al., 2017; Persidsky et al., 2000; Verma et al., 2010). Conversely, disrupted BBB could in turn activate astrocyte and microglial cells as an innate immune response (Alquisiras-Burgos et al., 2021). Elevated levels of glial fibrillary acidic protein (GFAP) were noted in COVID-19 patients which is a marker for astrogliosis (Heimfarth et al., 2022). As astrocytes are principal producers of cytokines and chemokines in natural immune response, it could be held that they can cause neuroinflammation and neurotoxicity after infection (Tavčar et al., 2021) and also serve as a host for viral replication (Crunfl et al., 2021). A post-mortem study conducted on the brains of COVID-19 patients showed astrocytes to be the major site of infection and replication of SARS-CoV-2 (Crunfl et al., 2021).

**Pro-inflammatory cytokines**

The pro-inflammatory cytokines in the brain are mainly produced by activated microglia (Wang & Jin, 2015). Depending on the physiological state, the action of cytokines in the regulation of adult neurogenesis varies. Under physiological conditions, IL-6 and TNF-α activate neurotrophic factors and promote neuroregeneration and IL-2 participates in BDNF signaling and hippocampal functioning. However, in a proinflammatory environment, the action of these cytokines leans more towards neurodegeneration and is implicated in the pathogenesis of neuropsychological disorders (Baune et al., 2012; Beck et al., 2005; Eker et al., 2014; Murphy et al., 2000). Chronic neuroinflammation directly impairs adult hippocampal neurogenesis though there are controversial results (Fan & Pang, 2017). Proinflammatory cytokine IL-1β, IL-6, and IFN-α causes a reduction in neural cell proliferation and suppresses adult hippocampal neurogenesis (Borsini et al., 2017; Borsini et al., 2018; Koo & Duman, 2008). TNF-α has a dual effect on adult neurogenesis in vivo. TNFR1 receptor activation causes suppression of neurogenesis while TNFR2 activation favors neurogenesis. I. *vitro* effect of TNF-α was predominantly suppressive to adult neurogenesis (Chen & Palmer, 2013). A dose-dependent inhibition of adult neurogenesis was produced by overexpression of IL-1β (Wu et al., 2012). Nuclear factor-Kb signaling is found to be the mediator for the anti-neurogenic effect of IL-1β (Koo et al., 2010). Chronic expression of IL-1β in DG both in *vitro* and in *vivo* resulted in a
reduction in hippocampal neurogenesis (Mathieu et al., 2010). IL-6 is considered to be the pivotal cytokine that inhibits adult neurogenesis (Wang & Jin, 2015). IL-6 impairs neurogenesis by promoting NPCs towards gliogenesis (Vallieres et al., 2002). Chronic overexpression of IL-6 in astroglia causes a significant reduction in new neuron production without affecting gliogenesis (Vallieres et al., 2002). Neural stem cells exposed to IL-6 and TNF-α exhibited a marked reduction in neurogenesis (Monje, Toda & Palmer, 2003).

There is conflicting evidence on the in vitro effect of IFN-γ on adult neurogenesis (Wang & Jin, 2015). However, in vivo studies show insignificant neurogenesis suppressing effect by IFN-γ (Monje, Toda & Palmer, 2003).

Neurotrophic factors like brain-derived neurotrophic factor (BDNF), insulin-like growth factor-1 (IGF-1), nerve growth factor (NGF), glia-derived nerve factor (GDNF), fibroblast growth factor 2 (FGF-2), and epidermal growth factor (EGF) play a key role in the regulation of adult neurogenesis (Saikarthik, Saraswathi & Al-Atram, 2021).

There exists an inverse relationship between BDNF and pro-inflammatory cytokines, IL-6, IL-2, TNF-α, INF-γ, IL-1β in pro-inflammatory states (Yap et al., 2021). IL-1β was shown to inhibit the neuronal expression of BDNF in the presence of glial cells (Rage, Silhol & Tapia-Arancibia, 2006). Inflammatory cytokines interfere with BDNF signaling by influencing TrkB phosphorylation (Cortese et al., 2011). Administration of IFN-α causes a reduction in BDNF levels (Lotrich, Albusaysi & Ferrell, 2013). Chronic neuroinflammation causes a reduction in the microglial release of neurotrophic factors like IGF-1, thereby causing neurodegeneration (Labandeira-Garcia et al., 2017; Suh et al., 2013). TNF-α inhibits IGF-1 signalling in neurons (Venters et al., 1999).

Serum BDNF levels were found to be decreased in COVID-19-positive patients and were found to be restored during recovery (Azoulay et al., 2020). No significant difference was noted in the levels of IGF between COVID-19 positive and normal patients. However increased levels of IGF were associated with hypertension, neurogenic disease and shock which were noted in severe cases of COVID-19 (Feizollahi et al., 2022). Thus, the role of BDNF and IGF is found to be, and hence further studies are necessary to study the effect of these neurotrophic factors on neurogenesis in the post-acute COVID-19 phase.

**Anti-inflammatory cytokines and chemokines**

A wide range of actions on adult neurogenesis is demonstrated by anti-inflammatory cytokines and chemokines. Anti-inflammatory cytokines IL-4, IL-10 that are released during neuroinflammation promote neurogenesis. In COVID-19, IL-10 levels are increased which promotes neuronal migration (Butovsky et al., 2006; Lorkiewicz & Waszkiewicz, 2021). Increased expression of TGF-β was observed in COVID-19 patients which has pro-neurogenic effects (Samsami et al., 2022; Xiong et al., 2020). Chronic expression of TGF-β improves adult hippocampal neurogenesis (Mathieu, Piantanida & Pitossi, 2010). A recent study found that chemokines viz. stromal cell-derived factor-1 (SDF-1) and monocyte chemoattractant protein-1 (MCP-1) levels to be higher in COVID-19 patients 3 months after their hospital discharge (Serrano-Castro et al., 2022). They are released by astrocytes and their levels are upregulated during neuroinflammatory states. The receptors of SDF-1a, an isof orm of SDF-1 viz. CXCR4 and CXCR7 and the receptor
for MCP-1, CCR2 are highly expressed in NSCs (Ni et al., 2004; Peng et al., 2004; Widera et al., 2004). Both these chemokines play a major role in the migration of NSCs during neurogenesis. They also were shown to play a positive role in neuronal proliferation and differentiation (Lee et al., 2013; Wu et al., 2009). Mildly symptomatic and severe cases of COVID-19 presented with higher levels of fractalkine (Khalil, Elemam & Maghazachi, 2021). Neuronal CX3CL-1 (fractalkine)/CX3CR1 signalling has a regulatory role in adult neurogenesis with disruption in the signalling causing decreased survival and proliferation of NPCs in rodent model (Bachstetter et al., 2011). CCL11 (eotaxin-1) which acts through receptor CCR3 was found to be increased in the earlier phase of COVID-19 and its levels remained steady post infection (Khalil, Elemam & Maghazachi, 2021). Increased levels of peripheral CCL11 decreased adult neurogenesis and affected learning and memory in animal model (Villeda et al., 2011). A predominantly positive impact of neuroinflammation on adult neurogenesis is exhibited through anti-inflammatory cytokines and chemokines.

CONCLUSION
From the above discussion, we could postulate that neuroinflammation in PACS has the potential to cause alterations in adult neurogenesis. COVID-19 worsens pre-existing neuroinflammatory and neurodegenerative conditions like major depressive disorder, Alzheimer’s disease, and Parkinson’s disease in addition to causing new such conditions. Some of the features of PACS including depression, memory loss, and cognitive disorder has been associated with impaired adult neurogenesis. With neuroinflammation having both beneficial and detrimental effects on neurogenesis, based on the prevalence of neuropsychiatric symptoms in PACS, the detrimental effects seem to outweigh the beneficial ones. Hence, impairment in adult neurogenesis can be a potential cause for the neuropsychiatric symptoms/disorders in PACS. However, preclinical studies to specifically analyze adult neurogenesis in SARS-CoV-2 infection are crucial. A better comprehension of the process of adult neurogenesis in PACS may help elucidate the potential role of the regenerative capacity of neural precursor cells and adult neurogenesis in battling the neuropsychiatric symptoms/disorders in PACS. Targeted therapeutic strategies to manage neuroinflammation and impaired adult neurogenesis are the need of the hour to prevent the development of neurological complications of PACS.

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Author Contributions
- Jayakumar Saikarthik conceived and designed the experiments, analyzed the data, prepared figures and/or tables, and approved the final draft.
- Ilango Saraswathi conceived and designed the experiments, analyzed the data, prepared figures and/or tables, authored or reviewed drafts of the article, and approved the final draft.
- Abdulaziz Alarifi conceived and designed the experiments, prepared figures and/or tables, and approved the final draft.
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- Suresh Mickeymaray performed the experiments, authored or reviewed drafts of the article, and approved the final draft.
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- Saleem Shaikh performed the experiments, prepared figures and/or tables, authored or reviewed drafts of the article, and approved the final draft.
- Mathew Jeraud conceived and designed the experiments, performed the experiments, analyzed the data, prepared figures and/or tables, and approved the final draft.
- Abdulaziz S. Alothaim conceived and designed the experiments, analyzed the data, prepared figures and/or tables, authored or reviewed drafts of the article, and approved the final draft.

Data Availability
The following information was supplied regarding data availability:
This is a literature review and there is no raw data.

REFERENCES
Åberg MA, Åberg ND, Palmer TD, Alborn A-M, Carlsson-Skwirut C, Bang P, Rosengren LE, Olsson T, Gage FH, Eriksson PS. 2003. IGF-I has a direct proliferative effect in adult hippocampal progenitor cells. Molecular and Cellular Neuroscience 24(1):23–40 DOI 10.1016/S1044-7431(03)00082-4.

Achar A, Ghosh C. 2020. COVID-19-associated neurological disorders: the potential route of CNS invasion and blood-brain barrier relevance. Cells 9(11):2360 DOI 10.3390/cells9112360.

Ahmed H, Patel K, Greenwood DC, Halpin S, Lewthwaite P, Salawu A, Eyre L, Breen A, O’Connor R, Jones A. 2020. Long-term clinical outcomes in survivors of severe acute respiratory syndrome and Middle East respiratory syndrome coronavirus outbreaks after
hospitalisation or ICU admission: a systematic review and meta-analysis. *Journal of Rehabilitation Medicine* 52:jrm00063 DOI 10.2340/16501977-2694.

Ajami B, Bennett JL, Krieger C, Tetzlaff W, Rossi F. 2007. Local self-renewal can sustain CNS microglia maintenance and function throughout adult life. *Nature Neuroscience* 10(12):1538–1543 DOI 10.1038/nn2014.

Alquisiras-Burgos I, Peralta-Arrieta I, Alonso-Palomares LA, Zacapa-Gómez AE, Salmerón-Bárckenas EG, Aguilara P. 2021. Neurological complications associated with the blood-brain barrier damage induced by the inflammatory response during SARS-CoV-2 infection. *Molecular Neurobiology* 58(2):520–535 DOI 10.1007/s12035-020-02134-7.

Apple DM, Fonseca RS, Kokovay E. 2017. The role of adult neurogenesis in psychiatric and cognitive disorders. *Brain Research* 1655:270–276 DOI 10.1016/j.brainres.2016.01.023.

Araki T, Ikekaya Y, Koyama R. 2021. The effects of microglia- and astrocyte-derived factors on neurogenesis in health and disease. *European Journal of Neuroscience* 54(5):5880–5901 DOI 10.1111/ejn.14969.

Araújo L, Arata V, Figueiredo RG. 2021. Olfactory disorders in post-acute COVID-19 syndrome. *Sinusitis* 5(2):116–122 DOI 10.3390/sinusitis5020012.

Aziz M, Goyal H, Haghbin H, Lee-Smith WM, Gajendran M, Perisetti A. 2021. The association of loss of smell to COVID-19: a systematic review and meta-analysis. *The American Journal of the Medical Sciences* 361(2):216–225 DOI 10.1016/j.amjms.2020.09.017.

Azkur AK, Akdis M, Azkur D, Sokolowska M, van de Veen W, Brüggen MC, O’Mahony L, Gao Y, Nadeau K, Akdis CA. 2020. Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in COVID-19. *Allergy* 75(7):1564–1581 DOI 10.1111/all.14364.

Azoulay D, Shehadeh M, Chepa S, Shaoul E, Baroum M, Horowitz NA, Kaykov E. 2020. Recovery from SARS-CoV-2 infection is associated with serum BDNF restoration. *The Journal of Infection* 81(3):e79–e81 DOI 10.1016/j.jinf.2020.06.038.

Bachstetter AD, Morganti JM, Jernberg J, Schlunk A, Mitchell SH, Brewster KW, Hudson CE, Cole MJ, Harrison JK, Bickford PC, Gemma C. 2011. Fractalkine and CX3CR1 regulate hippocampal neurogenesis in adult and aged rats. *Neurobiology of Aging* 32(11):2030–2044 DOI 10.1016/j.neurobiolaging.2009.11.022.

Baig AM, Khaleeq A, Ali U, Syeda H. 2020. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. *ACS Chemical Neuroscience* 11(7):995–998 DOI 10.1021/acschemneuro.0c00122.

Bam E, Milon G, Prudhomme N, Fillion G, Haour F. 1991. Receptors for interleukin-1 (α and β) in mouse brain: mapping and neuronal localization in hippocampus. *Neuroscience* 43(1):21–30 DOI 10.1016/0306-4522(91)90412-H.

Barrientos RM, Kitt MM, Watkins LR, Maier SF. 2015. Neuroinflammation in the normal aging hippocampus. *Neuroscience* 309(1–11):84–99 DOI 10.1016/j.neuroscience.2015.03.007.

Barry D, McDermott K. 2005. Differentiation of radial glia from radial precursor cells and transformation into astrocytes in the developing rat spinal cord. *Glia* 50:187–197 DOI 10.1002/(ISSN)1098-1136.

Baune B, Camara M-L, Eyre H, Jawahar C, Anscomb H, Körner H. 2012. Tumour necrosis factor-alpha mediated mechanisms of cognitive dysfunction. *Translational Neuroscience* 3(3):263–277 DOI 10.2478/s13380-012-0027-8.

Beck RD Jr, King MA, Ha GK, Cushman JD, Huang Z, Petitto JM. 2005. IL-2 deficiency results in altered septal and hippocampal cytoarchitecture: relation to development and neurotrophins. *Journal of Neuroimmunology* 160(1–2):146–153 DOI 10.1016/j.jneuroim.2004.11.006.
Berger T, Lee H, Thuret S. 2020. Neurogenesis right under your nose. Nature Neuroscience 23(3):297–298 DOI 10.1038/s41593-020-0596-8.

Bernardi S, Toffoli B, Zennaro C, Tikellis C, Monticone S, Losurdo P, Bellini G, Thomas MC, Fallo F, Veglio F. 2012. High-salt diet increases glomerular ACE/ACE2 ratio leading to oxidative stress and kidney damage. Nephrology Dialysis Transplantation 27(5):1793–1800 DOI 10.1093/ndt/gfr600.

Block ML, Zecca L, Hong J-S. 2007. Microglia-mediated neurotoxicity: uncovering the molecular mechanisms. Nature Reviews Neuroscience 8(1):57–69 DOI 10.1038/nrn2038.

Bobermin LD, Quincozes-Santos A, Santos CL, Varela APM, Teixeira TF, Wartchow KM, Lissner LJ, da Silva A, Thomaz NK, Santi L. 2020. Zika virus exposure affects neuron-glia communication in the hippocampal slices of adult rats. Scientific Reports 10(1):1–11 DOI 10.1038/s41598-020-78735-y.

Boesveldt S, Postma EM, Boak D, Welge-Luessen A, Schöpf V, Mainland JD, Martens J, Ngai J, Duffy VB. 2017. Anosmia—a clinical review. Chemical Senses 42(7):513–523 DOI 10.1093/chemse/bjx025.

Borsini A, Alboni S, Horowitz MA, Tojo LM, Cannazza G, Su K-P, Pariante CM, Zunszain PA. 2017. Rescue of IL-1β-induced reduction of human neurogenesis by omega-3 fatty acids and antidepressants. Brain, Behavior, and Immunity 65(11):230–238 DOI 10.1016/j.bbi.2017.05.006.

Borsini A, Cattaneo A, Malpighi C, Thuret S, Harrison NA, Consortium MI, Zunszain PA, Pariante CM. 2018. Interferon-alpha reduces human hippocampal neurogenesis and increases apoptosis via activation of distinct STAT1-dependent mechanisms. International Journal of Neuropsychopharmacology 21:187–200 DOI 10.1093/ijnp/pyx083.

Bouayed J, Bohn T. 2021. The link between microglia and the severity of COVID-19: the “two-hit” hypothesis. Journal of Medical Virology 93(7):4111–4113 DOI 10.1002/jmv.26984.

Brundin P, Nath A, Beckham JD. 2020. Is COVID-19 a perfect storm for Parkinson’s disease? Trends in Neurosciences 43(12):931–933 DOI 10.1016/j.tins.2020.10.009.

Butosky O, Ziv Y, Schwartz A, Landa G, Talpalar AE, Pluchino S, Martinos G, Schwartz M. 2006. Microglia activated by IL-4 or IFN-γ differentially induce neurogenesis and oligodendrogenesis from adult stem/progenitor cells. Molecular and Cellular Neuroscience 31(1):149–160 DOI 10.1016/j.mcn.2005.10.006.

Carfì A, Bernabei R, Landi F. 2020. Persistent symptoms in patients after acute COVID-19. JAMA 324(6):603–605 DOI 10.1001/jama.2020.12603.

Ceriello A, Stoian AP, Rizzo M. 2020. COVID-19 and diabetes management: what should be considered? Diabetes Research and Clinical Practice 163:108151 DOI 10.1016/j.diabres.2020.108151.

Chen X, Ling J, Mo P, Zhang Y, Jiang Q, Ma Z, Cao Q, Hu W, Zou S, Chen L, Yao L, Luo M, Chen T, Deng L, Liang K, Song S, Yang R, Zheng R, Gao S, Gui X, Ke H, Hou W, Lundkvist Å, Xiong Y. 2020. Restoration of leukomonocyte counts is associated with viral clearance in COVID-19 hospitalized patients. medRxiv DOI 10.1101/2020.03.03.20030437.

Chen Z, Palmer TD. 2013. Differential roles of TNFR1 and TNFR2 signaling in adult hippocampal neurogenesis. Brain, Behavior, and Immunity 30:45–53 DOI 10.1016/j.bbi.2013.01.083.

Chiu A, Fischbein N, Wintemberg M, Zaharchuk G, Yun PT, Zeineh M. 2021. COVID-19-induced anosmia associated with olfactory bulb atrophy. Neuroradiology 63(1):147–148 DOI 10.1007/s00234-020-02554-1.

Chiveri L, Verrengia E, Muscia F, Nuzzago C, Raimondi E, Vecchio E, Bompiano D, Mazzone A, Fociani P, Corbellino M. 2021. Limbic encephalitis in a COVID-19 patient? Journal of Neurovirology 27(3):498–500 DOI 10.1007/s13365-021-00971-3.
Ciaccio M, Lo Sasso B, Scazzone C, Gambino CM, Ciaccio AM, Bivona G, Piccoli T, Giglio RV, Agnelo L. 2021. COVID-19 and Alzheimer's disease. Brain Sciences 11(3):305 DOI 10.3390/brainsci11030305.

Coperchini F, Chiavato I, Croce L, Magri F, Rotondi M. 2020. The cytokine storm in COVID-19: an overview of the involvement of the chemokine/chemokine-receptor system. Cytokine & Growth Factor Reviews 53(25):25–32 DOI 10.1016/j.cytogfr.2020.05.003.

Cortese GP, Barrientos RM, Maier SF, Patterson SL. 2011. Aging and a peripheral immune challenge to reduce mature brain-derived neurotrophic factor and activation of TrkB, PLCγ1, and ERK in hippocampal synaptoneurosomes. The Journal of Neuroscience 31(11):4274–4279 DOI 10.1523/JNEUROSCI.5818-10.2011.

Crunfli F, Carregari VC, Veras FP, Vendramini PH, Valença AGF, Antunes ASLM, Brandão-Teles C, da Silva Zuccoli G, Reis-de-Oliveira G, Silva-Costa LC. 2021. SARS-CoV-2 infects brain astrocytes of COVID-19 patients and impairs neuronal viability. medRxiv DOI 10.1101/2020.10.09.20207464.

Czeisler M, Lane RI, Petrosky E, Wiley JF, Christensen A, Njai R, Weaver MD, Robbins R, Facser-Childs ER, Barger LK, Czeisler CA, Howard ME, Rajaratnam SMW. 2020. Mental health, substance use, and suicidal ideation during the COVID-19 pandemic—United States. MMWR. Morbidity and Mortality Weekly Report 69(32):1049–1057 DOI 10.15585/mmwr.mm6932a1.

Debuc B, Smadja DM. 2021. Is COVID-19 a new hematologic disease? Stem Cell Reviews and Reports 17(1):4–8 DOI 10.1007/s12015-020-09987-4.

DeCarolis NA, Eisch AJ. 2010. Hippocampal neurogenesis as a target for the treatment of mental illness: a critical evaluation. Neuropharmacology 58(6):884–893 DOI 10.1016/j.neuropharm.2009.12.013.

Del Zoppo G. 2010. The neurovascular unit in the setting of stroke. Journal of Internal Medicine 267(2):156–171 DOI 10.1111/j.1365-2796.2009.02199.x.

DeOre BJ, Tran KA, Andrews AM, Ramirez SH, Galie PA. 2021. SARS-CoV-2 spike protein disrupts blood-brain barrier integrity via RhoA activation. Journal of Neuroimmune Pharmacology 16(4):722–728 DOI 10.1007/s11481-021-10029-0.

Desforges M, Le Coupanec A, Dubeau P, Bourgoin A, Laioie L, Dubé M, Talbot PJ. 2020. Human coronaviruses and other respiratory viruses: underestimated opportunistic pathogens of the central nervous system? Viruses 12(1):14 DOI 10.3390/v12010014.

Dixit NM, Churchill A, Nsair A, Hsu JJ. 2021. Post-acute COVID-19 syndrome and the cardiovascular system: what is known? American Heart Journal Plus: Cardiology Research and Practice 5(11):100025 DOI 10.1016/j.ahjo.2021.100025.

Duman RS. 2004. Role of neurotrophic factors in the etiology and treatment of mood disorders. NeuroMolecular Medicine 5(1):11–25 DOI 10.1385/NMM:5:1:011.

Dyer AH, Vahdatpour C, Sanfelio A, Tropea D. 2016. The role of insulin-like growth factor 1 (IGF-1) in brain development, maturation and neuroplasticity. Neuroscience 325(1):89–99 DOI 10.1016/j.neuroscience.2016.03.056.
Eker SS, Yavasci EO, Cangur S, Kiriş S, Sarandol E. 2014. Can BDNF and IL-2 be indicators for the diagnosis in schizophrenic patients with depressive symptoms? *Acta Neuropsychiatrica* 26(5):291–297 DOI 10.1017/neu.2014.13.

Esposito G, Pesce M, Seguella L, Sanseverino W, Lu J, Sarnelli G. 2020. Can the enteric nervous system be an alternative entrance door in SARS-CoV2 neuroinvasion? *Brain, Behavior, and Immunology* 87(1):93–94 DOI 10.1016/j.bbi.2020.04.060.

Fabbri VP, Foschini MP, Lazzarotto T, Gabrielli I, Cenacchi G, Gallo C, Aspide R, Frascaroli G, Cortelli P, Riefolo M. 2021. Brain ischemic injury in COVID-19-infected patients: a series of 10 post-mortem cases. *Brain Pathology* 31(1):205–210 DOI 10.1111/bpa.12901.

Fan L-W, Pang Y. 2021. Dysregulation of neurogenesis by neuroinflammation: key differences in neurodevelopmental and neurological disorders. *Neural Regeneration Research* 12(3):366–371 DOI 10.4103/1673-5374.202926.

Fan Y-Y, Huo J. 2021. A1/A2 astrocytes in central nervous system injuries and diseases: angels or devils? *Neurochemistry International* 148(4):105080 DOI 10.1016/j.neuint.2021.105080.

Faulkner JR, Herrmann JE, Woo MJ, Tansey KE, Doan NB, Sofroniew MV. 2004. Reactive astrocytes protect tissue and preserve function after spinal cord injury. *Journal of Neuroscience* 24(9):2143–2155 DOI 10.1523/JNEUROSCI.3547-03.2004.

Feizollahi P, Matin S, Roghani SA, Mostafaei S, Safarzadeh E, Taghadosi M. 2022. Evaluation serum levels of insulin growth factor-1 (IGF-1) and its association with clinical parameters in severe COVID-19. *Inflammopharmacology* 30(1):199–205 DOI 10.1007/s10787-021-00908-6.

Francesca V, Sandra S, Alessandra S, Gualtiero G, Luciana G, Laura C. 2006. A molecular study of hippocampus in dogs with convulsion during canine distemper virus encephalitis. *Brain Research* 1098(1):186–195 DOI 10.1016/j.brainres.2006.04.051.

Gallagher TM, Buchmeier MJ. 2001. Coronavirus spike proteins in viral entry and pathogenesis. *Virology* 279(2):371–374 DOI 10.1006/viro.2000.0757.

Galougahi MK, Ghorbani J, Bakhshayeshkaram M, Naeini AS, Haseli S. 2020. Olfactory bulb magnetic resonance imaging in SARS-CoV-2-induced anosmia: the first report. *Academic Radiology* 27(6):892–893 DOI 10.1016/j.acra.2020.04.002.

Galvão RP, García-Verdugo JM, Alvarez-Buylla A. 2008. Brain-derived neurotrophic factor signaling does not stimulate subventricular zone neurogenesis in adult mice and rats. *Journal of Neuroscience* 28(50):13368–13383 DOI 10.1523/JNEUROSCI.2918-08.2008.

García-Segura LM, Pérez J, Pons S, Rejas MT, Torres-Alemán I. 1991. Localization of insulin-like growth factor I (IGF-I)-like immunoreactivity in the developing and adult rat brain. *Brain Research* 560(1–2):167–174 DOI 10.1016/0006-8993(91)91228-S.

Garg P, Arora U, Kumar A, Wig N. 2020. The “post-COVID” syndrome: how deep is the damage? *Journal of Medical Virology* 93(2):673 DOI 10.1002/jmv.26465.

Gheblawi M, Wang K, Viveiros A, Nguyen Q, Zhong J-C, Turner AJ, Raizada MK, Grant MB, Oudit GY. 2020. Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system: celebrating the 20th anniversary of the discovery of ACE2. *Circulation Research* 126(10):1456–1474 DOI 10.1161/CIRCRESAHA.120.317015.

Glass CK, Saijo K, Winner B, Marchetto MC, Gage FH. 2010. Mechanisms underlying inflammation in neurodegeneration. *Cell* 140(6):918–934 DOI 10.1016/j.cell.2010.02.016.

Glass WG, Subbarao K, Murphy B, Murphy PM. 2004. Mechanisms of host defense following severe acute respiratory syndrome-coronavirus (SARS-CoV) pulmonary infection of mice. *The Journal of Immunology* 173(6):4030–4039 DOI 10.4049/jimmunol.173.6.4030.
Goldberg E, Podell K, Sodickson DK, Fieremans E. 2021. The brain after COVID-19: compensatory neurogenesis or persistent neuroinflammation? EClinicalMedicine 31:100684 DOI 10.1016/j.eclinm.2020.100684.

Grammatopoulos TN, Jones SM, Ahmadi FA, Hoover BR, Snell LD, Skoch J, Jhaveri VV, Poczobutt AM, Weyhenmeyer JA, Zawada WM. 2007. Angiotensin type 1 receptor antagonist losartan, reduces MPTP-induced degeneration of dopaminergic neurons in substantia nigra. Molecular Neurodegeneration 2(1):1–17 DOI 10.1186/1750-1326-2-1.

Gupta K, Mohanty SK, Mittal A, Kalra S, Kumar S, Mishra T, Ahuja J, Sengupta D, Ahuja G. 2021. The cellular basis of loss of smell in 2019-nCoV-infected individuals. Briefings in Bioinformatics 22(2):873–881 DOI 10.1093/bib/bbaa168.

Harvey CJDC, Schofield GM, Williden M. 2018. The use of nutritional supplements to induce ketosis and reduce symptoms associated with keto-induction: a narrative review. PeerJ 6(10):e4488 DOI 10.7717/peerj.4488.

Hashimoto T, Perlot T, Rehan A, Trichereau J, Ishiguro H, Paolino M, Sigl V, Hanada T, Hanada R, Lipinski S. 2012. ACE2 links amino acid malnutrition to microbial ecology and intestinal inflammation. Nature 487(7408):477–481 DOI 10.1038/nature11228.

He L-H, Ren L-F, Li J-F, Wu Y-N, Li X, Zhang L. 2020. Intestinal flora as a potential strategy to fight SARS-CoV-2 infection. Frontiers in Microbiology 11:1388 DOI 10.3389/fmicb.2020.01388.

Heimfarth L, Passos FRS, Monteiro BS, de Souza Araújo AA, Júnior LJQ, Quintans JDSS. 2022. Serum glial fibrillary acidic protein is a body fluid biomarker: a valuable prognostic for neurological disease-A systematic review. International Immunopharmacology 107(18):108624 DOI 10.1016/j.intimp.2022.108624.

Hernández VS, Zetter MA, Guerra EC, Hernández-Araúza I, Karuzin N, Hernández-Pérez OR, Eiden LE, Zhang L. 2021. ACE2 expression in rat brain: implications for COVID-19 associated neurological manifestations. bioRxiv DOI 10.1101/2021.05.01.442293.

Hoffmann M, Kleiné-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu N-H, Nitsche A. 2020. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 181(2):271–280.e8 DOI 10.1016/j.cell.2020.02.052.

Hopkins RO, Weaver LK, Pope D, Orme JF Jr, Bigler ED, Larson-Lohr V. 1999. Neuropsychological sequelae and impaired health status in survivors of severe acute respiratory distress syndrome. American Journal of Respiratory and Critical Care Medicine 160(1):50–56 DOI 10.1164/ajrccm.160.1.9708059.

Hosseini S, Wilk E, Michaelens-Preusse K, Gerhauser I, Baumgärtner W, Geffers R, Schughart K, Korte M. 2018. Long-term neuroinflammation induced by influenza A virus infection and the impact on hippocampal neuron morphology and function. Journal of Neuroscience 38(12):3060–3080 DOI 10.1523/JNEUROSCI.1740-17.2018.

Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X. 2020. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet 395(10223):497–506 DOI 10.1016/S0140-6736(20)30183-5.

Hueston CM, O’Leary JD, Hoban AE, Kozareva DA, Pawley LC, O’Leary OF, Cryan JF, Nolan YM. 2018. Chronic interleukin-1β in the dorsal hippocampus impairs behavioural pattern separation. Brain, Behavior, and Immunity 74:252–264 DOI 10.1016/j.bbi.2018.09.015.

Hui D, Joynt G, Wong KT, Gomersall C, Li T, Antonio G, Ko F, Chan M, Chan D, Tong M. 2005. Impact of severe acute respiratory syndrome (SARS) on pulmonary function, functional capacity and quality of life in a cohort of survivors. Thorax 60(5):401–409 DOI 10.1136/thx.2004.030205.
Imai Y, Kuba K, Neely GG, Yaghubian-Malhami R, Perkmann T, van Loo G, Ermolaeva M, Veldhuizen R, Leung YC, Wang H. 2008. Identification of oxidative stress and Toll-like receptor 4 signaling as a key pathway of acute lung injury. Cell 133(2):235–249 DOI 10.1016/j.cell.2008.02.043.

Jeong GU, Lyu J, Kim K-D, Chung YC, Yoon GY, Lee S, Hwang I, Shin W-H, Ko J, Lee J-Y, Kwon Y-C. 2022. SARS-CoV-2 infection of microglia elicits pro-inflammatory activation and apoptotic cell death. bioRxiv DOI 10.1101/2022.01.04.475015.

Jha MK, Lee W-H, Suk K. 2016. Functional polarization of neuroglia: implications in neuroinflammation and neurological disorders. Biochemical Pharmacology 103(10):1–16 DOI 10.1016/j.bcp.2015.11.003.

John GR, Lee SC, Brosnan CF. 2003. Cytokines: powerful regulators of glial cell activation. The Neuroscientist 9(1):10–22 DOI 10.1177/1073858402239587.

Kamel AS, Abdelkader NF, Abd El-Rahman SS, Emara M, Zaki HF, Khattab MM. 2018. Stimulation of ACE2/ANG(1-7)/Mas axis by diminazene ameliorates Alzheimer’s disease in the D-galactose-ovariectomized rat model: role of PI3K/Akt pathway. Molecular Neurobiology 55(10):8188–8202 DOI 10.1007/s12035-018-0966-3.

Kandemirli SG, Altundag A, Yildirim D, Tekcan Sanli DE, Saatci O. 2021. Olfactory bulb MRI and paranasal sinus CT findings in persistent COVID-19 anosmia. Academic Radiology 28(1):28–35 DOI 10.1016/j.acra.2020.10.006.

Kase Y, Okano H. 2020. Expression of ACE2 and a viral virulence-regulating factor CCN family member 1 in human iPSC-derived neural cells: implications for COVID-19-related CNS disorders. Inflammation and Regeneration 40(1):1–8 DOI 10.1186/s41232-020-00143-6.

Kehoe PG, Wong S, Mulhim NA, Palmer LE, Miners JS. 2016. Angiotensin-converting enzyme 2 is reduced in Alzheimer’s disease in association with increasing amyloid-β and tau pathology. Alzheimer’s Research & Therapy 8(1):1–10 DOI 10.1186/s13195-016-0217-7.

Kempermann G, Song H, Gage FH. 2015. Neurogenesis in the adult hippocampus. Cold Spring Harbor Perspectives in Biology 7(9):a018812 DOI 10.1101/cshperspect.a018812.

Kempuraj D, Selvakumar GP, Ahmed ME, Raikwar SP, Thangavel R, Khan A, Zaheer SA, Iyer SS, Burton C, James D, Zaheer A. 2020. COVID-19, mast cells, cytokine storm, psychological stress, and neuroinflammation. The Neuroscientist 26(5–6):402–414 DOI 10.1177/1073858420941476.

Khalil BA, Elemam NM, Maghazachi AA. 2021. Chemokines and chemokine receptors during COVID-19 infection. Computational and Structural Biotechnology Journal 19(1):976–988 DOI 10.1016/j.csbj.2021.01.034.

Kirby ED, Muroy SE, Sun WG, Covarrubias D, Leong MJ, Barchas LA, Kaufer D. 2013. Acute stress enhances adult rat hippocampal neurogenesis and activation of newborn neurons via secreted astrocytic FGF2. eLife 2:e00362 DOI 10.7554/eLife.00362.

Klein R, Soung A, Sissoko C, Nordvig A, Canoll P, Mariani M, Jiang X, Bricker T, Goldman J, Rosoklija G, Arango V, Underwood M, Mann JJ, Boon A, Dowrk A, Boldrini M. 2021. COVID-19 induces neuroinflammation and loss of hippocampal neurogenesis. Research Square 29:rs.3.rs-1031824 DOI 10.21203/rs.3.rs-1031824/v1.

Klempin F, Beis D, Mosienko V, Kempermann G, Bader M, Alenina N. 2013. Serotonin is required for exercise-induced adult hippocampal neurogenesis. Journal of Neuroscience 33(19):8270–8275 DOI 10.1523/JNEUROSCI.5855-12.2013.

Klempin F, Mosienko V, Matthes S, Villela DC, Todiras M, Penninger JM, Bader M, Santos RAS, Alenina N. 2018. Depletion of angiotensin-converting enzyme 2 reduces brain...
serotonin and impairs the running-induced neurogenic response. *Cellular and Molecular Life Sciences* 75(19):3625–3634 DOI 10.1007/s00018-018-2815-y.

**Kohman RA, DeYoung EK, Bhattacharya TK, Peterson LN, Rhodes JS. 2012.** Wheel running attenuates microglia proliferation and increases expression of a proneurogenic phenotype in the hippocampus of aged mice. *Brain, Behavior, and Immunity* 26(5):803–810 DOI 10.1016/j.bbi.2011.10.006.

**Koo JW, Duman RS. 2008.** IL-1β is an essential mediator of the antineurogenic and anhedonic effects of stress. *Proceedings of the National Academy of Sciences of the United States of America* 105(2):751–756 DOI 10.1073/pnas.0708092105.

**Koo JW, Russo SJ, Ferguson D, Nestler EJ, Duman RS. 2010.** Nuclear factor-κB is a critical mediator of stress-impaired neurogenesis and depressive behavior. *Proceedings of the National Academy of Sciences of the United States of America* 107(6):2669–2674 DOI 10.1073/pnas.0910658107.

**Kritas S, Ronconi G, Caraffa A, Gallenga C, Ross R, Conti P. 2020.** Mast cells contribute to coronavirus-induced inflammation: new anti-inflammatory strategy. *Journal of Biological Regulators and Homeostatic Agents* 34:9–14 DOI 10.23812/20-Editorial-Kritas.

**Kuipers MT, van der Poll T, Schultz MJ, Wieland CW. 2011.** Bench-to-bedside review: damage-associated molecular patterns in the onset of ventilator-induced lung injury. *Critical Care* 15(6):1–11 DOI 10.1186/cc10437.

**Labandeira-Garcia JL, Costa-Besada MA, Labandeira CM, Villar-Cheda B, Rodriguez-Perez AI. 2017.** Insulin-like growth factor-1 and neuroinflammation. *Frontiers in Aging Neuroscience* 9:9124 DOI 10.3389/fnagi.2017.00365.

**Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, Azman AS, Reich NG, Lessler J. 2020.** The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. *Annals of Internal Medicine* 172(9):577–582 DOI 10.7326/M20-0504.

**Lavrentyev EN, Malik KU. 2009.** High glucose-induced Nox1-derived superoxides downregulate PKC-βII, which subsequently decreases ACE2 expression and ANG (1-7) formation in rat VSMCs. *American Journal of Physiology-Heart and Circulatory Physiology* 296(1):H106–H118 DOI 10.1152/ajpheart.00239.2008.

**Lee H, Kang JE, Lee JK, Bae J-S, Jin HK. 2013.** Bone-marrow-derived mesenchymal stem cells promote proliferation and neuronal differentiation of Niemann-Pick type C mouse neural stem cells by upregulation and secretion of CCL2. *Human Gene Therapy* 24(7):655–669 DOI 10.1089/hum.2013.001.

**Leta V, Rodriguez-Violante M, Abundes A, Rukavina K, Teo JT, Falup-Pecurariu C, Irincu L, Rota S, Bhidayasiri R, Storch A. 2021.** Parkinson’s disease and post-COVID-19 syndrome: the Parkinson’s long-COVID spectrum. *Movement Disorders* 36(6):1287–1289 DOI 10.1002/mds.28622.

**Li Puma DD, Piacentini R, Leone L, Gironi K, Marcocci ME, De Chiara G, Palamara AT, Grassi C. 2019.** Herpes simplex virus type-1 infection impairs adult hippocampal neurogenesis via amyloid-β protein accumulation. *Stem Cells* 37(11):1467–1480 DOI 10.1002/stem.3072.

**Li X, Geng M, Peng Y, Meng I, Lu S. 2020.** Molecular immune pathogenesis and diagnosis of COVID-19. *Journal of Pharmaceutical Analysis* 10(2):102–108 DOI 10.1016/j.jpha.2020.03.001.

**Li YC, Bai WZ, Hashikawa T. 2020.** The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *Journal of medical virology* 92(6):552–555 DOI 10.1002/jmv.25728.
Littlefield AM, Setti SE, Priester C, Kohman RA. 2015. Voluntary exercise attenuates LPS-induced reductions in neurogenesis and increases microglia expression of a proneurogenic phenotype in aged mice. *Journal of Neuroinflammation* 12(1):1–12 DOI 10.1186/s12974-015-0362-0.

Liu S, Liu J, Miura Y, Tanabe C, Maeda T, Terayama Y, Turner AJ, Zou K, Komano H. 2014. Conversion of Aβ43 to Aβ40 by the successive action of angiotensin-converting enzyme 2 and angiotensin-converting enzyme. *Journal of Neuroscience Research* 92(9):1178–1186 DOI 10.1002/jnr.23404.

Lledo P-M, Valley M. 2016. Adult olfactory bulb neurogenesis. *Cold Spring Harbor Perspectives in Biology* 8(8):a018945 DOI 10.1101/cshperspect.a018945.

Lorkiewicz P, Waszkiewicz N. 2021. Biomarkers of post-COVID depression. *Journal of Clinical Medicine* 10(18):4142 DOI 10.3390/jcm10184142.

Lotrich FE, Albusaysi S, Ferrell RE. 2013. Brain-derived neurotrophic factor serum levels and genotype: association with depression during interferon-α treatment. *Neuropsychopharmacology* 38(6):985–995 DOI 10.1038/npp.2012.263.

Lu Y, Li X, Geng D, Mei N, Wu P-Y, Huang C-C, Jia T, Zhao Y, Wang D, Xiao A. 2020. Cerebral micro-structural changes in COVID-19 patients—an MRI-based 3-month follow-up study. *EClinicalMedicine* 25:100484 DOI 10.1016/j.eclinm.2020.100484.

Maltezou HC, Pavli A, Tsakris A. 2021. Post-COVID syndrome: an insight on its pathogenesis. *Vaccines* 9(5):497 DOI 10.3390/vaccines9050497.

Manjili RH, Zarei M, Habibi M, Manjili MH. 2020. COVID-19 as an acute inflammatory disease. *The Journal of Immunology* 205(1):12–19 DOI 10.4049/jimmunol.2000413.

Marxreiter F, Regensburger M, Winkler J. 2013. Adult neurogenesis in Parkinson’s disease. *Cellular and Molecular Life Sciences* 70(3):459–473 DOI 10.1007/s00018-012-1062-x.

Mathieu P, Battista D, Depino A, Roca V, Graciarella M, Pitossi F. 2010. The more you have, the less you get: the functional role of inflammation on neuronal differentiation of endogenous and transplanted neural stem cells in the adult brain. *Journal of Neurochemistry* 112(6):1368–1385 DOI 10.1111/j.1471-4159.2009.06548.x.

Mathieu P, Piantanida AP, Pitossi F. 2010. Chronic expression of transforming growth factor-beta enhances adult neurogenesis. *Neuroimmunomodulation* 17(3):200–201 DOI 10.1159/000258723.

Matias I, Morgado J, Gomes FCA. 2019. Astrocyte heterogeneity: impact to brain aging and disease. *Frontiers in Aging Neuroscience* 11:401 DOI 10.3389/fnagi.2019.00059.

Matschke J, Lütgehetmann M, Hagel C, Sperhake JP, Schröder AS, Edler C, Mushumba H, Fitzek A, Allweiss L, Dandri M. 2020. Neuropathology of patients with COVID-19 in Germany: a post-mortem case series. *The Lancet Neurology* 19(11):919–929 DOI 10.1016/S1474-4422(20)30308-2.

McPherson CA, Aoyama M, Harry GJ. 2011. Interleukin (IL)-1 and IL-6 regulation of neural progenitor cell proliferation with hippocampal injury: differential regulatory pathways in the subgranular zone (SGZ) of the adolescent and mature mouse brain. *Brain, Behavior, and Immunity* 25(5):850–862 DOI 10.1016/j.bbi.2010.09.003.

Meinhardt J, Radke J, Dittmayer C, Franz J, Thomas C, Mothes R, Laue M, Schneider J, Brünink S, Greuel S, Lehmann M, Hassan O, Aschman T, Schumann E, Chua RL, Conrad C, Eils R, Stenzel W, Windgassen M, Rösler L, Goebel H-H, Gelderblom HR, Martin H, Nitsche A, Schulz-Schaeffer WJ, Hakrouts S, Winkler MS, Tampe B, Scheibe F, Körtvélyssey P, Reinhold D, Siegmund B, Kühl AA, Elezkurtaj S, Horst D, Oesterhelweg L, Tsokos M, Ingold-Heppner B, Stadelmann C, Drosten C, Corman VM, Radbruch H,
Heppner FL. 2021. Olfactory transmucosal SARS-CoV-2 invasion as a port of central nervous system entry in individuals with COVID-19. *Nature Neuroscience* 24(2):168–175 DOI 10.1038/s41593-020-00758-5.

Misane I, Kruis A, Piemanen AW, Ögren SO, Stiedl O. 2013. GABAA receptor activation in the CA1 area of the dorsal hippocampus impairs consolidation of conditioned contextual fear in C57BL/6 mice. *Behavioural Brain Research* 238(13):160–169 DOI 10.1016/j.bbr.2012.10.027.

Möhle L, Mattei D, Heimesaat Markus M, Bereswill S, Fischer A, Alutis M, French T, Hambardzumyan D, Matzinger P, Dunay Ildiko R, Wolf Susanne A. 2016. Ly6Chi monocytes provide a link between antibiotic-induced changes in gut microbiota and adult hippocampal neurogenesis. *Cell Reports* 15(9):1945–1956 DOI 10.1016/j.celrep.2016.04.074.

Monje ML, Toda H, Palmer TD. 2003. Inflammatory blockade restores adult hippocampal neurogenesis. *Science* 302(5651):1760–1765 DOI 10.1126/science.1088417.

Montani D, Savale L, Noel N, Meyrignac O, Colle R, Gasnier M, Corruble E, Beurnier A, Jutant E-M, Pham T, Lecq A-L, Papon J-F, Monnet X. 2022. Post-acute COVID-19 syndrome. *European Respiratory Review* 31(163):210185 DOI 10.1183/16000617.0185-2021.

Mori T, Shimizu K, Hayashi M. 2004. Differential expression patterns of TrkB ligands in the macaque monkey brain. *NeuroReport* 15(16):2507–2511 DOI 10.1097/00001756-200411150-00015.

Moriguchi T, Harii N, Goto J, Harada D, Sugawara H, Takamino J, Ueno M, Sakata H, Kondo K, Myose N. 2020. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. *International Journal of Infectious Diseases* 94(20):55–58 DOI 10.1016/j.ijid.2020.03.062.

Mracsko E, Veltkamp R. 2014. Neuroinflammation after intracerebral hemorrhage. *Frontiers in Cellular Neuroscience* 8:1538 DOI 10.3389/fncel.2014.00388.

Mu Y, Lee SW, Gage FH. 2010. Signaling in adult neurogenesis. *Current Opinion in Neurobiology* 20(4):416–423 DOI 10.1016/j.conb.2010.04.010.

Munoñ-Fontela C, Dowling WE, Funnell SGP, Riveros-Balta AX, Albrecht RA, Andersen H, Baric RS, Carroll MW, Cavaleri M, Qin C, Crozier J, Dallmeier K, de Waal L, de Wit E, Delang L, Dohme E, Duprex WP, Falzarano D, Finch CL, Frieman MB, Graham BS, Gralinski LE, Guilfoyle K, Haagmans BL, Hamilton GA, Hartman AL, Hertst S, Kaptein SJF, Klimstra WB, Knezevic PR, Krause PR, Kuhn JH, Le Grand R, Lewis MG, Liu W-C, Maisonnasse P, McElroy AK, Munster V, Oreshkova N, Rasmussen AL, Rocha-Pereira J, Rockx B, Rodrigez E, Rogers TF, Salguero FJ, Schotsaert M, Stittelaar KJ, Thibaut HJ, Tseng C-T, Vergara-Alert J, Beer M, Brasel T, Chan JFW, Garcia-Sastre A, Neys J, Perlman S, Reed DS, Richt JA, Roy CJ, Segalés J, Vasan SS, Renao-Restrepo AM, Barouch DH. 2020. Animal models for COVID-19. *Nature* 586(7830):509–515 DOI 10.1038/s41586-020-2787-6.

Murphy PS, Borthwick L, Alatares M, Gauldie J, Kaplan D, Richardson P. 2000. Reciprocal actions of interleukin-6 and brain-derived neurotrophic factor on rat and mouse primary sensory neurons. *European Journal of Neuroscience* 12(6):1891–1899 DOI 10.1046/j.1460-9586.2000.00074.x.

Nakajima K, Honda S, Tohyama Y, Imai Y, Kohsaka S, Kurihara T. 2001. Neurotrophin secretion from cultured microglia. *Journal of Neuroscience Research* 65:322–331 DOI 10.1002/(ISSN)1097-4547.

Nakamura ZM, Nash RP, Laughon SL, Rosensteil DL. 2021. Neuropsychiatric complications of COVID-19. *Current Psychiatry Reports* 23(5):1–9 DOI 10.1007/s11920-021-01237-9.
Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, Cook JR, Nordvig AS, Shalev D, Sehrawat TS. 2021. Post-acute COVID-19 syndrome. Nature Medicine 27(4):601–615 DOI 10.1038/s41591-021-01283-z.

Nestler EJ, Barrot M, DiLeone RJ, Eisch AJ, Gold SJ, Monteggia LM. 2002. Neurobiology of depression. Neuron 34(1):13–25 DOI 10.1016/S0896-6273(02)00653-0.

Ni HT, Hu S, Sheng WS, Olson JM, Cheeran MC-J, Chan AS, Lokensgard JR, Peterson PK. 2004. High-level expression of functional chemokine receptor CXCR4 on human neural precursor cells. Developmental Brain Research 152(2):159–169 DOI 10.1016/j.devbrainres.2004.06.015.

Nikayin S, Rabiee A, Hashem MD, Huang M, Bienvenu OJ, Turnbull AE, Needham DM. 2016. Anxiety symptoms in survivors of critical illness: a systematic review and meta-analysis. General Hospital Psychiatry 43(2):23–29 DOI 10.1016/j.genhosppsych.2016.08.005.

Nile SH, Nile A, Qiu J, Li L, Jia X, Kai G. 2020. COVID-19: pathogenesis, cytokine storm and therapeutic potential of interferons. Cytokine & Growth Factor Reviews 53(10223):66–70 DOI 10.1016/j.cytogfr.2020.05.002.

Nuzzo D, Vasto S, Scalisi L, Cottone S, Cambula G, Rizzo M, Giacomazza D, Picone P. 2021. Post-acute COVID-19 neurological syndrome: a new medical challenge. Journal of Clinical Medicine 10(9):1947 DOI 10.3390/jcm10091947.

Oh M-D, Park WB, Choe PG, Choi S-J, Kim J-I, Chae J, Park SS, Kim E-C, Oh HS, Kim EJ. 2016. Viral load kinetics of MERS coronavirus infection. New England Journal of Medicine 375(13):1303–1305 DOI 10.1056/NEJMc1511695.

Orihuela R, McPherson CA, Harry GJ. 2016. Microglial M1/M2 polarization and metabolic states. British Journal of Pharmacology 173(4):649–665 DOI 10.1111/bph.13139.

Pagliaro P, Penna C. 2020. ACE/ACE2 ratio: a key also in 2019 coronavirus disease (Covid-19)? Frontiers in Medicine 7:H1080 DOI 10.3389/fmed.2020.00335.

Palus M, Vancova M, Sirmarova J, Elsterova J, Perner J, Ruzek D. 2017. Tick-borne encephalitis virus infects human brain microvascular endothelial cells without compromising blood-brain barrier integrity. Virology 507(4):110–122 DOI 10.1016/j.virol.2017.04.012.

Parker AM, Sricharoenchai T, Raparla S, Schneck KW, Bienvenu OJ, Needham DM. 2015. Posttraumatic stress disorder in critical illness survivors: a metaanalysis. Critical Care Medicine 43(5):1121–1129 DOI 10.1097/CCM.0000000000000882.

Parnet P, Amindari S, Wu C, Brunke-Reese D, Goujon E, Weyhenmeyer JA, Dantzer R, Kelley KW. 1994. Expression of type I and type II interleukin-1 receptors in mouse brain. Molecular Brain Research 27(1):63–70 DOI 10.1016/0169-328X(94)90185-6.

Pathania M, Yan LD, Bordey A. 2010. A symphony of signals conducts early and late stages of adult neurogenesis. Neuropharmacology 58(6):865–876 DOI 10.1016/j.neuropharm.2010.01.010.

Pedersen SF, Ho Y-C. 2020. SARS-CoV-2: a storm is raging. The Journal of Clinical Investigation 130(5):2202–2205 DOI 10.1172/JCI137647.

Peirce JM, Alviña K. 2019. The role of inflammation and the gut microbiome in depression and anxiety. Journal of Neuroscience Research 97(10):1223–1241 DOI 10.1002/jnr.24476.

Peng H, Huang Y, Rose J, Erichsen D, Herek S, Fujii N, Tamamura H, Zheng J. 2004. Stromal cell-derived factor 1-mediated CXCR4 signaling in rat and human cortical neural progenitor cells. Journal of Neuroscience Research 76:35–50 DOI 10.1002/1053-8462(20040115)76:1<35::AID-JNR1>3.0.CO;2-R.

Persidsky Y, Zheng J, Miller D, Gendelman HE. 2000. Mononuclear phagocytes mediate blood-brain barrier compromise and neuronal injury during HIV-1-associated dementia. Journal of Leukocyte Biology 68(3):413–422 DOI 10.1189/jlb.68.3.413.
Pezzini A, Padovani A. 2020. Lifting the mask on neurological manifestations of COVID-19. Nature Reviews Neurology 16(11):636–644 DOI 10.1038/s41582-020-0398-3.

Quesseveur G, David DJ, Gaillard MC, Pla P, Wu MV, Nguyen HT, Nicolas V, Auregan G, David I, Dranovsky A, Hantraye P, Hen R, Gardier AM, Déglon N, Giaud BP. 2013. BDNF overexpression in mouse hippocampal astrocytes promotes local neurogenesis and elicits anxiolytic-like activities. Translational Psychiatry 3(4):e253 DOI 10.1038/tp.2013.30.

Rabiee A, Nikayin S, Hashem MD, Huang M, Dinglas VD, Bienvenu OJ, Turnbull AE, Needham DM. 2016. Depressive symptoms after critical illness: a systematic review and meta-analysis. Critical Care Medicine 44(9):1744–1753 DOI 10.1097/CCM.0000000000001811.

Rage F, Silhol M, Tapia-Arancibia L. 2006. IL-1β regulation of BDNF expression in rat cultured hypothalamic neurons depends on the presence of glial cells. Neurochemistry International 49(5):433–441 DOI 10.1016/j.neuint.2006.03.002.

Recinto P, Samant ARH, Chavez G, Kim A, Yuan CJ, Soleiman M, Grant Y, Edwards S, Wee S, Koob GF. 2012. Levels of neural progenitors in the hippocampus predict memory impairment and relapse to drug seeking as a function of excessive methamphetamine self-administration. Neuropsychopharmacology 37(5):1275–1287 DOI 10.1038/npp.2011.315.

Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, Koffel JB. 2021. PRISMA-S: an extension to the PRISMA statement for reporting literature searches in systematic reviews. Journal of the Medical Library Association 109(2):174–200 DOI 10.5195/jmla.2021.962.

Rhea EM, Banks WA. 2019. Role of the blood-brain barrier in central nervous system insulin resistance. Frontiers in Neuroscience 13:7300 DOI 10.3389/fnins.2019.00521.

Rice GI, Thomas DA, Grant PJ, Turner AJ, Hooper NM. 2004. Evaluation of angiotensin-converting enzyme (ACE), its homologue ACE2 and neprilysin in angiotensin peptide metabolism. Biochemical Journal 383(1):45–51 DOI 10.1042/BJ20040634.

Roddy D, O’Keane V. 2019. Cornu ammonis changes are at the core of hippocampal pathology in depression. Chronic Stress 3:2470547019849376 DOI 10.1080/2470547019849376.

Roddy DW, Farrell C, Doolin K, Roman E, Tozzi L, Frodl T, O’Keane V, O’Hanlon E. 2019. The hippocampus in depression: more than the sum of its parts? Advanced hippocampal substructure segmentation in depression. Biological Psychiatry 85(6):487–497 DOI 10.1016/j.biopsych.2018.08.021.

Rodriguez-Pallares J, Rey P, Parga J, Muñoz A, Guerra M, Labandeira-Garcia J. 2008. Brain angiotensin enhances dopaminergic cell death via microglial activation and NADPH-derived ROS. Neurobiology of Disease 31(1):58–73 DOI 10.1016/j.nbd.2008.03.003.

Rodriguez-Perez AI, Borrajo A, Diaz-Ruiz C, Garrido-Gil P, Labandeira-Garcia JL. 2016. Crosstalk between insulin-like growth factor-I and angiotensin-II in dopaminergic neurons and glial cells: role in neuroinflammation and aging. Oncotarget 7(21):30049–30067 DOI 10.18632/oncotarget.9174.

Rogers JP, Chesney E, Oliver D, Pollak TA, McGuire P, Fusar-Poli P, Zandi MS, Lewis G, David AS. 2020. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. The Lancet Psychiatry 7(7):611–627 DOI 10.1016/S2215-0366(20)30203-0.

Rubin R. 2020. As their numbers grow, COVID-19 long haulers stump experts. JAMA 324(14):1381–1383 DOI 10.1001/jama.2020.17709.

Ryan SM, O’Keeffe GW, O’Connor C, Keeshan K, Nolan YM. 2013. Negative regulation of TLX by IL-1β correlates with an inhibition of adult hippocampal neural precursor cell proliferation. Brain, Behavior, and Immunity 33:7–13 DOI 10.1016/j.bbi.2013.03.005.
Saikarthik J, Saraswathi I, Al-Atram AA. 2021. Does COVID-19 Affect Adult Neurogenesis? A Neurochemical Perspective.

Samsami M, Fatemi A, Jalili Khoshnoud R, Kohansal K, Hussien BM, Soghala S, Taheri M, Ghafoori-Fard S. 2022. Abnormal transcript levels of cytokines among Iranian COVID-19 patients. *Journal of Molecular Neuroscience* 72(1):27–36 DOI 10.1007/s12031-021-01941-4.

Seltzer S. 2020. Linking ACE2 and angiotensin II to pulmonary immunovascular dysregulation in SARS-CoV-2 infection. *International Journal of Infectious Diseases* 101(2):32–45 DOI 10.1016/j.ijid.2020.09.041.

Serrano-Castro PJ, Estivill-Torrús G, Cabezudo-Garcia P, Reyes-Bueno JA, Ciano Petersen N, Aguilar-Castillo MJ, Suárez-Pérez J, Jiménez-Hernández MD, Moya-Molina MÁ, Oliver-Martos B, Arrabal-Gómez C, Rodríguez de Fonseca F. 2020. Impact of SARS-CoV-2 infection on neurodegenerative and neuropsychiatric diseases: a delayed pandemic? *Neurología* (English Edition) 35(4):245–251 DOI 10.1016/j.nrleng.2020.04.002.

Serrano-Castro PJ, Garzón-Maldonado FJ, Casado-Naranjo I, Ollero-Ortiz A, Mínguez-Castellanos A, Iglesias-Espinosa M, Baena-Palomino P, Sánchez-Sanchez V, Sánchez-Pérez RM, Rubí-Callejon J, Estévez-María JC, Galeano-Bilbao B, Romero-Imbroda J, Sobrino B, Arrabal-Gomez C, Oliver-Martos B, Muñoz-Becerra L, Requena N, González Álvarez de Sotomayor MDM, Estivill-Torrus G, Suarez J, Ciano-Petersen NL, Pons-Pons G, Reyes-Bueno JA, Cabezudo-Garcia P, Aguilar-Castillo MJ, De la Cruz Cosme C, Duque-Holguaera M, Cuartero-Rodriguez E, Vilches-Carrillo RM, Carrera-Muñoz I, Carnero-Pardo C, Ramirez-Garcia T, Oropesa JM, Dominguez-Mayoral A, Pelaez-Viñas N, Valiente L, de Fonseca FR. 2022. The cognitive and psychiatric subacute impairment in severe Covid-19. *Scientific Reports* 12(1):3563 DOI 10.1038/s41598-022-07559-9.

Shen S-W, Duan C-L, Chen X-H, Wang Y-Q, Sun X, Zhang Q-W, Cui H-R, Sun F-Y. 2016. Neurogenic effect of VEGF is related to increase of astrocytes transdifferentiation into new mature neurons in rat brains after stroke. *Neuropharmacology* 108:451–461 DOI 10.1016/j.neuropharm.2015.11.012.

Shi Y, Li Z, Yang C, Liu C. 2021. The role of gut-brain axis in SARA-CoV-2 neuroinvasion: culprit or innocent bystander? *Brain, Behavior, and Immunity* 94:476–477 DOI 10.1016/j.bbi.2021.01.024.

Shohayeb B, Diab M, Ahmed M, Ng DCH. 2018. Factors that influence adult neurogenesis as potential therapy. *Translational Neurodegeneration* 7(1):4 DOI 10.1186/s40035-018-0109-9.

Singh M, Bansal V, Feschotte C. 2020. A single-cell RNA expression map of human coronavirus entry factors. *Cell Reports* 32(12):108175 DOI 10.1016/j.celrep.2020.108175.

Smith JA, Das A, Ray SK, Banik NL. 2012. Role of pro-inflammatory cytokines released from microglia in neurodegenerative diseases. *Brain Research Bulletin* 87(1):10–20 DOI 10.1016/j.brainresbull.2011.10.004.

Solomon IH, Normandin E, Bhattacharyya S, Caserji SS, Keller K, Ali AS, Adams G, Hornick JI, Padera RF Jr, Sabeti P. 2020. Neuropathological features of Covid-19. *New England Journal of Medicine* 383(10):989–992 DOI 10.1056/NEJMcc2019373.

Song H, Stevens CF, Gage FH. 2002. Astroglia induce neurogenesis from adult neural stem cells. *Nature* 417(6884):39–44 DOI 10.1038/417039a.

Suh HS, Zhao ML, Derico L, Choi N, Lee SC. 2013. Insulin-like growth factor 1 and 2 (IGF1, IGF2) expression in human microglia: differential regulation by inflammatory mediators. *Journal of Neuroinflammation* 10(1):1–12 DOI 10.1186/1742-2094-10-37.

Sulzer D, Antonini A, Leta V, Nordvig A, Smeyne RJ, Goldman JE, Al-Dalahmah O, Zecca L, Sette A, Bubacco L. 2020. COVID-19 and possible links with Parkinson’s disease and...
parkinsonism: from bench to bedside. npj Parkinson’s Disease 6(1):1–10 DOI 10.1038/s41531-020-00123-0.

Tang Q, Wang Y, Ou L, Li J, Zheng K, Zhan H, Gu J, Zhou G, Xie S, Zhang J, Huang W, Wang S, Wang X. 2021. Downregulation of ACE2 expression by SARS-CoV-2 worsens the prognosis of KIRC and KIRP patients via metabolism and immunoregulation. International Journal of Biological Sciences 17(8):1925–1939 DOI 10.7150/ijbs.57802.

Tavčar P, Potokar M, Kolenc M, Korva M, Avšič-Županc T, Zorec R, Jorgačevski J. 2021. Neurotropic viruses, astrocytes, and COVID-19. Frontiers in Cellular Neuroscience 15:1

Thakur KT, Miller EH, Glendinning MD, Al-Dalahmah O, Banu MA, Boehme AK, Boubour AL, Bruce SS, Chong AM, Claassen J. 2021. COVID-19 neuropathology at columbia university irving medical center/New York presbyterian hospital. Brain 144(9):2696–2708 DOI 10.1093/brain/awab148.

Tjalkens RB, Popichak KA, Kirkley KA. 2017. Inflammatory activation of microglia and astrocytes in manganese neurotoxicity. Advances in Neurobiology 18:159–181 DOI 10.1007/978-3-319-60189-2.

Toda T, Parylak SL, Linker SB, Gage FH. 2019. The role of adult hippocampal neurogenesis in brain health and disease. Molecular Psychiatry 24(1):67–87 DOI 10.1038/s41380-018-0036-2.

Triana S, Metz-Zumaran C, Ramirez C, Kee C, Doldan P, Shahriz A, Schraivogel D, Ghosh AR, Sharma AK, Steinmetz LM. 2021. Single-cell analyses reveal SARS-CoV-2 interference with intrinsic immune response in the human gut. Molecular Systems Biology 17(4):e10232 DOI 10.15252/msb.202110232.

Tu Y, Zhang Y, Li Y, Zhao Q, Bi Y, Lu X, Kong Y, Wang L, Lu Z, Hu L. 2021. Post-traumatic stress symptoms in COVID-19 survivors: a self-report and brain imaging follow-up study. Molecular Psychiatry 26(12):7475–7480 DOI 10.1038/s41380-021-01223-w.

Vallieres L, Campbell IL, Gage FH, Sawchenko PE. 2002. Reduced hippocampal neurogenesis in adult transgenic mice with chronic astrocytic production of interleukin-6. Journal of Neuroscience 22(2):486–492 DOI 10.1523/JNEUROSCI.22-02-00486.2002.

Van Riel D, Verdijk R, Kuiken T. 2015. The olfactory nerve: a shortcut for influenza and other viral diseases into the central nervous system. The Journal of Pathology 235(2):277–287 DOI 10.1002/path.4461.

Vardhana SA, Wolchok JD. 2020. The many faces of the anti-COVID immune response. Journal of Experimental Medicine 217(6):166 DOI 10.1084/jem.20200678.

Vargas G, Geraldo LHM, Salomão NG, Paes MV, Lima FRS, Gomes FCA. 2020. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and glial cells: insights and perspectives. Brain, Behavior 7:100127 DOI 10.1016/j.bbih.2020.100127.

Venters HD, Tang Q, Liu Q, VanHoy RW, Dantzer R, Kelley KW. 1999. A new mechanism of neurodegeneration: a proinflammatory cytokine inhibits receptor signaling by a survival peptide. Proceedings of the National Academy of Sciences of the United States of America 96(17):9879–9884 DOI 10.1073/pnas.96.17.9879.

Verma S, Kumar M, Gurjave U, Lum S, Nerurkar VR. 2010. Reversal of West Nile virus-induced blood-brain barrier disruption and tight junction proteins degradation by matrix metalloproteinases inhibitor. Virology 397(1):130–138 DOI 10.1016/j.virol.2009.10.036.

Viana SD, Nunes S, Reis F. 2020. ACE2 imbalance as a key player for the poor outcomes in COVID-19 patients with age-related comorbidities—Role of gut microbiota dysbiosis. Ageing Research Reviews 62(12):101123 DOI 10.1016/j.arr.2020.101123.
Villar-Cheda B, Valenzuela R, Rodríguez-Perez AI, Guerra MJ, Labandeira-Garcia JL. 2012. Aging-related changes in the nigral angiotensin system enhances proinflammatory and pro-oxidative markers and 6-OHDA-induced dopaminergic degeneration. *Neurobiology of Aging* 33(1):204.e1–204.e11 DOI 10.1016/j.neurobiolaging.2010.08.006.

Villeda SA, Luo J, Mosher KI, Zou B, Britschgi M, Bieri G, Stan TM, Fainberg N, Ding Z, Eggel A, Lucin KM, Czirr E, Park J-S, Couillard-Després S, Aigner L, Li G, Peskind ER, Kaye JA, Quinn JF, Galasko DR, Xie XS, Rando TA, Wyss-Coray T. 2011. The ageing systemic milieu negatively regulates neurogenesis and cognitive function. *Nature* 477(7362):90–94 DOI 10.1038/nature10357.

Wang B, Jin K. 2015. Current perspectives on the link between neuroinflammation and neurogenesis. *Metabolic Brain Disease* 30(2):355–365 DOI 10.1007/s11011-014-9523-6.

Wang X-L, Iwanami J, Min L-J, Tsukuda K, Nakaoka H, Bai H-Y, Shan B-S, Kan-No H, Kukida M, Chisaka T. 2016. Deficiency of angiotensin-converting enzyme 2 causes deterioration of cognitive function. *npj Aging and Mechanisms of Disease* 2(1):1–8 DOI 10.1038/npjamd.2016.24.

WHO. 2022. COVID-19: symptoms and severity. Available at https://www.who.int/westernpacific/emergencies/covid-19/information/asymptomatic-covid-19 (accessed 26 April 2022).

Widera D, Holtkamp W, Entschladen F, Niggemann B, Zänker K, Kaltschmidt B, Kaltschmidt C. 2004. MCP-1 induces migration of adult neural stem cells. *European Journal of Cell Biology* 83(8):381–387 DOI 10.1078/0171-9335-00403.

Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. 2020. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. *JAMA* 324(8):782–793 DOI 10.1001/jama.2020.12839.

Winner B, Kohl Z, Gage FH. 2011. Neurodegenerative disease and adult neurogenesis. *European Journal of Neuroscience* 33(6):1139–1151 DOI 10.1111/j.1460-9586.2011.07613.x.

Woo MS, Malsy J, Pöttgen J, Seddiq Zai S, Ufer F, Hadjilaou A, Schmiedel S, Addo MM, Gerloff C, Heesen C, Schulze Zur Wiesch J, Friese MA. 2020. Frequent neurocognitive deficits after recovery from mild COVID-19. *Brain Communications* 2(2):fca205 DOI 10.1093/braincomms/fcaa205.
COVID-19 patients. *Emerging Microbes & Infections* **9**(1):761–770
DOI 10.1080/22221751.2020.1747363.

Yap NY, Toh YL, Tan CJ, Acharya MM, Chan A. 2021. Relationship between cytokines and brain-derived neurotrophic factor (BDNF) in trajectories of cancer-related cognitive impairment. *Cytokine* **144**(323–330):155556 DOI 10.1016/j.cyto.2021.155556.

Yapici-Eser H, Koroglu YE, Oztop-Cakmak O, Keskin O, Gursoy A, Gursoy-Ozdemir Y. 2021. Neuropsychiatric symptoms of COVID-19 explained by SARS-CoV-2 proteins’ mimicry of human protein interactions. *Frontiers in Human Neuroscience* **15**:22
DOI 10.3389/fnhum.2021.656313.

Yuan Y-M, Luo L, Guo Z, Yang M, Ye R-S, Luo C. 2015. Activation of renin-angiotensin–aldosterone system (RAAS) in the lung of smoking-induced pulmonary arterial hypertension (PAH) rats. *Journal of the Renin-Angiotensin-Aldosterone System* **16**(2):249–253
DOI 10.1177/1470320315576256.

Zhang L, Zhang J, You Z. 2018. Switching of the microglial activation phenotype is a possible treatment for depression disorder. *Frontiers in Cellular Neuroscience* **306**:621
DOI 10.3389/fncel.2018.00306.

Zhang Y, Gao Q, Wu Z, Xue H, Liu B, Zhao P. 2019. Dexmedetomidine promotes hippocampal neurogenesis and improves spatial learning and memory in neonatal rats. *Drug Design, Development and Therapy* **13**:4439–4449
DOI 10.2147/DDDT.

Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X. 2020. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *The Lancet* **395**(10229):1054–1062
DOI 10.1016/S0140-6736(20)30566-3.

Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R. 2020. A novel coronavirus from patients with pneumonia in China, 2019. *New England Journal of Medicine* **382**(8):727–733
DOI 10.1056/NEJMoA2001017.