Acta Neurologica Belgica (2023) 123:1247–1256
https://doi.org/10.1007/s13760-023-02291-1

REVIEW ARTICLE

The functional and structural changes in the hippocampus of COVID-19 patients

Ali Nouraeinejad[1]

Received: 14 February 2023 / Accepted: 15 May 2023 / Published online: 25 May 2023

Abstract

Since the hippocampus is predominantly susceptible to injuries caused by COVID-19, there are increasing data indicating the likelihood of post-infection memory loss and quickening neurodegenerative disorders, such as Alzheimer's disease. This is due to the fact that the hippocampus has imperative functions in spatial and episodic memory as well as learning. COVID-19 activates microglia in the hippocampus and induces a CNS cytokine storm, leading to loss of hippocampal neurogenesis. The functional and structural changes in the hippocampus of COVID-19 patients can explain neuronal degeneration and reduced neurogenesis in the human hippocampus. This will open a window to explain memory and cognitive dysfunctions in "long COVID" through the resultant loss of hippocampal neurogenesis.

Keywords Hippocampus · Memory · Neurogenesis · COVID-19 · Central nervous system · Neuroinflammation

Introduction

At the beginning of the coronavirus disease 2019 (COVID-19) outbreak, it was urgent to manage the acute complications of the disease; however, the management of the long-term sequelae of COVID-19 has become a major concern afterward [1–5].

Post-COVID syndrome, also known as "long COVID" or "persistent COVID," typifies a broad collection of complaints stated by COVID-19 patients after "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2) infection [1–11].

Studies have extensively illustrated that "long COVID" after discharge from hospital consist of an assortment of neuropsychiatric complaints, such as defective instant verbal memory and learning, deferred verbal memory difficulties, verbal fluency problems, working memory issues, anxiety, depression, and post-traumatic stress disorder (PTSD) [5, 12]. These complaints can persist for at least one year [13]. In some COVID-19 patients, cognitive impairments can even deteriorate over time [14]. Although several pathological mechanisms have been proposed [3], the pathological basis of these complaints remains unidentified.

Long-term outcomes of other inflammatory circumstances (e.g., sepsis, after major surgery, or respiratory difficulties, such as pneumonia and acute respiratory distress syndrome) have been found to negatively affect an individual's life in numerous features [15–19]. This is also the case for patients with "long COVID" due to neuroinflammation [1–5]. These include a number of aspects of daily activities, such as employment, education, housework, and hobbies, even years after the initial inflammatory involvement has been cleared [5, 20].

A better understanding of the pathological factors causing these long-term complications will help in targeted therapy selection at an appropriate stage of the disease [1–5].

Since the hippocampus is predominantly susceptible to injuries caused by COVID-19 [3], there are increasing data indicating the likelihood of post-infection memory loss and quickening neurodegenerative disorders, such as Alzheimer's disease [5, 21]. This review discusses the involvement of the hippocampus in COVID-19 patients, especially those patients with "long COVID." This will help identify the pathological factors associated with long-term neuropsychiatric complications of COVID-19. In addition, this can provide an insight into the pathobiology of neurodegenerative disorders, such as Alzheimer's disease.

✉ Ali Nouraeinejad
AliNouraeinejad@yahoo.com

[1] Faculty of Brain Sciences, Institute of Ophthalmology, University College London (UCL), London, UK

The hippocampus

The hippocampus, as an extension of the temporal component of the cerebral cortex [22, 23], is a complex brain component located deep into the temporal lobe [23, 24]. The hippocampus is a component of "the hippocampal formation" and contains several limbs [23].

The hippocampus has imperative functions in spatial and episodic memory [24] as well as learning [23]. The persistent creation of new neurons in the adult hippocampus has long been reported [25]. These new neural cells are derived from self-reproducing multipotent adult neural stem cells (NSCs) located in the subgranular zone (SGZ) of the dentate gyrus (DG) [26, 27]. Neurogenesis in the adult dentate gyrus grants an assortment of forms of hippocampus-dependent learning and memory [27–32]. As a vulnerable configuration, the hippocampus can be upset by a range of neurological and psychiatric disorders [23, 33].

COVID-19 activates microglia in the hippocampus and induces a CNS cytokine storm, leading to loss of hippocampal neurogenesis

Microglia, which are highly complex cells with very active and driving processes even in the state of non-pathological circumstances, represent resident macrophage-like cells in the central nervous system (CNS) [34–37]. Microglia are responsible for synaptic structuring and restoration of neuronal maintenance for the period of development [34–36]. They perform phagocytosis of apoptotic cells in the developing brain, myelin revenue, regulation of neuronal excitability (a large and fast alteration of membrane voltage in reaction to a very small stimulus), phagocytic debris elimination, brain defense, and renovate [34–36]. Even though they monitor the cerebral microenvironment to provide the homeostasis of the CNS and proper modification of neuronal processes by eradicating dendritic spines and synapses for the period of neuronal development, microglia can shift to an activated, neurotoxic status [34, 35, 37].

The activation of microglia in the hippocampus of deceased patients with "long COVID" and cognitive impairments as well as mild COVID-19 animal model, which was illustrated to be regulated by elevated levels of C–C motif chemokine ligand 11 (CCL11), was found to be connected with inhibited neurogenesis [37]. The inhibited neurogenesis in the hippocampus can clarify impaired memory formation in patients with "long COVID" and cognitive impairments [37]. In addition, CCL11 has been linked to aging and inhibition of neurogenesis [38]. In agreement with these findings, patients with "long COVID" and cognitive impairments showed higher levels of serum CCL11 than those with "long COVID" who did not have cognitive deficits [37].

The result of CCL11 on microglial activation in the hippocampus and prevention of neurogenesis necessitates supplementary examinations of the implications of chemokines and cytokines distinctive of brain networks to offer an outline to manage the neurologic and psychiatric complaints of "long COVID." Therefore, CCL11 levels in the plasma or cerebrospinal fluid can be used as a biomarker to potentially identify COVID-19 patients with cognitive deficits.

Tumor necrosis factor alpha (TNF-α), interleukin-1 alpha (IL-1α), complement component 1q (C1q), and IL-1β are inflammatory mediators secreted by activated pro-inflammatory microglia [34, 35, 39]. They can then activate pro-inflammatory astrocytes and fuel a secondary inflammatory response [34, 35, 39–41]. After microglial and astrocytic activation, neuroinflammation results in reactive oxygen species (ROS) and oxidative stress production [34, 35, 39]. This consequently disturbs hippocampal neuronal cells, leading to memory difficulties and neuronal apoptosis [35, 39, 42–44]. These results can explain the potential damaging consequences of SARS-CoV-2-linked glial activation, neuroinflammation, and apoptosis.

Other studies have also reported that animals and humans deceased from COVID-19 showed evidence of reduced neurogenesis in the hippocampal dentate gyrus through microglial activation and microglial and neuronal expression of IL-1β and IL-6 [45]. Notably, IL-1β and IL-6, which are elevated in COVID brains, have antineurogenic effects on the hippocampus [45]. Therefore, anti-IL-6 and anti-IL-1β treatments [46] may be useful in restricting an expanded cytokine storm in COVID-19 patients. These reports advocate the concept that the COVID-19 cytokine storm is mainly responsible for neuroinflammation and neuronal injury, leading to distorted neurotransmission and brain function.

COVID-19 results in neuronal degeneration and reduced neurogenesis in the human hippocampus

When hippocampal tissue samples collected from deceased COVID-19 patients were examined, hippocampal samples showed enormous degeneration of neuronal cells and irregularities in glial cell morphology [39]. Hippocampal tissue samples showed morphological alterations in pyramidal cells, an escalation in cell death, a decrease in neurogenesis, and irregularity in the spatial allocation of neurons in the pyramidal and granular layers [39]. The death of pyramidal cells and apoptosis of granular cells in the hippocampus of the COVID-19 group were also recorded [39].

Morphological features and allocation of astrocytes and microglial cells were also shown to change in these samples

[39]. Therefore, memory impairment secondary to these changes in the hippocampus may cause a long-term neurological complication in patients with "long COVID."

Furthermore, neurogenesis was reduced in the COVID-19 group, and these neural stem cells may have encountered apoptosis [39]. This can be due to the microglial activation and the subsequent production of inflammatory cytokines, such as TNF-α, IL-6, and IL-1β, which can cause neuroinflammation, leading to impaired neurogenesis and reduced inhabited neural stem cells proliferation [5, 39]. This eventually results in cognitive decline due to the destruction of spatial memory and learning [5, 39, 47, 48].

A reported decrease in the dendritic length and number of dendritic spines of pyramidal neurons in the hippocampus of the COVID-19 group also revealed a decrease in synaptic plasticity and, accordingly, memory loss [39].

Changes in gray matter volumes in neuropsychiatric long COVID syndrome

Although confirmation for long-term brain constructional alterations (i.e. on the neural correlates of the neuropsychiatric complaints of "long COVID") is limited, one investigation found brain architectural irregularities in "long COVID" (three months after acute COVID-19), which were enlarged bilateral gray matter volumes in olfactory cortices, hippocampi, insulas, left Rolandic operculum, left Heschl's gyrus, and right cingulate gyrus in COVID-19 patients compared to healthy controls [14]. They also recorded a link between gray matter volume changes and indications of memory decline and loss of smell [14]. Another investigation, which was performed 6 months after acute COVID-19, acknowledged enlarged gray matter volumes in the bilateral hippocampus and amygdala, with gray matter volumes of the left hippocampus and amygdala being contrarily interrelated to post-traumatic stress symptoms [49]. In a recent cross-sectional study [50], gray matter volume in patients with "long COVID" was noticeably enlarged in a number of clusters (spanning fronto-temporal areas, insula, hippocampus, amygdala, basal ganglia, and thalamus in both hemispheres) than in healthy controls. The enlargement of gray matter volumes in patients with "long COVID," when compared to healthy controls, may indicate compensatory or recovery properties [50]. Two processes may explain the enlargement of gray matter volumes in patients with "long COVID." This may be due to the migration of neuroblasts or an amplified functional process leading to hypertrophy of neurons and augmentation of dendritic links [3, 50–52]. Apart from these compensatory or recovery properties, another explanation for enlarged gray matter volumes in COVID-19 patients may be the continuing inflammatory processes, leading to endothelial activation, microvascular impairment, and vasogenic boost of tissue water [3, 50, 53].

In contrast, others reported no gray matter volume alterations in patients with "long COVID" when compared to non-infected individuals [54]. A longitudinal investigation also recorded reduced cortical thickness in the orbitofrontal and parahippocampal gyrus in individuals formerly infected with SARS-CoV-2 compared to their pre-infection conditions [55].

Longitudinal neurocognitive profile of "long COVID"

The hippocampus has been called as one of the earliest and most distressed configurations of the brain throughout acute or chronic inflammatory circumstances owing to its specific susceptibility to neuroinflammatory incidents [1–5, 20, 35, 56]. This is in agreement with several animal replicas where cognitive defects (particularly learning and memory) are induced after the resolution of the primary inflammatory reaction [57–60]. This may be explained by the close anatomical links between the limbic system, which is accountable for both emotional reactions and many cognitive functions, and the hypothalamus, which is vital for the immune-brain bond [61].

The initial results of a longitudinal investigation [20] on the assessment of episodic verbal memory have illustrated weaker performance in COVID-19 patients than in healthy controls. They also recorded reduced brain volumes in particular brain regions of patients with severe COVID-19 compared with healthy controls and asymptomatic patients [20].

Outstandingly, a longitudinal brain imaging survey [55], which compared magnetic resonance imaging (MRI) probes before and after the COVID-19 outbreak in both cases of positive infection with SARS-CoV-2 and healthy controls, reported a larger loss of gray matter in COVID-19 patients, particularly in the orbitofrontal cortex and parahippocampal gyrus, higher indications of tissue injury in areas linked to taste and smell, and a greater decrease in general brain size, even in mild to moderate COVID-19 patients compared to controls [55]. Patients with "long COVID" also had poorer overall results in cognitive assessments compared with the control group [55].

Neurogenesis is disturbed in human hippocampal progenitor cells when they are exposed to serum samples from hospitalized COVID-19 patients with neurological complaints

In comparison to serum specimens of sex- and age-matched COVID-19 patients without delirium, an in vitro experimental investigation found that serum from hospitalized COVID-19 patients with delirium decreased hippocampal-dependent neurogenic, cell proliferative, and neuronal differentiation mechanisms while increasing apoptosis, and this ending was illustrated to be controlled by IL-6-induced secretion of the

downstream inflammatory cytokines IL-12 and IL-13 [62]. These findings support the notion that the brain construction of cytokines in reaction to peripheral inflammation is an imperative manner for the development of neurological complaints caused by COVID-19 [5, 62]. These findings are in agreement with other findings that high concentrations of in vitro IL-6 [63, 64], which resemble the peripheral blood of COVID-19 patients [65, 66], IL-1β, and interferon-alpha (IFN-α) [67–70] can decrease neurogenesis and amplify cell death in human hippocampal progenitor cells. Since higher amounts of IL-6 have also been recorded in the periphery and cerebrospinal fluid (CSF) of COVID-19 patients [66, 71–74], anti-IL-6 may be generally an imperative therapeutic idea for COVID-19 complications.

Furthermore, matching of cellular replica with serum specimens from patients in receipt of IFN-α therapy for hepatitis C also decreased neurogenesis and boosted cell death [75], suggesting the development of IFN-α-induced depression [34, 35, 62, 76]. Remarkably, in a similar manner to COVID-19 patients, individuals in receipt of IFN-α therapy can also experience cognitive defects, distraction, memory decline, and confusion [77].

Hippocampal-prefrontal connectivity prior to the COVID-19 pandemic may be used to predict stress reactivity

Adolescence is a developmental era outlined by the onset of puberty and is distinguished by the maturation of cognitive and affective networks [78, 79]. The social experiences of this developmental era play an important role in the onset of critical plasticity and maturation of the association cortex [80]. For instance, a study of children who witnessed Hurricane Irma in Florida reported decreased neurogenesis and distorted memory function in the hippocampus compared with non-exposed children [81].

Studies support the notion that stress influences systems that undergo considerable maturation during adolescence [3, 5, 82]. These systems include the hippocampus and amygdala and their connectivity to the prefrontal cortex areas [5, 82]. For example, the hippocampus, which is principally involved in cognitive operations such as memory, can be distressed by chronic stress, resulting in changes in volume [83], microstructure [81], utility [81, 84], and connectivity with other areas, especially the prefrontal cortex [83, 84]. Likewise, the amygdala, which is implicated in dealing with emotion, exhibits considerable changes following chronic stress at the neuronal level [85] as well as in its connectivity with the prefrontal cortex [86–88]. Remarkably, the resting-position operational connectivity of both the amygdala and hippocampus with the prefrontal cortex illustrates prolonged expansion for the duration of adolescence [82].

In this regard, when the functional connectivity of the hippocampus and amygdala subareas with the prefrontal cortex in two different periods, pre-pandemic compared to the COVID-19 pandemic, were comparatively examined in a cohort of adolescents and young adults [82], older participants experienced higher grades of COVID-specified stress, worry, and anxiety throughout the COVID-19 outbreak. These results showed that the existence of more adult-like connectivity between "posterior hippocampus" and "anterior ventromedial prefrontal cortex" earlier than the onset of the COVID-19 outbreak was related to higher grades of self-reported anxiety for the duration of the COVID-19 outbreak [82]. Since stress hormone receptors are highly located in the hippocampus [89], the expanded neurogenesis in the hippocampus may be disturbed by steroid hormones produced throughout stress [90, 91].

The explanation of memory and cognitive dysfunctions in "long COVID" through the loss of hippocampal neurogenesis

The hippocampus, a delicate structure within the brain, has various functions, especially in adult neurogenesis [3, 5, 11, 23]. Therefore, some of the long-standing complications of COVID-19, such as "brain fog" or cognitive impairment, can be suggestive of hippocampal injury [3, 5, 11, 23, 92, 93].

The hippocampus is involved in many functions, such as memory, spatial working memory through transient high gamma synchrony [94], executive functions, path integration, and spatial processing [3, 5, 35, 45, 94]. These hippocampal abilities rely on adult hippocampal neurogenesis [3, 5, 45, 95]. Notably, IL-1β and IL-6, which are elevated in COVID brains, have antineurogenic properties in the hippocampus [3, 5, 45]. Therefore, hippocampal injury may cause post-acute sequelae of COVID-19 (PASC) symptoms [3, 5, 45]. This is confirmed by neuroimaging probes in post-acute COVID-19 patients where disturbances in fractional anisotropy and diffusivity are indicative of microstructural and operational changes in the hippocampus [14].

Investigations have illustrated hippocampal hyperintensity and atrophy on brain MRI scans [96]. Even though no viral RNA of COVID-19 was directly isolated in the brain, the hippocampus in these investigations exhibited microglial activation, T lymphocyte infiltration, and elevations in the levels of IL-1 and IL-6, which are indicative of neuroinflammation [11]. In this regard, in addition to changes in the cellular morphology, spatial and structural changes occurred in the neuronal, microglial, and astrocytic cellular populations [97].

Prolonged inflammation, neuronal expression of interleukins, blood–brain barrier disturbance, and microglia activation were found to lead to distorted neurotransmission, impaired neurogenesis, and neuronal injury in the brains

of COVID-19 patients, thereby describing neuropsychiatric complaints of COVID-19 patients compared with uninfected healthy controls [45]. These implications on the hippocampus, especially the loss of hippocampal neurogenesis in the brains of COVID-19 patients, also elucidate learning, memory, and executive impairments in COVID-19 patients compared with uninfected healthy controls [45].

Decedents with depressive illness, who died from suicide, had elevated proinflammatory and reduced neurogenesis indicators in the postmortem hippocampus [98], accompanied by a smaller dentate gyrus, fewer granule neurons, and neural progenitor cells [99]. Thus, neuroinflammation is evidently involved in the pathogenesis of neuropsychiatric complaints, declining neurotransmitters and neurotrophins, and increasing excitotoxicity [3, 5, 100, 101].

Alzheimer's disease can be initiated or deteriorated in COVID-19 patients due to reduced hippocampal neurogenesis

The hippocampus, which is a brain structure involved in learning and memory, is particularly susceptible to injury in the early phases of Alzheimer's disease, an age-related neurodegenerative disease attributed to a gradual decline in memory and worsening of cognitive abilities [5, 27]. Changes in neurogenesis in the adult hippocampus signify an early vital incident in the course of Alzheimer's disease [5, 27]. Since hippocampal neurogenesis functions in structural plasticity and neural preservation, aberrant neurogenesis may exacerbate neuronal susceptibility to injury in Alzheimer's disease and lead to memory decline [5, 27]. This is due to the observations that encouragement of adult hippocampal neurogenesis advances pattern separation and spatial memory [30, 31], while a decrease in neurogenesis causes cognitive deficits related to aging and neurodegenerative diseases, including Alzheimer's disease [95, 102]. This is also supported by the finding that the hippocampus is one of the earliest areas to be distressed in Alzheimer's disease [103].

Histological brain analyses of post-mortem humans [104–106] and experimental animals [107] have specified that SARS-CoV-2 infection damages the neurogenic route in the hippocampus due to neuroinflammation. In this regard, the neuroinflammation-induced decline in hippocampal neurogenesis was also shown to act on the onset and progression of dementia in COVID-19 patients [108].

The proliferation and neuronal differentiation of neural stem cells can be suppressed by increased amounts of proinflammatory cytokines due to the pathogenic course of neurological disorders and anomalous amounts of stress hormones [5, 35, 108]. These factors can also interrupt the efficient incorporation of newborn neurons in the hippocampus in due course [5, 35, 108–112]. Impaired neurogenesis is known to be coupled with memory loss in neurological disorders due to neuroinflammation [3, 113]. This is also the case for COVID-19 where SARS-CoV-2 has the potential to infect neural stem cells in the hippocampus and brain organoids [3, 65, 108, 114, 115]. Clinical data also support the notion that Alzheimer's disease can be initiated [116] or deteriorated [117] in COVID-19 patients.

The high rate of "long COVID" symptoms, especially cognitive impairment, can justify the need for therapeutic interventions in affected individuals

The incidence of "long COVID" is anticipated at 10–30% of non-hospitalized patients, 50–70% of hospitalized patients [118, 119], and 10–12% of vaccinated patients [120]. "Long COVID" can be related to all ages and acute phase disease severities [121]. Other studies have estimated that 31–69% of COVID-19 survivors experience "long COVID" symptoms after initial recovery from SARS-CoV-2 infection [122, 123].

In a UK retrospective cohort study of 236,379 confirmed COVID-19 patients, one in three patients reported neuropsychiatric complaints six months after SARS-CoV-2 infection [124]. In a meta-analysis, fatigue and cognitive impairment were reported in 32 and 22% of patients with COVID-19, respectively, 12 weeks after infection [119]. Fatigue, cognitive impairment, joint pain, anxiety, and depression were found to be the primary clinical symptoms of "long COVID" in a meta-analysis of 36 studies [125]. Fatigue, malaise, and cognitive impairment were also reported to be the most prevalent symptoms experienced by "long COVID" patients [126].

Moreover, cognitive related symptoms were found to develop at later "long COVID" stages [127]. The persistent symptoms of "long COVID" reveal chronic damages to multiple organs [127]. Such health conditions impose a considerable burden on the quality of life of COVID survivors [128–130]. Mental health conditions, such as anxiety and depression, returned to normal over time in people with a history of COVID-19; however, increased risks of cognitive impairment (brain fog), seizures, dementia, psychosis, and other neurocognitive conditions continued for at least 2 years [131].

When objective versus subjective measures were used, higher rates of cognitive impairment were reported [119], indicating that a subset of those with cognitive impairment may not know and/or report their impairment.

Since a large number of patients with "long COVID" are unable to return to work [126], this scale of newly disabled people can contribute to labor shortages. Cognitive impairments in "long COVID" were found to be devastating, at the same magnitude as intoxication in the UK drink driving

limit or 10 years of cognitive aging [132], and may increase over time [121].

Although there are presently no effective treatments for "long COVID," treatments for certain "long COVID" symptoms have been effective for subsets of populations [121]. For example, a proposal to apply brain injury recovery treatments for cognitive impairment in COVID-19 survivors has been proposed by the author [1].

Since the current results advocate that cognitive impairment is related to neuroinflammation, anti-inflammatory therapies have been applied. However, in a prospective observational study of patients (median age, 61 years) who survived intensive care unit (ICU) admission due to severe COVID-19, researchers found that administration of IL-6 receptor antagonists and/or dexamethasone (a long-acting synthetic corticosteroid) did not change the overall incidence of cognitive impairment or subjective long-term results at six months post-ICU [133]. Objective cognitive impairment did not correlate with subjective cognitive impairment in this study [133], which was also reported in another cognition study [134].

Although these key clinical findings are vital to have a better perspective of "long COVID," especially cognitive impairment, current diagnostic and therapeutic selections are still inadequate, and clinical trials need to be scheduled to investigate leading hypotheses.

Conclusion

The hippocampus, which is important in memory, spatial working memory through transient high gamma synchrony, executive functions, path integration, and spatial processing, is recognized as one of the earliest and most distressed configurations of the brain throughout acute or chronic inflammatory circumstances owing to its specific susceptibility to neuroinflammatory incidents. This is also the case in COVID-19, which activates microglia in the hippocampus and induces a CNS cytokine storm, leading to the loss of hippocampal neurogenesis. The details of functional and structural changes of the hippocampus in COVID-19 patients, which were explored in this review, explain memory and cognitive dysfunctions in "long COVID" through the loss of hippocampal neurogenesis. The initial results of a longitudinal investigation on the assessment of episodic verbal memory have also practically illustrated weaker performance in COVID-19 patients than in healthy controls. This clinical outcome additionally confirms the role of the hippocampus in cognitive function in COVID-19 patients.

A better perspective of the cellular features of COVID-19 brain injury could assist in interventions to ease long-term neuropsychiatric complaints. These therapeutic aids may include antagonists of cytokines or other pathway modulators. Alleviating the long-term post–COVID-19 complications of cognition, emotion, and behavior would help reduce the disease burden. The neuropathology of COVID-19 may provide a replica for decoding the neurodegenerative mechanisms related to neuroinflammation in other brain diseases and for developing new therapeutic methods.

Acknowledgements The author would like to express his honest gratitude and high respect for the lifetime support of his father, Mohammad Nouraeinejad.

Author contributions The work has all been done by AN.

Funding The author received no financial support for the research, authorship, and/or publication of this article. Therefore, the author reported that there was no funding associated with the work featured in this article.

Data availability No applicable.

Code availability No applicable.

Declarations

Conflicts of interest The author declares no conflict of interest.

Ethical approval No applicable.

Consent to participate No applicable.

Consent to publication The author has full right to publish this manuscript.

References

1. Nouraeinejad A (2022) A proposal to apply brain injury recovery treatments for cognitive impairment in COVID-19 survivors. Int J Neurosci. https://doi.org/10.1080/00207454.2022.2084091
2. Nouraeinejad A (2022) Visuospatial impairment is of concern in patients with COVID-19. Int J Neurosci 7:1–2. https://doi.org/10.1080/00207454.2022.2145474
3. Nouraeinejad A (2022) The pathological mechanisms underlying brain fog or cognitive impairment in long COVID. Int J Neurosci 21:1–4. https://doi.org/10.1080/00207454.2022.2150845
4. Nouraeinejad A (2023) The potential risk of falling among COVID-19 survivors with cognitive impairment. Brain Inj 37(1):85–86. https://doi.org/10.1080/02699052.2022.2144948
5. Nouraeinejad A (2023) Brain fog as a Long-term Sequela of COVID-19. SN Compr Clin Med. 5(1):9. https://doi.org/10.1007/s42399-022-01352-5
6. Zhao YM, Shang YM, Song WB, Li QQ, Xie H, Xu QF, Jia JL, Li LM, Mao HL, Zhou XM, Luo H, Gao YF, Xu AG (2020) Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. E Clin Med 25:100463. https://doi.org/10.1016/j.eclinm.2020.100463
7. Shaw B, Daskareh M, Gholamrezanezhad A (2021) The lingering manifestations of COVID-19 during and after convalescence: update on long-term pulmonary consequences of coronavirus disease 2019 (COVID-19). Radiol Med 126(1):40–46. https://doi.org/10.1007/s11547-020-01295-8

8. Oronsky B, Larson C, Hammond TC, Oronsky A, Kesari S, Lybeck M, Reid TR (2021) A Review of Persistent Post-COVID Syndrome (PPCS). Clin Rev Allergy Immunol 20:1–9. https://doi.org/10.1007/s12016-021-08848-3
9. Xydakis MS, Albers MW, Holbrook EH, Lyon DM, Shih RY, Frasnelli JA, Pagenstecher A, Kupke A, Enquist LW, Perlman S (2021) Post-viral effects of COVID-19 in the olfactory system and their implications. Lancet Neurol 20(9):753–761. https://doi.org/10.1016/S1474-4422(21)00182-4
10. Kara S, Candelore T, Youssef P, Nedd K (2021) Evidence of Post-COVID-19 transverse myelitis demyelination. Cureus. 13(10):e19087. https://doi.org/10.7759/cureus.19087
11. Stoyanov GS, Stoyanov D, Ivanov M, Tonchev AB, Popov H, Petkova L (2022) COVID-19-associated encephalopathy (COVEP): basic aspects of neuropathology. Encyclopedia 2:1773–1789. https://doi.org/10.3390/encyclopedia2040122
12. Jaywant A, Vanderlind WM, Alexopoulos GS, Fridman CB, Perlis RH, Gunning FM (2021) Frequency and profile of objective cognitive deficits in hospitalized patients recovering from COVID-19. Neuropsychopharmacology 46:2235–2240
13. Mendez R, Balanza-Martinez V, Luperdi SC et al (2022) Long-term neuropsychiatric outcomes in COVID-19 survivors: A 1-year longitudinal study. J Intern Med 291:247–251
14. Lu Y, Li X, Geng D et al (2020) Cerebral micro-structural changes in COVID-19 patients—an MRI-based 3-month follow-up study. EClinicalMedicine 25:100484
15. Iwashyna TJ (2012) Trajectories of recovery and dysfunction after acute illness, with implications for clinical trial design. Am J Respir Crit Care Med 186(4):302–304
16. Semmler A, Widmann CN, Okulla T, Urbach H, Kaiser M, Widman G et al (2013) Persistent cognitive impairment, hippocampal atrophy and EEG changes in sepsis survivors. J Neurol Neurosurg Psychiat 84(1):62–69
17. Widmann CN, Schewe JC, Heneka MT (2014) Sepsis-associated encephalopathy versus sepsis-induced encephalopathy–authors' reply. Lancet Neurol 13(10):968–969
18. Widmann CN, Sinning J, Ghanem A, Brosseron F, Heneka M, Wagner M (2017) [P2–088]: Chronic and acute systemic inflammation and long-term cognitive decline. Alzh Dement. 01(13):P640–P640
19. Lage C, González-Suárez A, Alcalde-Hierro MP, Sampedro-González MI, Villanueva-Eguaras Á, Sánchez-Crespo MR et al (2021) Major surgery affects memory in individuals with cerebral amyloid-β pathology. J Alzheimers Dis 79(2):863–874
20. Widmann CN, Wieberneit M, Bieler L, Bernsen S, Gräfenkämper R, Brosseron F, Schmeel C, Tacik P, Skowasch D, Radbruch A, Heneka MT (2021) Longitudinal neurocognitive and pulmonological profile of long COVID-19: protocol for the covimmuneclin study. JMIR Res Protoc. 10(11):e30259. https://doi.org/10.2196/30259
21. Ritchie K, Chan D, Watermeyer T (2020) The cognitive consequences of the COVID-19 epidemic: collateral damage? Brain Commun. 2(2):069. https://doi.org/10.1093/braincomms/fcaa069
22. Gilbert PE, Brushfield AM (2009) The role of the CA3 hippocampal subregion in spatial memory: a process oriented behavioral assessment. Prog Neuropsychopharmacol Biol Psychiatry 33:774–781
23. Anand KS, Dhikav V (2012) Hippocampus in health and disease: an overview. Ann Indian Acad Neurol 15(4):239–246. https://doi.org/10.4103/0972-2327.104323.PMID:23349586;PMCID:PMC3548359
24. Dekeyzer S, De Kock I, Nikoubashman O, Vanden Bossche S, Van Eetvelde R, De Groote J, Acou M, Wiesmann M, Deblaere K, Achten E (2017) "Unforgettable" - a pictorial essay on anatomy and pathology of the hippocampus. Insights Imaging 8(2):199–212. https://doi.org/10.1007/s13244-016-0541-2
25. Altman J, Das GD (1965) Autoradiographic and histological evidence of postnatal hippocampal neurogenesis in rats. J Comp Neurol 124:319–335
26. Bonaguidi MA, Wheeler MA, Shapiro JS, Stadel RP, Sun GJ, Ming GL, Song H (2011) In vivo clonal analysis reveals self-renewing and multipotent adult neural stem cell characteristics. Cell 145:1142–1155
27. Mu Y, Gage FH (2011) Adult hippocampal neurogenesis and its role in Alzheimer's disease. Mol Neurodegener 22(6):85. https://doi.org/10.1186/1750-1326-6-85.PMID:22192775;PMCID:PMC3261815
28. Shors TJ, Miesegaes G, Beylin A, Zhao M, Rydel T, Gould E (2001) Neurogenesis in the adult is involved in the formation of trace memories. Nature 410:372–376
29. Deng W, Aimone JB, Gage FH (2010) New neurons and new memories: how does adult hippocampal neurogenesis affect learning and memory? Nat Rev Neurosci 11(5):339–350
30. Sahay A, Scobie KN, Hill AS, O'Carroll CM, Kheirbek MA, Burghardt NS, Fenton AA, Dranovsky A, Hen R (2011) Increasing adult hippocampal neurogenesis is sufficient to improve pattern separation. Nature 472:466–470
31. Stone SS, Teixeira CM, Devito LM, Zaslavsky K, Josselyn SA, Lozano AM, Frankland PW (2011) Stimulation of entorhinal cortex promotes adult neurogenesis and facilitates spatial memory. J Neurosci 31:13469–13484
32. Aimone JB, Deng W, Gage FH (2011) Resolving new memories: a critical look at the dentate gyrus, adult neurogenesis, and pattern separation. Neuron 70:589–596
33. Frisoni GB, Fox NC, Jack CR Jr, Scheltens P, Thompson PM (2010) The clinical use of structural MRI in Alzheimer disease. Nat Rev Neurol 6:67–77
34. Nouraeinejad A (2012) The immunoregulatory effect of interferon-alpha 2b in Ocular Behçet's Disease. Institute of Ophthalmology, University College London, PhD
35. Nouraeinejad A (2017) Differential Diagnosis in Optometry and Ophthalmology, 2nd edn. Noruzi Publication, Iran
36. Bachiller S, Jiménez-Ferrer I, Paulus A, Yang Y, Swanberg M, Deierborg T, Boza-Serrano A (2018) Microglia in neurological diseases: a road map to brain-disease dependent-inflammatory response. Front Cell Neurosci 18(12):488. https://doi.org/10.3389/fncel.2018.00488.PMID:30618635;PMCID:PMC6305407
37. Fernández-Castañeda A, Lu P, Geraghty AC et al (2022) Mild respiratory COVID can cause multi-lineage neural cell and myelin dysregulation. Cell 185(14):2452-2468.e16
38. Villeda SA, Luo J, Mosher KI et al (2011) The ageing systemic milieu negatively regulates neurogenesis and cognitive function. Nature 477:90–94
39. Bayat AH, Azimi H, Hassani Moghaddam M, Ebrahimi V, Fathi M, Vakili K, Mahmoudiasl GR, Forouzesh M, Boroujeni ME, Nariman Z, Abbaszadeh HA, Aryan A, Aliaghaei A, Abdollahifar MA (2022) COVID-19 causes neuronal degeneration and reduces neurogenesis in human hippocampus. Apoptosis 27(11–12):852–868. https://doi.org/10.1007/s10495-022-01754-9
40. Saijo K, Winner B, Carson CT, Collier JG, Boyer L, Rosenfeld MG et al (2009) A Nurr1/CoREST pathway in microglia and astrocytes protects dopaminergic neurons from inflammation-induced death. Cell 137(1):47–59
41. Liddelow SA, Guttenplan KA, Clarke LE, Bennett FC, Bohlen CJ, Schirmer L et al (2017) Neurotoxic reactive astrocytes are induced by activated microglia. Nature 541(7638):481–487
42. Qin L, Wu X, Block ML, Liu Y, Breese GR, Hong JS et al (2007) Systemic LPS causes chronic neuroinflammation and progressive neurodegeneration. Glia 55(5):453–462
43. Lee Y-J, Choi D-Y, Choi IS, Kim KH, Kim YH, Kim HM et al (2012) Inhibitory effect of 4-O-methylhonokiol on lipopolysaccharide-induced neuroinflammation, amyloidogenesis and

memory impairment via inhibition of nuclear factor-kappaB in vitro and in vivo models. J Neuroinflamm 9(1):1–19
44. Zhu B, Wang ZG, Ding J, Liu N, Wang DM, Ding LC et al (2014) Chronic lipopolysaccharide exposure induces cognitive dysfunction without affecting BDNF expression in the rat hippocampus. Exp Ther Med 7(3):750–754
45. Soung AL, Vanderheiden A, Nordvig AS, Sissoko CA, Canoll P, Mariani MB, Jiang X, Bricker T, Rosoklija GB, Arango V, Underwood M, Mann JJ, Dwork AJ, Goldman JE, Boon ACM, Boldrini M, Klein RS (2022) COVID-19 induces CNS cytokine expression and loss of hippocampal neurogenesis. Brain 145(12):4193–4201. https://doi.org/10.1093/brain/awac270.PMID:36004663;PMCID:PMC9452175
46. Bozzi G, Mangioni D, Minoia F et al (2021) Anakinra combined with methylprednisolone in patients with severe COVID-19 pneumonia and hyperinflammation: An observational cohort study. J Allergy Clin Immunol 147:561-566.e4
47. Vadodaria KC, Gage FH (2014) SnapShot: adult hippocampal neurogenesis. Cell 156(5):1114–1114
48. Bassani TB, Bonato JM, Machado MM, Coppola-Segovia V, Moura EL, Zanata SM et al (2018) Decrease in adult neurogenesis and neuroinflammation are involved in spatial memory impairment in the streptozotocin-induced model of sporadic Alzheimer's disease in rats. Mol Neurobiol 55(5):4280–4296
49. 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. Mol Psychiatry 26(12):7475–7480. https://doi.org/10.1038/s41380-021-01223-w
50. Besteher B, Machnik M, Troll M, Toepffer A, Zerekidze A, Rocktäschel T, Heller C, Kikinis Z, Brodoehl S, Finke K, Reuken PA, Opel N, Stallmach A, Gaser C, Walter M (2022) Larger gray matter volumes in neuropsychiatric long-COVID syndrome. Psychiatry Res 317:114836. https://doi.org/10.1016/j.psychres.2022.114836
51. Curtis MA, Kam M, Nannmark U, Anderson MF, Axell MZ, Wikkelso C, Holtås S, van Roon-Mom WM, Björk-Eriksson T, Nordborg C, Frisén J, Dragunow M, Faull RL, Eriksson PS (2007) Human neuroblasts migrate to the olfactory bulb via a lateral ventricular extension. Science 315(5816):1243–1249. https://doi.org/10.1126/science.1136281
52. Karstensen HG, Vestergaard M, Baaré WFC, Skimminge A, Djurhuus B, Ellefsen B, Brüggemann N, Klausen C, Leffers AM, Tommerup N, Siebner HR (2018) Congenital olfactory impairment is linked to cortical changes in prefrontal and limbic brain regions. Brain Imaging Behav 12(6):1569–1582. https://doi.org/10.1007/s11682-017-9817-5
53. Whitmore HAB, Kim LA (2021) Understanding the role of blood vessels in the neurologic manifestations of coronavirus disease 2019 (COVID-19). Am J Pathol 191(11):1946–1954. https://doi.org/10.1016/j.ajpath.2021.04.017
54. Duan K, Premi E, Pilotto A, Cristillo V, Benussi A, Libri I, Giunta M, Bockholt HJ, Liu J, Campora R, Pezzini A, Gasparotti R, Magoni M, Padovani A, Calhoun VD (2021) Alterations of frontal-temporal gray matter volume associate with clinical measures of older adults with COVID-19. Neurobiol Stress. 14:100326. https://doi.org/10.1016/j.ynstr.2021.100326
55. Douaud G, Lee S, Alfaro-Almagro F, Arthofer C, Wang C, McCarthy P, Lange F, Andersson JLR, Griffanti L, Duff E, Jbabdi S, Taschler B, Keating P, Winkler AM, Collins R, Matthews PM, Allen N, Miller KL, Nichols TE, Smith SM (2022) SARS-CoV-2 is associated with changes in brain structure in UK Biobank. Nature 604(7907):697–707. https://doi.org/10.1038/s41586-022-04569-5
56. Widmann CN, Heneka MT (2014) Long-term cerebral consequences of sepsis. Lancet Neurol 13(6):630–636
57. Hellstrom IC, Danik M, Luheshi GN, Williams S (2005) Chronic LPS exposure produces changes in intrinsic membrane properties and a sustained IL-beta-dependent increase in GABAergic inhibition in hippocampal CA1 pyramidal neurons. Hippocampus 15(5):656–664
58. Semmler A, Frisch C, Debeir T, Ramanathan M, Okulla T, Klockgether T et al (2007) Long-term cognitive impairment, neuronal loss and reduced cortical cholinergic innervation after recovery from sepsis in a rodent model. Exp Neurol 204(2):733–740
59. Deng X, Ai W, Lei D, Luo X, Yan X, Li Z (2012) Lipopolysaccharide induces paired immunoglobulin-like receptor B (PirB) expression, synaptic alteration, and learning-memory deficit in rats. Neuroscience 03(209):161–170
60. Bowyer JF, Sarkar S, Burks SM, Hess JN, Tolani S, O'Callaghan JP et al (2020) Microglial activation and responses to vasculature that result from an acute LPS exposure. Neurotoxicology 77:181–192
61. Hiramoto RN, Rogers CF, Demissie S, Hsueh CM, Hiramoto NS, Lorden JF et al (1997) Psychoneuroendocrine immunology: site of recognition, learning and memory in the immune system and the brain. Int J Neurosci 92(3–4):259–285
62. Borsini A, Merrick B, Edgeworth J, Mandal G, Srivastava DP, Vernon AC, Nebbia G, Thuret S, Pariante CM (2022) Neurogenesis is disrupted in human hippocampal progenitor cells upon exposure to serum samples from hospitalized COVID-19 patients with neurological symptoms. Mol Psychiatry 27(12):5049–5061. https://doi.org/10.1038/s41380-022-01741-1
63. Borsini A, Di Benedetto MG, Giacobbe J, Pariante CM (2020) Pro- and anti-inflammatory properties of interleukin (IL6) in vitro: relevance for major depression and for human hippocampal neurogenesis. Int J Neuropsychopharmacol 23:738–750
64. Borsini A, Nicolaou A, Camacho-Munoz D, Kendall AC, Di Benedetto MG, Giacobbe J et al (2021) Omega-3 polyunsaturated fatty acids protect against inflammation through production of LOX and CYP450 lipid mediators: relevance for major depression and for human hippocampal neurogenesis. Mol Psychiatry 26:6773–6788
65. Zhang B-Z, Chu H, Han S et al (2020) SARS-CoV-2 infects human neural progenitor cells and brain organoids. Cell Res 30(10):928–931
66. McElvaney OJ, McEvoy NL, McElvaney OF, Carroll TP, Murphy MP, Dunlea DM et al (2020) Characterization of the inflammatory response to severe COVID-19 illness. Am J Respiratory Crit care Med 202:812–821
67. Crupi R, Cambiaghi M, Spatz L, Hen R, Thorn M, Friedman E et al (2010) Reduced adult neurogenesis and altered emotional behaviors in autoimmune-prone B-cell activating factor transgenic mice. Biol Psychiatry 67:558–566
68. Borsini A, Alboni S, Horowitz MA, Tojo LM, Cannazza G, Su KP et al (2017) Rescue of IL-1 beta-induced reduction of human neurogenesis by omega-3 fatty acids and antidepressants. Brain Behav Immun 65:230–238
69. Borsini A, Cattaneo A, Malpighi C, Thuret S, Harrison NA, Consortium MRCI, et al. 2018 Interferon-alpha reduces human hippocampal neurogenesis and increases apoptosis via activation of dependent mechanisms. Int J Neuropsychopharmacol. 21:187–200
70. Koo JW, Wohleb ES (2021) How stress shapes neuroimmune function: implications for the neurobiology of psychiatric disorders. Biol Psychiatry 90:74–84
71. Zhao Y, Qin L, Zhang P, Li K, Liang L, Sun J et al (2020) Longitudinal COVID-19 profiling associates IL-1RA and IL-10 with disease severity and RANTES with mild disease. JCI Insight 5:e139834

72. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y et al (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan. China Lancet 395:497–506
73. Bodro M, Compta Y, Llanso L, Esteller D, Doncel-Moriano A, Mesa A et al (2020) Increased CSF levels of IL-1beta, IL-6, and ACE in SARS-CoV-2-associated encephalitis. Neurol Neuroimmunol Neuroinflamm 7:e821
74. Brodin P (2021) Immune determinants of COVID-19 disease presentation and severity. Nat Med 27:28–33
75. Borsini A, Pariante CM, Zunszain PA, Hepgul N, Russell A, Zajkowska Z et al (2019) The role of circulatory systemic environment in predicting interferon-alpha-induced depression: The neurogenic process as a potential mechanism. Brain Behav Immun 81:220–227
76. Nouraeinejad A (2000) Handbook of ocular drugs, and ocular side effects of systemic drugs. Tabib Publication, Tehran
77. Perini G, Cotta Ramusino M, Sinforiani E, Bernini S, Petrachi R, Costa A (2019) Cognitive impairment in depression: recent advances and novel treatments. Neuropsychiatr Dis Treat 15:1249–1258
78. Luna B, Marek S, Larsen B, Tervo-Clemmens B, Chahal R (2015) An integrative model of the maturation of cognitive control. Annu Rev Neurosci 38:151–170
79. Casey BJ, Heller AS, Gee DG, Cohen AO (2019) Development of the emotional brain. Neurosci Lett 693:29–34
80. Larsen B, Luna B (2018) Adolescence as a neurobiological critical period for the development of higher-order cognition. Neurosci Biobehav Rev 94:179–195
81. Conley MI, Skalaban LJ, Rapuano KM, Gonzalez R, Laird AR, Dick AS et al (2021) Altered hippocampal microstructure and function in children who experienced Hurricane Irma. Dev Psychobiol 63:864–877
82. Perica MI, Ravindranath O, Calabro FJ, Foran W, Luna B (2021) Hippocampal-Prefrontal Connectivity Prior to the COVID-19 Pandemic Predicts Stress Reactivity. Biol Psychiatry Glob Open Sci. 1(4):283–290. https://doi.org/10.1016/j.bpsgos.2021.06.010
83. Admon R, Leykin D, Lubin G, Engert V, Andrews J, Pruessner J, Hendler T (2013) Stress-induced reduction in hippocampal volume and connectivity with the ventromedial prefrontal cortex are related to maladaptive responses to stressful military service. Hum Brain Mapp 34:2808–2816
84. Chen J, Wei Z, Han H, Jin L, Xu C, Dong D et al (2019) An effect of chronic stress on prospective memory via alteration of resting-state hippocampal subregion functional connectivity. Sci Rep 9:19698
85. Boyle LM (2013) A neuroplasticity hypothesis of chronic stress in the basolateral amygdala. Yale J Biol Med 86:117–125
86. Golkar A, Johansson E, Kasahara M, Osika W, Perski A, Savic I (2014) The influence of work-related chronic stress on the regulation of emotion and on functional connectivity in the brain. PLoS ONE 9:e104550
87. Guadagno A, Kang MS, Devenyi GA, Mathieu AP, Rosa-Neto P, Chakravarty M, Walker CD (2018) Reduced resting-state functional connectivity of the basolateral amygdala to the medial prefrontal cortex in preweaning rats exposed to chronic early-life stress. Brain Struct Funct 223:3711–3729
88. Liu WZ, Zhang WH, Zheng ZH, Zou JX, Liu XX, Huang SH et al (2020) Identification of a prefrontal cortex-to-amygdala pathway for chronic stress-induced anxiety. Nat Commun 11:2221
89. Van Eekelen JA, Jiang W, De Kloet ER, Bohn MC (1988) Distribution of the mineralocorticoid and the glucocorticoid receptor mRNAs in the rat hippocampus. J Neurosci Res 21:88–94
90. Gould E, Tanapat P (1999) Stress and hippocampal neurogenesis. Biol Psychiatry 46:1472–1479
91. Snyder JS, Soumier A, Brewer M, Pickel J, Cameron HA (2011) Adult hippocampal neurogenesis buffers stress responses and depressive behaviour. Nature 476:458–461
92. Al-Sarraj S, Troakes C, Hanley B, Osborn M, Richardson MP, Hotopf M, Bullmore E, Everall IP (2021) Invited review: the spectrum of neuropathology in COVID-19. Neuropathol Appl Neurobiol 47(1):3–16. https://doi.org/10.1111/nan.12667
93. Lou JJ, Movassaghi M, Gordy D, Olson MG, Zhang T, Khurana MS, Chen Z, Perez-Rosendahl M, Thammachantha S, Singer EJ, Magaki SD, Vinters HV, Yong WH (2021) Neuropathology of COVID-19 (neuro-COVID): clinicopathological update. Free Neuropathol 18(2):2. https://doi.org/10.17879/freeneuropathology-2021-2993.PMID:33554218;PMCID:PMC7861505
94. Yamamoto J, Suh J, Takeuchi D, Tonegawa S (2014) Successful execution of working memory linked to synchronized high-frequency gamma oscillations. Cell 157:845–857
95. Clelland CD, Choi M, Romberg C et al (2009) A functional role for adult hippocampal neurogenesis in spatial pattern separation. Science 325:210–213
96. Moriguchi T, Harii N, Goto J, Harada D, Sugawara H, Takamino J, Ueno M, Sakata H, Kondo K, Myose N, Nakao A, Takeda M, Haro H, Inoue O, Suzuki-Inoue K, Kubokawa K, Ogihara S, Sasaki T, Kinouchi H, Kojin H, Ito M, Onishi H, Shimizu T, Sasaki Y, Enomoto N, Ishihara H, Furuya S, Yamamoto T, Shimada S (2020) A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. Int J Infect Dis 94:55–58. https://doi.org/10.1016/j.ijid.2020.03.062
97. Poloni TE, Medici V, Moretti M, Visonà SD, Cirrincione A, Carlos AF, Davin A, Gagliardi S, Pansarasa O, Cereda C, Tronconi L, Guaita A, Ceroni M (2021) COVID-19-related neuropathology and microglial activation in elderly with and without dementia. Brain Pathol 31(5):e12997. https://doi.org/10.1111/bpa.12997
98. Mahajan GJ, Vallender EJ, Garrett MR et al (2018) Altered neuro-inflammatory gene expression in hippocampus in major depressive disorder. Prog Neuropsychopharmacol Biol Psychiatry 82:177–186
99. Boldrini M, Galfalvy H, Dwork AJ et al (2019) Resilience is associated with larger dentate gyrus, while suicide decedents with major depressive disorder have fewer granule neurons. Biol Psychiatry 85(10):850–862
100. Roman M, Irwin MR (2020) Novel neuroimmunologic therapeutics in depression. Brain Behav Immun 83:7–21
101. Boldrini M, Canoll PD, Klein RS (2021) How COVID-19 Affects the Brain. JAMA Psychiat 78(6):682–683. https://doi.org/10.1001/jamapsychiatry.2021.0500
102. Lazarov O, Mattson MP, Peterson DA, Pimplikar SW, van Praag H (2010) When neurogenesis encounters aging and disease. Trends Neurosci 33:569–579
103. Braak H, Braak E, Bohl J (1993) Staging of Alzheimer-related cortical destruction. Eur Neurol 33:403–408
104. Solomon IH, Normandin E, Bhattacharyya S et al (2020) Neuropathological features of Covid-19. N Engl J Med 383:989–992
105. Fabbri VP, Foschini MP, Lazzarotto T et al (2020) Brain ischemic injury in COVID-19-infected patients: a series of 10 post-mortem cases. Brain Pathol 31(1):205–210
106. Thakur KT, Miller EH, Glendinning MD et al (2021) COVID-19 neuropathology at Columbia University Irving Medical Center/New York Presbyterian Hospital. Brain J Neurol 144:2696–2708
107. Shou S, Liu M, Yang Y et al (2021) Animal Models for COVID-19: Hamsters, Mouse, Ferret, Mink, Tree Shrew, and Non-human Primates. Front Microbiol 12:626553
108. Radhakrishnan RK, Kandasamy M (2022) SARS-CoV-2-Mediated Neuropathogenesis, Deterioration of Hippocampal Neurogenesis and Dementia. Am J Alzheimers Dis Other Demen

37(153):33175221078418. https://doi.org/10.1177/15333175221078418
109. Kandasamy M, Couillard-Despres S, Raber KA et al (2010) Stem cell quiescence in the hippocampal neurogenic niche is associated with elevated transforming growth factor-β Signaling in an animal model of huntington disease. J Neuropathol Exp Neurol 69(7):717–728
110. Kandasamy M, Reilmann R, Winkler J, Bogdahn U, Aigner L (2011) Transforming growth factor-beta signaling in the neural stem cell niche: a therapeutic target for Huntington's disease. Neurol Res Int 2011:1–13
111. Aimone JB, Li Y, Lee SW, Clemenson GD, Deng W, Gage FH (2014) Regulation and Function of adult neurogenesis: from genes to cognition. Physiol Rev 94(4):991–1026
112. Shohayeb B, Diab M, Ahmed M, Ng DCH (2018) Factors that influence adult neurogenesis as potential therapy. Transl Neurodegener 7:4
113. Kandasamy M, Anusuyadevi M, Aigner KM et al (2020) TGF-β Signaling: a therapeutic target to reinstate regenerative plasticity in vascular dementia? Aging Dis 11(4):828–850
114. Yi SA, Nam KH, Yun J et al (2020) Infection of Brain Organoids and 2D Cortical Neurons with SARS-CoV-2 Pseudovirus. Viruses 12(9):1004. https://doi.org/10.3390/v12091004
115. McMahon CL, Staples H, Gazi M, Carrion R, Hsieh J (2021) SARSCoV-2 targets glial cells in human cortical organoids. Stem Cell Rep 16(5):1156–1164
116. Wang L, Davis PB, Volkow ND, Berger NA, Kaelber DC, Xu R (2022) Association of COVID-19 with new-onset alzheimer's disease. J Alzheimers Dis 89(2):411–414. https://doi.org/10.3233/JAD-220717
117. Wang Q, Davis PB, Gurney ME, Xu R (2021) COVID-19 and dementia: Analyses of risk, disparity, and outcomes from electronic health records in the US. Alzheimers Dement 17:1297–1306
118. Bull-Otterson L, Baca S, Saydah S et al (2022) Post-COVID conditions among adult COVID-19 survivors ages 18–64 and ≥65 years- United States, March 2020-November 2021. MMWR Morb Wkly Rep. 71:713–717. https://doi.org/10.15585/mmwr.mm7121e1
119. Ceban F, Ling S, Lui LMW, Lee Y, Gill H, Teopiz KM, Rodrigues NB, Subramaniapillai M, Di Vincenzo JD, Cao B, Lin K, Mansur RB, Ho RC, Rosenblat JD, Miskowiak KW, Vinberg M, Maletic V, McIntyre RS (2022) Fatigue and cognitive impairment in Post-COVID-19 Syndrome: A systematic review and meta-analysis. Brain Behav Immun 101:93–135. https://doi.org/10.1016/j.bbi.2021.12.020
120. Al-Aly Z, Bowe B, Xie Y (2022) Long COVID after breakthrough SARS-CoV-2 infection. Nat Med 28(7):1461–1467. https://doi.org/10.1038/s41591-022-01840-0
121. Davis HE, McCorkell L, Vogel JM, Topol EJ (2023) Long COVID: major findings, mechanisms and recommendations. Nat Rev Microbiol 21(3):133–146. https://doi.org/10.1038/s41579-022-00846-2
122. Tenforde MW, Kim SS, Lindsell CJ et al (2020) Symptom duration and risk factors for delayed return to usual health among outpatients with COVID-19 in a multistate health care systems network - United States. MMWR Morb Mortal Wkly Rep 69(30):993–998. https://doi.org/10.15585/mmwr.mm6930e1.PMID:32730238;PMCID:PMC7392393
123. Su Y, Yuan D, Chen DG et al (2022) Multiple early factors anticipate post-acute COVID-19 sequelae. Cell 185(5):881–895. https://doi.org/10.1016/j.cell.2022.01.014
124. Taquet M, Geddes JR, Husain M, Luciano S, Harrison PJ (2021) 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. Lancet Psychiatry 8(5):416–427. https://doi.org/10.1016/S2215-0366(21)00084-5
125. Chen C, Haupert SR, Zimmermann L, Shi X, Fritsche LG, Mukherjee B (2022) Global Prevalence of Post-Coronavirus Disease 2019 (COVID-19) Condition or Long COVID: A Meta-Analysis and Systematic Review. J Infect Dis 226(9):1593–1607. https://doi.org/10.1093/infdis/jiac136.PMID:35429399;PMCID:PMC9047189
126. Davis HE, Assaf GS, McCorkell L, Wei H, Low RJ, Re'em Y, Redfield S, Austin JP, Akrami A (2021) Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. E Clin Med. 38:101019. https://doi.org/10.1016/j.eclinm.2021.101019
127. Koc HC, Xiao J, Liu W, Li Y, Chen G (2022) Long COVID and its management. Int J Biol Sci 18(12):4768–4780. https://doi.org/10.7150/ijbs.75056.PMID:35874958;PMCID:PMC9305273
128. Szekanecz Z, Vályi-Nagy I (2021) Posztakut COVID-19 szindróma [Post-acute COVID-19 syndrome]. Orv Hetil 162(27):1067–1078. https://doi.org/10.1556/650.2021.32282
129. Al-Aly Z, Xie Y, Bowe B (2021) High-dimensional characterization of post-acute sequelae of COVID-19. Nature 594(7862):259–264. https://doi.org/10.1038/s41586-021-03553-9
130. Zarei M, Bose D, Nouri-Vaskeh M, Tajiknia V, Zand R, Ghasemi M (2022) Long-term side effects and lingering symptoms post COVID-19 recovery. Rev Med Virol 32(3):e2289. https://doi.org/10.1002/rmv.2289
131. Taquet M, Sillett R, Zhu L, Mendel J, Camplisson I, Dercon Q, Harrison PJ (2022) Neurological and psychiatric risk trajectories after SARS-CoV-2 infection: an analysis of 2-year retrospective cohort studies including 1 284 437 patients. Lancet Psychiatry 9(10):815–827. https://doi.org/10.1016/S2215-0366(22)00260-7
132. Holdsworth DA, Chamley R, Barker-Davies R, O'Sullivan O, Ladlow P, Mitchell JL, Dewson D, Mills D, May SLJ, Cranley M, Xie C, Sellon E, Mulae J, Naylor J, Raman B, Talbot NP, Rider OJ, Bennett AN, Nicol ED (2022) Comprehensive clinical assessment identifies specific neurocognitive deficits in working-age patients with long-COVID. PLoS ONE 17(6):e0267392. https://doi.org/10.1371/journal.pone.0267392
133. Duindam HB, Kessels RPC, van den Borst B, Pickkers P, Abdo WF (2022) Long-term cognitive performance and its relation to anti-inflammatory therapy in a cohort of survivors of severe COVID-19. Brain Behav Immun Health. 25:100513. https://doi.org/10.1016/j.bbih.2022.100513
134. Blackmon K, Day GS, Powers HR, Bosch W, Prabhakaran D, Woolston D, Pedraza O (2022) Neurocognitive screening in patients following SARS-CoV-2 infection: tools for triage. BMC Neurol 22(1):285. https://doi.org/10.1186/s12883-022-02817-9.PMID:35907815;PMCID:PMC9338515