ISSN 1819-7124, Neurochemical Journal, 2024, Vol. 18, No. 3, pp. 397–405. © The Author(s), 2024. This article is an open access publication.

REVIEW ARTICLES

Brain Mechanisms Involved in Post COVID Syndrome: A Narrative Review

N. V. Gulyaeva[a, b, *]

[a] *Research and Clinical Center for Neuropsychiatry of Moscow Healthcare Department, Moscow, 115419 Russia*
[b] *Institute of Higher Nervous Activity and Neurophysiology, Russian Academy of Sciences, Moscow, 117485 Russia*
**e-mail: nata_gul@ihna.ru*

Received June 15, 2024; revised July 16, 2024; accepted July 17, 2024

Abstract—Potentially, patients with COVID-19 can experience long-term disturbances after the acute infection period, even people with no symptoms or mild illness. Our current understanding of brain-associated post COVID-19 condition and why some people are more affected is limited. Post COVID syndrome or long COVID, with continuing symptoms of impaired brain functioning, in particular, 'brain fog', chronic fatigue, cognitive decline, mood disturbances, anxiety, and depression, is due to multiple molecular mechanisms. This narrative review updates most important cellular and molecular brain mechanisms as well as system mechanisms underlying post COVID syndrome.

Keywords: COVID-19, post COVID syndrome, long COVID, immune dysregulation, neuroinflammation, coagulopathy, brain vascular injury, neuroendocrine imbalance, neurochemical imbalance, demyelination, neuroplasticity, neurodegeneration

DOI: 10.1134/S1819712424700156

INTRODUCTION

COVID-19 was initially considered a pulmonary disease with extrapulmonary manifestations. As the pandemic spread, it became clear that the disease affects various organs/systems, including the central and peripheral nervous systems [1]. COVID-19 is a multi-systemic disease which can target the lungs, the cardiovascular system, other organs of the body, and can also affect regions of the brain for expanded periods of time. Post COVID-19 condition, also known as post COVID syndrome (PCS) or long COVID, refers to long-term symptoms that some people experience after they have had COVID-19. Though most people fully convalesce from COVID-19, current evidence suggests that up to 20% of people experience a variety of mid and long-term effects after they recover from their initial illness [2]. According to other sources, international evidence on COVID-19 estimates the incidence of PCS about 10–30% of non-hospitalized cases, 50–70% of hospitalized cases and 10–12% of vaccinated cases [3].

Most long COVID symptoms disappear within 6-12 months, but in some cases, it can take longer. During the PCS, the SARS-CoV-2 nucleocapsid antigen is present in cerebrospinal fluid in the absence of viral RNA [4]. The symptoms of PCS might persist from the initial illness or develop after recovery; they can come and go or relapse over time. Indeed, the term "post COVID condition" or PCS may be regarded as an umbrella name for the wide variety of ongoing, novel or recurring symptoms of physical and mental health consequences occurring in a number of patients a month or later after SARS-CoV-2 infection, including the patients with initially mild or even asymptomatic acute infection. A prospective cohort study showed that factors that were found to be associated with a higher risk of developing PCS were female gender, older age and active smoking, but not severity of the acute disease [5].

The impacts of COVID-19 infection on mental health are mediated by increased stress load and result in affective and neurological symptoms including anxiety, depression, difficulty thinking and/or concentrating, headache, sleep problems, dizziness, pins-and-needles feeling, changes in smell or taste [6]. People with COVID-19 who had severe illness might have organ damage affecting the lungs, heart, kidneys, and brain. This damage may be associated with inflammation and problems with the immune system. COVID-19 illness can induce the development of new conditions, such as diabetes or a heart or nervous system condition. People with severe symptoms of COVID-19 often needed to be treated in a hospital intensive care unit. This could result in extreme weakness and post-traumatic stress disorder (PTSD) triggered by regarding severe COVID-19 illness as a terrifying event.

Understanding of post COVID conditions remains incomplete. This narrative review aims to update most

important cellular and molecular brain mechanisms underlying PCS or long COVID.

COGNITIVE AND AFFECTIVE SYMPTOMS OF POST COVID SYNDROM

Impaired brain functioning in PCS is associated with a number of neurological and psychiatric symptoms including 'brain fog'; extreme and chronic fatigue; headaches; headedness; cognitive dysfunction, such as concentration problems, short-term memory deficits, general memory loss, a specific decline in attention, language and praxis abilities, encoding and verbal fluency, impairment of executive functions and psychomotor coordination; confusion; compromised sleep; loss of smell and/or taste; mood changes, anxiety, depression, and PTSD [1, 7]. Obviously, multiple molecular mechanisms underlie these symptoms. Numerous psychoneurological symptoms of PCS are believed to be associated with many mechanisms, in particular, systemic inflammation, neuroinflammation, neuroendocrine and neurochemical disbalance [4].

Post COVID-19 cognitive complaints at 9 months and 15 months and fatigue are highly common and frequently continuing [8]. Neuropsychological measures of PCS patients' cognitive status shows that COVID-19 is capable of eliciting persistent measurable neurocognitive alterations predominantly significant in the areas of attention and working memory [9]. Standard neuropsychological tests and experimental cognitive tasks revealed that frequent PCS cognitive symptoms, described as 'brain fog', are associated with significant attention deficits in both neuropsychological measurements and cognitive tasks [10]. Reduced performance was revealed in tasks involving interference resolution and selective and sustained attention, and about 61% of patients reported major routine prospective memory problems. Neuropsychological deficits in patients with cognitive complaints associated with PCS show persistent impact on attention abilities, both as the singularly affected domain and coupled with decreased performance in executive functions, learning, and long-term memory [11]. Importantly, psychosocial assessment of PCS patients can detect fragile persons at risk of cognitive impairments and may be useful for prognostic purpose [12].

Severe acute SARS-CoV-2 infection is associated not only with considerable cognitive impairment, but also with an increased risk for mental health comorbidities. Depression appears to contribute to cognitive symptoms of PCS. In patients with PCS, depression symptom severity was significantly associated with the severity of cognitive impairment [13]. This association was driven mainly by lesser performance in verbal fluency, attention, and delayed recall tasks among PCS patients with higher severity of depression symptoms. Main predictor of self-reported memory disturbances were perceived sleep problems. Importantly, neither PTSD severity nor anxiety severity were significant predictors of cognitive impairment or self-reported memory disturbances [13]. People hospitalized with COVID-19 had more anxiety after discharge, which is associated with PSC neurologic symptoms [4]. Interestingly, depression-, anxiety- and PTSD-spectrum disturbances in PCS may not be directly associated with disease-related and premorbid features [14].

Patients with severe COVID-19 experience high levels of stress and thus are at risk for developing acute stress disorder ASD and/or PTSD. Though remitted COVID-19 patients experience lower levels of stress and use less emotion-focused strategies, those who develop PTSD after COVID-19 infection demonstrate high levels of stress and use more disengagement and emotion-focused types of coping strategies [15] The role of psychological factors in PCS is very important indeed. Hospitalized subjects were more likely to report persistent symptoms of PTSD than asymptomatic or home-treated subjects [16]. PCS symptoms could be significantly predicted by the severity of antagonism, hyperarousal, and difficulty identifying emotions. It is suggested that emotional dysregulation can affect key physiological processes and contribute to the development of organ pathologies.

Patients with PCS may demonstrate brain hypometabolism, hypoperfusion of the cerebral cortex and changes in the brain structure and functional connectivity [1]. Abnormal brain diffusivity was reported in patients with PCS. Microstructural abnormalities were revealed in PCS six months after acute COVID-19. Similarly to seen in stress conditions, the restricted diffusivity and higher fractional anisotropy suggest augmented myelination or higher magnetic susceptibility from iron deposition [17]. In female patients, elevated amygdala mean diffusivity was revealed suggesting that fatigue, anxiety, and perceived stress in PCS may be potentially associated with chronic neuroinflammation.

Interestingly, the persistent changes induced by COVID-19 on brain structure overlap with those associated with PTSD of other origins. Common elements are hypometabolism in the insula and caudate nucleus, reduced hippocampal volumes, and subarachnoid hemorrhages; white matter hyperintensities are prevalent in both PTSD and PCS [18]. Another important issue suggests that long COVID is a very recent myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)-like illness arising from the single pandemic virus, SARS-CoV-2. Some authors believe that the ME/CFS-like ongoing effects of PCS are based on similar mechanisms involving neuroinflammation, though with some specific signaling induced by the initial COVID infection [19]. Though the initial triggers are different, identical symptoms in ME/CFS and PCS support the existence of common dysfunctional CNS component(s).

Alterations of the limbic system may be intimately associated with both cognitive and affective symptoms of PCS. In a study of multimodal emotion recognition abilities, patients 6–9 months following SARS-CoV-2 infection were divided into groups with severe, moderate or mild according to respiratory symptom severity in the acute phase. The long-term consequences of SARS-Cov-2 infection on the limbic system were shown in these groups at both the behavioural and neuroimaging levels [20]. In the context of PCS, there is a growing understanding of the potential implications for the pituitary gland [21]. The virus can directly affect the pituitary, leading to abnormalities in hormone production and regulation. This can result in symptoms such as fatigue, changes in appetite, and mood disturbances. A number of PSC symptoms may be explained by deficiencies in ACTH and growth hormone production from the pituitary gland. Corticotropin insufficiency can result in the dysregulation of the body's stress response and can lead to prolonged feelings of stress, fatigue, and mood disturbances in PCS patients. Simultaneously, somatotropin insufficiency can affect growth, muscle function, and energy metabolism, potentially causing symptoms such as muscle weakness, exercise intolerance, and changes in body composition [21].

BRAIN MOLECULAR AND CELLULAR MECHANISMS UNDERLYING POST COVID SYNDROM

The question of what mechanisms are initiated by viral infection is all the more relevant because in many patients with PCS, the disease itself was asymptomatic or mild. In COVID-19, pathologic changes in the central nervous system most often demonstrate signs of nonspecific neuroinflammation with microglia activation and lymphoid infiltrates, ischemic/hypoxic encephalopathy, acute cerebrovascular disorders, and microthrombosis [22]. The underlying global mechanisms involved in the development of post COVID brain damage (neuroinvasion, neuroinfection, cerebral vascular injury, neuroinflammation, demyelination and hypoxia) are important and contribute significantly to the development of both neurological and psychiatric symptoms. It should also be considered that a substantial proportion of the data from which conclusions have been drawn about the mechanisms of the development of post COVID brain dysfunction have been derived either from experimental models or from samples of patients who have died from very severe disease. Therefore, when discussing the real causes of the long-lasting PCS after an asymptomatic or mild course of COVID disease, the question remains whether this syndrome correlates with virus persistence or latency, or whether it is the result of a persistent neurochemical imbalance caused, in particular, by metabolic abnormalities or epigenetic changes in genes encoding neurotrophic factors. Undoubtedly, both direct effects of SARS-CoV-2 on brain cells and indirect effects due to local or systemic immune response of the organism to the virus, and, most probably, combinations of these factors are involved in the mechanisms of development of post COVID brain diseases [23–25].

Let us consider the most important systemic effects of COVID for brain pathologies in PCS. It has been shown that the proportion of CD14lowCD16+ nonclassical monocytes, as well as CD4 and CD8 lymphocytes expressing IL-4+ and IL-6+ simultaneously, is increased in patients with PCS accompanied by a sharp decrease in the level of circulating cortisol (by about 50%) [26]. This indicates global post COVID long-term disorders of the neurohumoral and immune system of the whole organism, which undoubtedly affect brain functioning. The hypothalamic-pituitary-adrenal (HPA) axis is one of the most important neuroendocrine targets of SARS-CoV-2, whose changes influence the course of the post infection period [27]. Corticosteroid deficiency associated with critical illness, direct cytopathologic effects of SARS-CoV-2 infection on the adrenal glands, pituitary and hypothalamus, immune-mediated inflammation, small vessel vasculitis, microthrombotic events, cortisol receptor resistance and impaired postreceptor signaling, as well as dysregulation of ACTH and cortisol, may contribute significantly to the development of PCS.

COVID-19 causes lung disease, which in severe cases leads to systemic hypoxemia caused by decreased O_2/CO_2 exchange in the lungs, indirectly affecting the cerebral vasculature. Microvascular damage and dramatic changes in cerebral blood flow have been shown even in patients who recovered from mild COVID-19 infection without any neurologic symptoms [28]. Fibrinogen in the blood can fold into an abnormal "amyloid" form of fibrin, which (like other β-amyloids and prions) is relatively resistant to proteolysis (fibrinolysis). In the plasma of patients with PCS, fibrin accumulates in the form of amyloid-like microclots ("fibrinaloids") that can persist and interact with other proteins, leading to the production of various autoantibodies [29]. The microclots are able to obstruct capillaries and thus limit the movement of red blood cells and, consequently, the exchange of oxygen, creating hypoxic foci in the brain.

Inflammation, necessary to fight infections, becomes a threat when it exceeds the immune system's ability to control it. In addition, inflammation is a cause and/or symptom of many different diseases, including metabolic, psychiatric, neurodegenerative, autoimmune, and cardiovascular diseases [30]. The neuroinflammatory process is considered to be a key factor in the etiology of PCS brain pathology symptoms, suggesting that SARS-CoV-2 structural proteins may directly induce inflammatory processes in the brain independently and/or in addition to peripheral pro-inflammatory effects, which together may be key

reasons for the development of neurological and neuropsychiatric symptoms during PCS [31]. The S-protein SARS-CoV-2 causes blood-brain barrier (BBB) dysfunction and neuronal damage either directly or through activation of brain mast cells and microglia and release of various pro-inflammatory molecules in the brain [32]. In turn, the cytokine storm in COVID-19 can cause disruption of the BBB leading to the entry of cytokines and SARS-CoV-2 into the brain. This triggers an immune response in the brain by activating microglia, astrocytes, and other immune cells, leading to neuroinflammation [33]. Neuroinvasion of the virus, which spreads to brain compartments, particularly through transsynaptic transmission, is accompanied by binding of the spike viral protein (S-protein) to the angiotensin-converting enzyme 2 (ACE2) receptor [34, 35]. Stimulating the release of chemokines, cytokines and other proinflammatory molecules accompanied by BBB disruption, this process engulfs microglia and astrocytes, and their activation increases neuroinflammation and neuronal death, contributing to neurodegenerative changes. Brain vascular damage is mediated by the coronavirus adhesion protein, although the exact molecular mechanisms remain incompletely understood [36].

Resident brain cells, astrocytes, neurons, oligodendrocytes, and microglia, as well as infiltrating immune cells, monocytes, T cells, and macrophages, are involved in the formation of complex intercellular networks and multiple interactions. Alterations in microglia, which play a regulatory role in inflammation, contribute to the disturbance of brain homeostasis and neuroimmune responses. Neuroinflammation can provoke structural damage, reduces regeneration, promotes neuronal death, modulates synapse remodeling, and thus may adversely affect brain function. Although neuroinvasion may vary, SARS-CoV-2 infection supports persistent neuroinflammation with local cytokine production, microglia activation, and secondary neuronal death [24]. Inflammatory processes in the body and neuroinflammation are maintained as a result of increased expression of various cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin 6 (IL-6), interleukin 10 (IL-10), interleukin 1 beta (IL-1β), chemokine CCL3 [37, 38]. Pro-inflammatory factors can initiate a "cytokine storm" by stimulating immune T helper 1 (Th1) [39].

Ependymal, glial cells and neurons are exposed to neuroinflammation during the acute phase of the disease, but the effects on the brain may persist for a long period. Most studies have confirmed that SARS-CoV-2 can directly infect and replicate in certain types of brain cells, mainly endothelial cells, vascular plexus cells and astrocytes. Vascular plexus cells are among the most susceptible to SARS-CoV-2 infection and, particularly because of their localization at the border of the brain and cerebrospinal fluid, may serve as an entry route for neuroinvasion [40]. Astrocytes are present in brain tissue, the BBB, and vascular structures of the brain, being a target for virus replication (particularly as a result of neuropilin-1 expression, which makes them susceptible to SARS-CoV-2 invasion). Infected astrocytes can induce cell death of nearby neuronal cells, and perivascular astrocytes, like vascular cells, experience a greater viral load during SARS-CoV-2 infection, which pathologically alters brain vascular properties.

COVID-19-induced immune and inflammatory responses in the brain trigger numerous specific brain mechanisms that contribute significantly to the manifestation of post COVID neurological and psychiatric symptoms. For example, an association between SARS-CoV-2-mediated neuroinflammation and nigrostriatal dopaminergic abnormalities and impaired α-synuclein metabolism has been postulated [41]. The involvement of tachykinins, primarily substance P, a neuropeptide expressed in the nervous and immune systems and providing interaction between them, in post COVID conditions is considered [42]. Attempts have been made to link the mechanisms of PCS with the resulting cholinergic insufficiency [43]. Neuronal and glial metabolite abnormalities in PCS were studied using brain proton magnetic resonance spectroscopy. In people with PCS accompanied by persistent neuropsychiatric symptoms, the lower-than-normal total N-acetyl compounds and glutamate + glutamine indicate neuronal injury, while the lower-than-normal myo-inositol reflects glial dysfunction, possibly related to mitochondrial dysfunction [44].

Demyelination is considered as one of the mechanisms of central nervous system damage, causing neurological and psychiatric disorders. During SARS-CoV-2 infection and subsequent PCS, factors that may cause demyelination include direct effects of the virus on oligodendrocytes, inflammation, and cerebrovascular abnormalities causing myelin damage. The limited number of studies so far that have used specific methods for myelin quantification have identified changes in white matter tracts 3 and 10 months after the acute period of COVID-19 indicating demyelination [45].

The hippocampus plays a key role in the realization of cognitive functions as well as emotions. In this regard, postmortem changes observed specifically in the hippocampus may underlie the development of the observed neurological and psychiatric disorders after SARS-CoV-2 infection. Preclinical studies have shown that the hippocampus is subject to a high viral load [46]. Postmortem studies of human hippocampus and data received from experimental animal models have revealed alterations in neurogenesis, dendritic state and immune response, as well as high levels of apoptosis and neuroinflammation. Given the key role of the hippocampus in learning, memory, and the formation of the emotional sphere, as well as the known selective sensitivity of the hippocampus to external

influences, in particular through the development of neuroinflammation [47], the complaints of cognitive decline, neuropsychological changes, depressive and anxiety symptoms characteristic of PCS may be directly related to hippocampal dysfunction. Recently, it has been demonstrated that COVID-19 actually activates microglia in the hippocampus and causes a cytokine storm leading to suppression of hippocampal neurogenesis [48]. Chronic neuroinflammation alters adult hippocampal neurogenesis by suppressing it through the action of proinflammatory cytokines [49]. Disorders of adult neurogenesis are associated with various brain diseases such as depression, anxiety, cognitive decline and dementia. Also, blood clotting disorders and thrombosis inducing acute cerebral ischemic hypoxia inhibit hippocampal synaptic transmission and exacerbate neuronal apoptosis [39].

Various inflammatory biomarkers such as proinflammatory cytokines, chemokines, acute phase proteins and adhesion molecules are implicated in psychiatric disorders and play an important role in the development of neuropsychiatric symptoms [33]. Indeed, biomarkers of post COVID depression include elevated levels of interleukin IL-6, its soluble receptor (sIL-6R),interleukin 1β (IL-1), tumor necrosis factor α (TNF-α), interferon γ (IFN-γ), interleukin 10 (IL-10), interleukin 2 (IL-2), its soluble receptor (sIL-2R), C-reactive protein (CRP), monocyte chemoattractant protein-1 (MCP-1), serum amyloid A (SAA1), and metabolites of the kynurenine pathway, as well as decreased levels of brain-derived neurotrophic factor (BDNF) and tryptophan (TRP) [50]. Such biomarkers point to an etiopathogenesis of post COVID depression consistent with the leading inflammatory hypothesis for the development of major depressive disorder.

In spite of active research, mechanisms for persistent cognitive symptoms ("brain fog") following acute and often mild COVID-19 remain obscure. In a large prospective cohort of people who underwent testing a median of 9 months after acute COVID-19 it was found that (a) cognitive dysfunction is common; (b) it is not influenced by mood, fatigue, or sleepiness; and (c) it is correlated with MRI changes in very few people [51]. Single-cell gene expression analysis in the cerebrospinal fluid showed data consistent with monocyte recruitment, chemokine signaling, cellular stress, and suppressed interferon response, especially in myeloid cells. Longitudinal analysis showed slow recovery accompanied by key alterations in inflammatory genes and increased protein levels of interleukin 8 (CXCL8), chemokine CCL3L1, and soluble triggering receptor expressed on myeloid cells 2 (sTREM2). These findings suggest that the prognosis for brain fog following COVID-19 correlates with myeloid-related chemokine and interferon-responsive genes [51].

To search for neurological markers of PCS, the soluble biomolecules present in the plasma and the proteins associated with plasma neuronal-enriched extracellular vesicles were investigated in 33 PCS patients with neurological impairment (PCS), 12 COVID-19 survivors without any PCS symptoms (Cov), and 28 pre-COVID-19 healthy controls [52]. Interleukin 1β was significantly increased in both PCS and Cov groups and interleukin 8 was elevated in PCS group only. Both brain-derived neurotrophic factor (BDNF) and cortisol were significantly elevated in PCS and Cov groups as compared to healthy controls. Plasma neuronal-enriched extracellular vesicles from people with PCS had significantly elevated protein markers of neuronal dysfunction, including amyloid β 1-42, tau phosphorylated at threonine-181 (pTau181) and TAR DNA-binding protein 43 (TDP-43). This study confirmed chronic peripheral inflammation with increased stress after COVID-19 infection [52]. Another study showed that the plasma proteome of patients with neurologic symptoms of PCS differed from COVID-19 convalescents without persistent symptoms and healthy control subjects more substantially than the two combined post COVID-19 groups differed from healthy controls [53]. Proteomic differences in PCS patients 3-9 months following acute COVID-19 demonstrated alterations in inflammatory proteins and pathways as compared to healthy control subjects. Proteomic associations with PCS symptoms of brain fog and fatigue included changes in markers of DNA repair, oxidative stress, and neutrophil degranulation. A correlation was revealed between PCS patients lower subjective impression of recovery to pre-COVID-19 baseline with an increase in the concentration of the oxidative phosphorylation protein cytochrome C oxidase subunit 7A1 (COX7A1), which was also associated with neurologic symptoms and fatigue, as well as impairment in quality of life and cognitive dysfunction. The results of this study confirms ongoing inflammatory changes and mitochondrial involvement in PCS [53].

Since COVID-19 is characterized by systemic inflammation, hypoxia resulting from respiratory failure, and neuroinflammation, it is hypothesized that these events may initiate or exacerbate the patient's pre-existing psychiatric and cognitive disorders, contributing to further PCS-related impairment. According to brain pathomorphologic studies, both astrocyte and microglia changes are observed in COVID-19 patients, as COVID-19 activates a potent glial cell response that acts as a key regulator of inflammatory, protective, and repair processes in the brain [54]. However, this unified astrocyte response to brain adverse effects in a certain subgroup of patients may not complete after infection and restoration of the physiological state of glia does not occur, leading to homeostatic failure underlying the specific neuropsychiatric symptoms associated with PCS. Primarily, SARS-CoV-2 infection can provoke brain lesions vulnerable due to pre-existing CNS changes mediated by priming of microglia and other cells. Such conditions

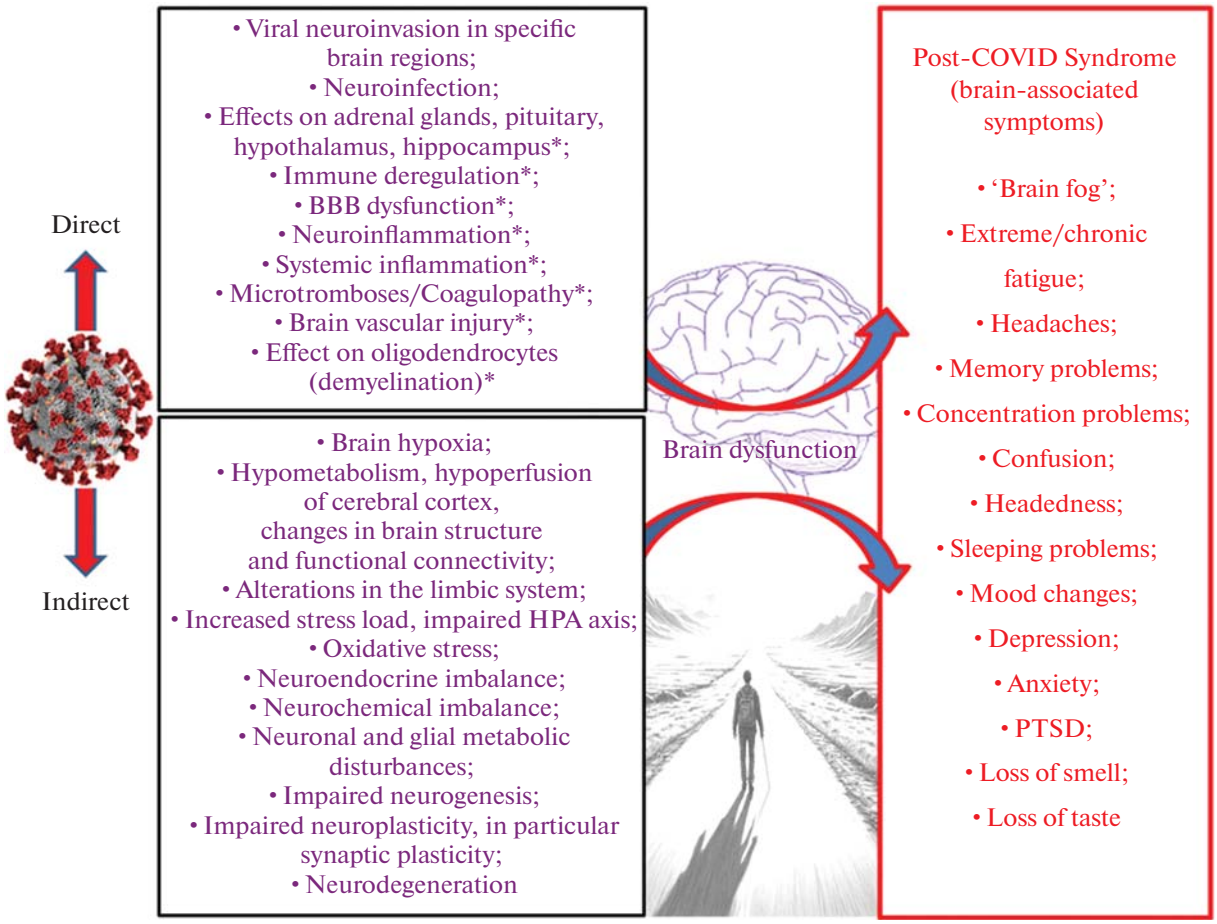

Fig. 1. Main mechanisms (molecular, cellular, and systemic) underlying brain-associated symptoms of post COVID syndrome. *Processes that can be induced directly by SARS-CoV-2, but also indirectly as a result of secondary processes. BBB—brain blood barrier; HPA—hypothalamic-pituitary-adrenal axis; PTSD—posttraumatic stress disorder.

may be induced or exacerbated by aging, pre-existing psychiatric and somatic diseases. In these situations, COVID-19 may further induce priming of neuroimmunologic substrates, activating the immune response and autoimmune structures in the CNS. Meanwhile, minor environmental exposures that activate the immune system, including stress, allergens, pollutants, or past brain lesions, may serve as a trigger for brain problems during SARS-CoV-2 infection [55]. Advanced age is an important determinant of coronavirus risk, in part due to age-related dynamic remodeling of the immune system, known as immunosenescence, as well as chronic systemic low activity inflammation. Both of these factors may provide conditions for the development of neuroinflammation, causing stable changes in the microenvironment of neurons and microglia [56].

On the other hand, it is debated that COVID-19 may increase the risk of developing neurodegenerative diseases or accelerate their progression [57]. Thus, the relationship between dementia and COVID-19/PCS brain pathologies [58], particularly between neurological complications of COVID-19 and Alzheimer's disease [59], is actively discussed. Risk factors/targets and underlying biological mechanisms common to these two disorders include the ACE2 receptor, apolipoprotein E (APOE), aging, neuroinflammation, and cellular pathways related to amyloid precursor protein (APP), β-amyloid (Aβ), and tau neuropathology, among others. For example, it has been shown that post COVID cognitive disorders are associated with tauopathy (the result of aberrant hyperphosphorylation of tau protein) [60], which may explain many of the symptoms of PCS [61].

CONCLUSIONS

It can be concluded that the mechanisms of neuropsychiatric complications of post COVID states are multifactorial, involving long-term damage to brain tissue as a result of direct or indirect viral damage to the central nervous system, prolonged systemic inflammation and neuroinflammation, oxidative stress, maladaptation of the blood coagulation sys-

tems, immune dysfunction, dysfunction of neurotransmitter systems and HPA axis, and psychosocial stress caused by social changes due to the pandemic [62]. In this review, we have updated most important cellular and molecular mechanisms of brain-related symptoms of PCS which are presented in the Fig. 1.

The emergence of COVID-19 was quickly followed by infection and the deaths of millions of people in the whole world. The European Working Group on SARS-CoV-2 discussed current understanding, unknowns, and recommendations on the neurological complications of COVID-19 [5]. Though many studies and scientific progress were focused on decreasing the burden of acute COVID-19 infection, the long-term effects experienced by survivors after the acute infection have been previously mostly disregarded. Now, an appreciation for PCS, a condition in which COVID-19-like symptoms continue or develop after the acute infection has passed, is growing. PCS, affecting dozens million adults over the world, often includes brain symptoms, devastating brain fog, cognitive issues, slow thinking, forgetfulness, impaired focusing, mood disturbances, etc. However, regarding the etiology and risk factors of PCS, as well as its effective diagnostics and treatment, many essential questions regarding PCS remain unanswered, mechanisms of its neurological complications and associated sequalae are still obscure, and new extensive studies are needed in this important area [5].

ABBREVATIONS

ACTH	adrenocorticotropic hormone
BBB	blood brain barrier
COVID-19	coronavirus disease 2019
HPA	hypothalamic-pituitary-adrenal
ME/CFS	myalgic encephalomyelitis/chronic fatigue syndrome
PCS	post COVID syndrome
PTSD	posttraumatic stress disorder
SARS-CoV-2	severe acute respiratory syndrome coronavirus

AUTHOR CONTRIBUTION

The author independently developed the concept and wrote the article.

FUNDING

This study was supported by the Moscow Center for Innovative Technologies in Healthcare of the Moscow government, Grant #1108-1/22.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This work does not contain any studies involving human and animal subjects.

CONFLICT OF INTEREST

The authors of this work declare that they have no conflicts of interest.

OPEN ACCESS

REFERENCES

1. Zawilska, J.B. and Kuczyńska, K., *J., Psychiatr. Res.*, 2022, vol. 156, pp. 349–360.
2. Coronavirus disease (COVID-19): Post COVID-19 condition. World Health Organization, https://www.who.int/news-room/questions-and-answers/item/coronavirus-disease-(COVID-19)-post-COVID-19-condition.
3. Long COVID. Department of Health, WA Government, https://www.healthywa.wa.gov.au/Articles/A_E/Coronavirus/Long-COVID.
4. Anderson, A.M, Letendre, S.L., and Ances, B.M., *Top. Antivir. Med.*, 2022, vol. 30, pp. 475–489.
5. Bai, F., Tomasoni, D., Falcinella, C., Barbanotti, D., Castoldi, R., Mulè, G., Augello, M., Mondatore, D., Allegrini, M., Cona, A., Tesoro, D., Tagliaferri, G., Viganò, O., Suardi, E., Tincati, C., Beringheli, T., Varisco, B., Battistini, C.L., Piscopo, K., Vegni, E., Tavelli, A., Terzoni, S., Marchetti, G., and Monforte, A.D., *Clin. Microbiol. Infect.*, 2022 vol. 28, 611.e9–611.e16.
6. Crook, H., Ramirez, A., Hosseini, A., Vavougyios, G., Lehmann, C., Bruchfeld, J., Schneider, A., D'Avossa, G., Lo Re, V., Salmoiraghi, A., Mukaetova-Ladinska, E., Katshu, M., Boneschi, F.M., Håkansson, K., Geerlings, M., Pracht, E., Ruiz, A., Jansen, J.F.A., Snyder, H., Kivipelto, M., and Edison, P., *Brain. Connect.*, 2023 vol. 13, pp. 178–210.
7. Malkova, A., Kudryavtsev, I., Starshinova, A., Kudlay, D., Zinchenko, Y., Glushkova, A., Yablonskiy, P., and Shoenfeld, Y., *Pathogens*, 2021, vol. 10, 1408.

8. Klinkhammer, S., Duits, A.A., Horn, J., Slooter, A.J.C., Verwijk, E., VanSanten, S., Visser-Meily, J.M.A., and Van Heugten, C., *J. Rehabil. Med.*, 2024, vol. 12, 56:jrm25315.
9. Lauria, A., Carfì, A., Benvenuto, F., Bramato, G., Ciciarello, F., Rocchi, S., Rota, E., Salerno, A., Stella, L., Tritto, M., Di Paola, A., Pais, C., Tosato, M., Janiri, D., Sani, G., Lo Monaco, R., Pagano, F.C., Fantoni, M., Bernabei, R., Landi, F., Bizzarro, A., and Gemelli Against COVID-19 Post-acute Care Group, *Front. Psychol.*, 2023, vol. 10, 14:1136667.
10. Arbula, S., Pisanu, E., Bellavita, G., Menichelli, A., Lunardelli, A., Furlanis, G., Manganotti P., Cappa, S., and Rumiati, R., *Sci. Rep.*, 2024, vol. 14, 4405.
11. García-Sánchez, C., Calabria. M., Grunden, N., Pons, C., Arroyo, J.A., Gómez-Anson, B., Lleó A., Alcolea, D., Belvís, R., Morollón, N., Mur, I., Pomar, V., and Domingo, P., *Brain Behav.*, 2022, vol. 12, e2508.
12. Picascia, M., Cerami, C., Panzavolta, A., Bernini, S., Calculli, A., Regalbuto, S., and Pisani, A., *Neurol. Sci.*, 2023, vol. 44, pp. 2635–2642.
13. Brown, L.A., Ballentine, E., Zhu, Y., McGinley, E.L., Pezzin, L., and Abramoff, B., Brain Behav. *Immun. Health*, 2022, vol. 22, 100460.
14. Fiabane, E., Pain, D., Aiello, E.N., Radici, A., Manera, M.R., Grossi, F., Ottonello, M., and Pistarini, C., *Psychiatry Res.*, 2022, vol. 316, 114757.
15. Dehelean, L., Papava, I., Musat, M.I., Bondrescu, M., Bratosin, F., Bucatos, B.O., Bortun, A.C., Mager, D.V., Romosan, R.S., Romosan, A.M., Paczeyka, R., Cut, T.G., Pescariu, S.A., and Laza, R., *Brain Sci.*, 2021, vol. 11, 1287.
16. Craparo, G., La Rosa. V.L., Commodari, E., Marino, G., Vezzoli, M., Faraci, P., Vicario, C.M., Cinà, G.S., Colombi, M., Arcoleo, G., Severino, M., Costanzo, G., Gori, A., and Mangiapane, E., *Int. J. Environ. Res. Public. Health*, 2022, vol. 20, 494.
17. Liang, H., Ernst, T., Oishi, K., Ryan, M.C., Herskovits, E., Cunningham, E., Wilson, E., Kottilil, S., and Chang, L., *NeuroImmune Pharm. Ther.* 2023, vol. 2, pp. 37–48.
18. Kotzalidis, G.D., Ferrara, O.M., Margoni, S., Ieritano, V., Restaino, A., Bernardi, E., Fischetti, A., Catinari, A., Monti, L., Chieffo, D.P.R., Simonetti, A., and Sani, G., *J. Pers. Med.*, 2023, vol. 13, 1140.
19. Tate, W., Walker, M., Sweetman, E., Helliwell, A., Peppercorn, K, Edgar, C., Blair, A., and Chatterjee, A., *Front. Neurol.*, 2022, vol. 13, 877772.
20. Thomasson, M., Voruz, P., Cionca, A., Jacot de Alcântara, I., Nuber-Champier, A., Allali, G., Benzakour, L., Lalive, P.H., Lövblad, K.O., Braillard, O., Nehme, M., Coen, M., Serratrice, J., Reny, J.L., Pugin, J., Guessous, I., Landis, B.N., Griffa, A., Van De Ville, D., Assal, F., and Péron, J.A., *Brain Commun.*, 2023, vol. 5, fcad177.
21. Taieb, A., Nassim, B.H.S., Asma, G., Jabeur, M., Ghada, S., and Asma, B.A., *Adv. Respir. Med.*, 2024, vol.14, pp. 96–109.
22. Sieracka,J., Sieracki, P., Kozera, G., Szurowska, E., Gulczyński, J., Sobolewski, P., Kloc, W., and Iżycka-Świeszewska, E., *Folia Neuropathol.*, 2021, vol. 59, pp. 1–16.
23. Aschman, T., Mothes, R., Heppner, F.L., and Radbruch, H., *Immunity*, 2022, vol. 55, pp. 1159–1172.
24. Peron, J.P.S., *Hum. Genet.*, 2023, vol. 142, pp. 1317–1326.
25. Putri, C., Arisa, J., Hananto, J.E., Hariyanto, T.I., and Kurniawan, A., *World J. Psychiatry*, 2021, vol. 11, pp. 821–829.
26. Klein, F.R., Renedo, M.F., and Vigliano, C.A., *Cureus*, 2022, vol. 14, e24852.
27. Jensterle, M., Herman, R., Janež, A., Mahmeed, W.A., Al-Rasadi, K., Al-Alawi, K., Banach, M., Banerjee, Y., Ceriello, A., Cesur, M., Cosentino, F., Galia, M., Goh, S.Y., Kalra, S., Kempler, P., Lessan, N., Lotufo, P., Papanas, N., Rizvi, A.A., Santos, R.D., Stoian, A.P., Toth, P.P., Viswanathan, V, and Rizzo, M., *Int. J. Mol. Sci.* 2022, vol. 23, 7326.
28. Qin, Z., Liu, F., Blair, R., Wang, C., Yang, H., Mudd, J., Currey, J.M., Iwanaga, N., He, J., Mi, R., Han, K., Midkiff, C.C., Alam, M.A., Aktas, B.H., Heide, R.S.V., Veazey, R., Piedimonte, G., Maness, N.J., Ergün, S., Mauvais-Jarvis, F., Rappaport, J., Kolls, J.K., and Qin, X., *Theranostics*, 2021, vol. 11, pp. 8076–8091.
29. Kell, D.B., Laubscher, G.J., and Pretorius, E., *Biochem. J.*, 2022, vol. 479, pp. 537–559.
30. Gałgańska, H., Jarmuszkiewicz, W., and Gałgański, Ł., *Cell. Commun. Signal.*, 2023, vol. 21, 280.
31. Frank, M.G, Fleshner, M., and Maier, SF., *Brain. Behav. Immun.*, 2023, vol. 111, pp. 259–269.
32. Theoharides, T.C., and Kempuraj, D., *Cells*, 2023, vol. 12, 688.
33. Saikarthik, J., Saraswathi, I., Alarifi, A., Al-Atram, A.A., Mickeymaray, S., Paramasivam, A., Shaikh, S., Jeraud, M., and Alothaim, A.S., *PeerJ.*, 2022, vol. 10, e14227.
34. Abdel Hafez, S.M.N., *J. Chem. Neuroanat.*, 2021, vol. 117, 102006.
35. Sodagar, A., Javed, R., Tahir, H., Razak, S.I.A., Shakir, M., Naeem, M., Yusof, A.H.A, Sagadevan, S., Hazafa, A., Uddin, J., Khan, A., and Al-Harrasi, A., *Biomolecules*, 2022, vol. 12, 971.
36. Suprewicz, Ł., Fiedoruk, K., Czarnowska, A., Sadowski, M., Strzelecka, A., Galie P.A., Janmey, P.A., Kułakowska, A., and Bucki, R., *Neurol. Neurochir. Pol.*, 2023, vol. 57, pp. 14–25.
37. Kulkarni, P.G., Sakharkar, A., and Banerjee, T., *Hypertens. Res.*, 2022, vol. 45, pp. 254–269.
38. Abdullah, M., Ali, A., Usman, M., Naz, A., Qureshi, J.A., Bajaber, M.A., and Zhang, X., *Nanoscale Adv.*, 2023, vol. 5, pp. 5705–5716.
39. Quan, M., Wang, X., Gong, M., Wang, Q., Li, Y., and Jia, J., *Lancet Reg. Health West. Pac.*, 2023, vol. 38, 100836.
40. Kong, W., Montano, M., Corley, M.J., Helmy, E., Kobayashi, H., Kinisu, M., Suryawanshi, R., Luo, X., Royer, L.A., Roan, N.R., Ott, M., Ndhlovu, L.C., and Greene W.C., *mBio*, 2022, vol. 13, e0230822.
41. Mancini, M., Natoli, S., Gardoni, F., Di Luca, M., and Pisani, A., *Int. J. Mol. Sci.*, 2023, vol. 24, 5618.
42. Janket, S.J., Fraser, D.D., Baird, A.E, Tamimi, F., Sohaei, D., Conte, H.A., Prassas, I., and Diamandis, E.P., *Lancet Microbe*, 2023, vol. 4, pp. e642–e650.

43. Lysenkov, S.P., Muzhenya, D.V., Tuguz, A.R., Urakova, T.U., Shumilov, D.S., Thakushinov, I.A., Thakushinov, R.A., Tatarkova, E.A., and Urakova, D.M., *Chin. J. Physiol.*, 2023, vol. 66, pp. 1–13.
44. Ernst, T., Ryan, M.C., Liang, H.J., Wang, J.P., Cunningham, E., Saleh, M.G., Kottilil, S., and Chang, L., *J. Infect. Dis*. 2023, vol. 228, pp. 1559–1570.
45. Khodanovich, M.Y., Kamaeva, D.A., and Naumova, A.V., *Int. J. Mol. Sci.*, 2022, vol. 23, 11291.
46. Zorzo, C., Solares, L., Mendez, M., and Mendez-Lopez, M., *Behav. Brain Res.*, 2023, vol. 455, 114662.
47. Gulyaeva, N.V., *Biochemistry* (Mosc.), 2023, vol. 88, pp. 565–589.
48. Nouraeinejad, A., *Acta Neurol. Belg.*, 2023, vol. 123, pp. 1247–1256.
49. Podgorny, O.V., and Gulyaeva, N.V., *J. Neurochem.*, 2021, vol. 157, pp. 370–392.
50. Lorkiewicz, P., and Waszkiewicz. N., *J. Clin. Med.*, 2021, vol. 10, 4142.
51. Hu, W.T., Kaluzova, M., Dawson, A., Sotelo, V., Papas, J., Lemenze, A., Shu, C., Jomartin, M., Nayyar, A., and Hussain, S., *Cell. Rep. Med.*, 2024, vol. 5, 101561.
52. Tang, N., Kido, T., Shi, J., McCafferty, E., Ford, J.M., Dal Bon, K., and Pulliam, L., *Cells*, 2024, vol. 13, 478.
53. Hanson, B.A., Visvabharathy, L., Orban, Z.S., Jimenez, M., Batra, A., Liotta, E.M., DeLisle, R.K., Klausner, J.D., Cohen, P., Padhye, A.S., Tachas, G., and Koralnik, I.J., *Brain Behav. Immun.*, 2023, vol. 114, pp. 462–474.
54. Steardo, L. Jr, Steardo, L., and Scuderi, C. *Neurochem. Res.*, 2023, vol. 48, pp. 1015–1025.
55. Tizenberg, B.N., Brenner, L.A., Lowry, C.A., Okusaga, O.O., Benavides, DR., Hoisington, A.J., Benros, M.E., Stiller, J.W, Kessler, R.C., and Postolache, T.T., *Curr. Psychiatry Rep.*, 2021, vol. 23, 68.
56. Müller, L., and Di Benedetto, S., *Immun. Ageing.*, 2023, vol. 20, 17.
57. Onaolapo, A., and Onaolapo, O., CNS Neurol. Disord. *Drug Targets*, 2022, vol. 21, pp. 818–829.
58. Toniolo, S., Scarioni, M., Di Lorenzo, F., Hort, J., Georges, J., Tomic, S., Nobili, F., and Frederiksen, K.S., Management Group of the EAN Dementia and Cognitive Disorders Scientific Panel, *J. Alzheimers Dis.*, 2021, vol. 82, pp. 883–898.
59. Amadoro, G., Latina, V., Stigliano, E., and Micera, A., *Cells*, 2023, vol. 12, 2601.
60. Sfera, A., Rahman, L., Zapata-Martín Del Campo, C.M., and Kozlakidis, Z., *Int. J. Mol. Sci.*, 2023, vol. 24, 12648.
61. Marwaha, B., *Front. Cell Infect. Microbiol.*, 2023, vol. 13, 1280600.
62. Yang, C.P., Chang, C.M., Yang, C.C., Pariante, C.M., and Su, K.P., *Brain. Behav Immun.*, 2022, vol. 103, pp. 19–27.