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REVIEW

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Biological correlates of the neuropsychiatric symptoms in SARS-CoV-2 infection: an updated review

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Abstract

Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome corona virus-2 (SARS-CoV-2) appeared in early 2019 and swiftly became a pandemic causing extensive morbidity and mortality. Many studies have recognized the neuropathological changes in the brain and hypothesized the possible link with cognitive dysfunction, neuropsychiatric symptoms and behavioral disturbances. Potential biological mechanisms may include direct neuronal micro-invasion, disturbances in the neuro-immuno-endocrine system and possibly alteration of neuronal excitability. SARS-CoV-2 facilitates down-regulation of the ACE2 (Angiotensin-2) receptors which could alter inflammatory response through various cellular and neurophysiological systems leading to disturbance in the hypo-thalamopituitary–adrenal (HPA) axis, escalation of the oxidative stress and disruption of the homeostasis of the neurotransmitter system, including serotonin, dopamine and GABA (gamma-aminobutyric acid), eventually resulting in the emergence of neuropsychiatric symptoms. Psychiatric symptoms that emerged are many, some of which may be unique to SARS-CoV-2 infection. These neuropsychiatric symptoms are acute or chronic with possibly distinct etiopathogenesis. This article discusses the possible biological correlates and neurobiology of the psychiatric symptoms of SARS-CoV-2 and their impact on the brain and behavior.

Keywords Neurotransmitters, Neuro-immuno dysregulation, biological correlates, Psychiatric symptoms, SARS-CoV-2

Introduction

SARS-CoV-2 (Severe Acute Respiratory Syndrome Corona Virus-2) causes coronavirus disease 2019 (COVID-19) and related medical complications. There is growing evidence for the neurotropic and neuro-invasive properties of SARS-CoV-2 and its ability to cause central nervous system (CNS) injury [1, 2]. SARS-CoV-2 affects neuropathogenesis due to its predilection for brain tissue besides pulmonary tissues. For example, SARS-CoV-2 may cause impairment in the brainstem structure, such as locus coeruleus in the pons, a major source of noradrenaline [3]. The neuro-cellular injuries associated with COVID-19 are mostly immune-mediated in addition to associated hypoxic–ischemic damage, which may play a role in the emergence of COVID-19 associated psychiatric conditions [4]. The pathogenesis of COVID-19 might

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vary or overlap between acute and chronic neuropsychiatric symptoms. The most common neuropsychiatric symptoms associated with COVID-19 infection are delirium, insomnia, fatigue, anxiety, post-traumatic disorder, psychosis, cognitive impairment, and mood disorders [5]. It has been suggested that many factors could be contributing to the pathophysiology of these symptoms including direct and indirect effects of the viral infection on the brain cells, cerebrovascular events due to hypercoagulable states, the impact of hypoxia and resultant anoxic brain injury, excessive inflammation secondary to altered immunological response, medical interventions, in addition to severe psychological and social stress associated with SARS-CoV-2 pandemic [6]. The etiology of psychiatric symptoms in COVID-19 survivors is likely not entirely attributable to neuropathological processes, as psychosocial factors also play a vital role. It is however beyond the scope of this review to discuss the etiological role of psychosocial factors. So, this narrative review highlights the available evidence for the possible biological mechanisms that may contribute to the development of neuropsychiatric symptoms.

Classification and etiology of neuropsychiatric symptoms of COVID-19

Acute and chronic neuropsychiatric symptoms in COVID-19 infection potentially differ or even overlap with the etiology of neurobiological signs and symptoms. Multiple etiologies contribute to the neuropsychiatric symptoms in acute SAR-CoV-2 infection, the most important being viral invasions of brain tissue and cytokine-induced immune disturbances. Chronic symptoms related to biological consequences of initial infection include neuronal/glial death, immune dysregulation, and virus reactivation [5]. In addition, psychosocial stressors inherent to the COVID-19 pandemic can further add to the pathology of neuropsychiatric symptoms. Unfortunately, due to methodological differences in studies assessing neuropsychiatric manifestations of COVID-19, there is also wide variation in the prevalence of acute and chronic neuropsychiatric symptoms reported. The chronic neuropsychiatric symptoms could be part of "Post COVID syndrome" or "Long COVID symptoms". Still, it remains a dilemma in the classification of chronicity. In most classifications, including CDC and NICE guidelines, the chronicity of symptoms is usually new and/or persistent after 4–12 weeks [7].

Acute neuropsychiatric symptoms

Delirium (42%) is the most common acute neuropsychiatric syndrome [8]. In older people, delirium might be the only presenting symptom and is often seen without other typical signs or symptoms [9]. Other symptoms during acute infection include insomnia, cognitive impairment, and mood disorders [5]. Psychosis seems to be limited to the acute stage of illness as well, and new-onset psychosis has been reported in several studies [5]. A large study reviewing electronic medical record data found that of 40,469 COVID-19-positive individuals, 22.5% had neuropsychiatric manifestations. The most common psychiatric manifestations included anxiety and other related disorders (4.6%), mood disorders (3.8%), and sleep disorders (3.4%), while 0.2% of patients had suicidal ideation [10]. Also, in a large metanalysis, delirium, agitation were 65% and 69%, respectively, in intensive care unit patients and psychotic spectrum disorders range from 0.9 to 4% [6, 11]. In fact, SARS-CoV-2 has demonstrated an association with delirium in a significant proportion of patients in the acute stage of the disease [11]. Emerging data also indicate rising cases of catatonia, especially the akinetic variant in COVID-19 patients [12].

Chronic neuropsychiatric symptoms

An estimated probability of having been newly diagnosed with a psychiatric illness at 3 months after COVID-19 diagnosis was 5.8% [13]. A metanalysis of 51 studies ($n = 18\,917$ patients) reports that most prevalent neuropsychiatric symptom was sleep disturbance (27.4%), fatigue (24.4%), objective cognitive impairment (20.2%), anxiety (19.1%) and 15.7% experience post-traumatic stress [14]. More specifically, within or after 6 months from the onset of acute COVID-19, 26% of patients may experience anxiety, 40% may experience depression and post-traumatic stress disorder (PTSD) has been shown to be found in up to 43% of all recovered patients [15]. In a one-month follow-up study 402 (psychiatric assessment was performed 31.29 ± 15.7 days after discharge, or 28.56 ± 11.73 days after emergency department visit) COVID-19 positive patients in Milan, self-rated psychopathology assessment showed evidence of PTSD (28%), depression (31%), anxiety (42%), obsessive compulsive symptoms (20%), and insomnia (40%) [16]. Importantly, the baseline systemic immune-inflammation index (SII), which reflects the immune response and systemic inflammation, is positively associated with scores of depressions and anxiety at follow-up [16]. In another study, short-term memory, attention, and concentration were particularly affected by COVID-19. Screening results did not correlate with hospitalization, treatment, viremia, or acute inflammation [17]. In another study assessing medium-term effects followed patients at 2–3 months from disease-onset, 55% reported fatigue. Patients exhibited changes in the thalamus, posterior thalamic radiations, and sagittal stratum on brain MRI and demonstrated impaired cognitive performance, specifically in the executive and visuospatial domains. In comparison to

the controls, these patients reported a greater number of symptoms associated with depression and suffered notable limitations across all aspects of their quality of life [18].

Cellular entry, mode of spread and dissemination to CNS

There are four important proteins identified in the SARS-CoV-2 virus, 1. nucleoprotein (N); 2. **s**pike glycoprotein (S) at the receptor-binding site: serves as the entry point for the virus; 3. small envelope glycoprotein (E) and 4. membrane glycoprotein (M). The spike proteins have two subunits, S1 (responsible for binding to receptors on the host) and S2 (responsible for fusion with the host cell membrane for cellular entry) [19]. SARS CoV-2 enters the host cells by binding to the S-proteins and subsequently on the host cellular ACE2 (angiotensin converting enzyme-2) receptors; this leads to membrane fusion and endocytosis [19]. The S1 and S2 subunits are cleaved by transmembrane serine protease 2 (TMPRSS2) or the lysosomal/endosomal cathepsin, a cysteine protease. The above process occurs at specific furin cleavage sites, allowing for the dissociation of the S1 subunit and exposure of the fusion peptide [19]. Conformational changes within the activated S2 subunit propel the hydrophobic fusion peptide toward the host cell membrane, resulting in disruption of the host cell lipid-bilayer and fusion of the viral and host cell membranes, allowing for the release of the viral RNA genome into the host cell [19]. After infecting the epithelial cells in the respiratory tract, the SARS-CoV-2 virus enters the bloodstream and spreads to other organs, including the brain [20]. The spike protein of SARS-CoV-2 is purported to interact with ACE2 expressed in the capillary endothelium resulting in damage to the blood–brain barrier (BBB), which then helps it enter into the CNS [21] (Fig. 1). Interestingly, the virus can also spread to the CNS through neuronal dissemination by active *retrograde* axonal transport from peripheral nerves such as the olfactory nerve

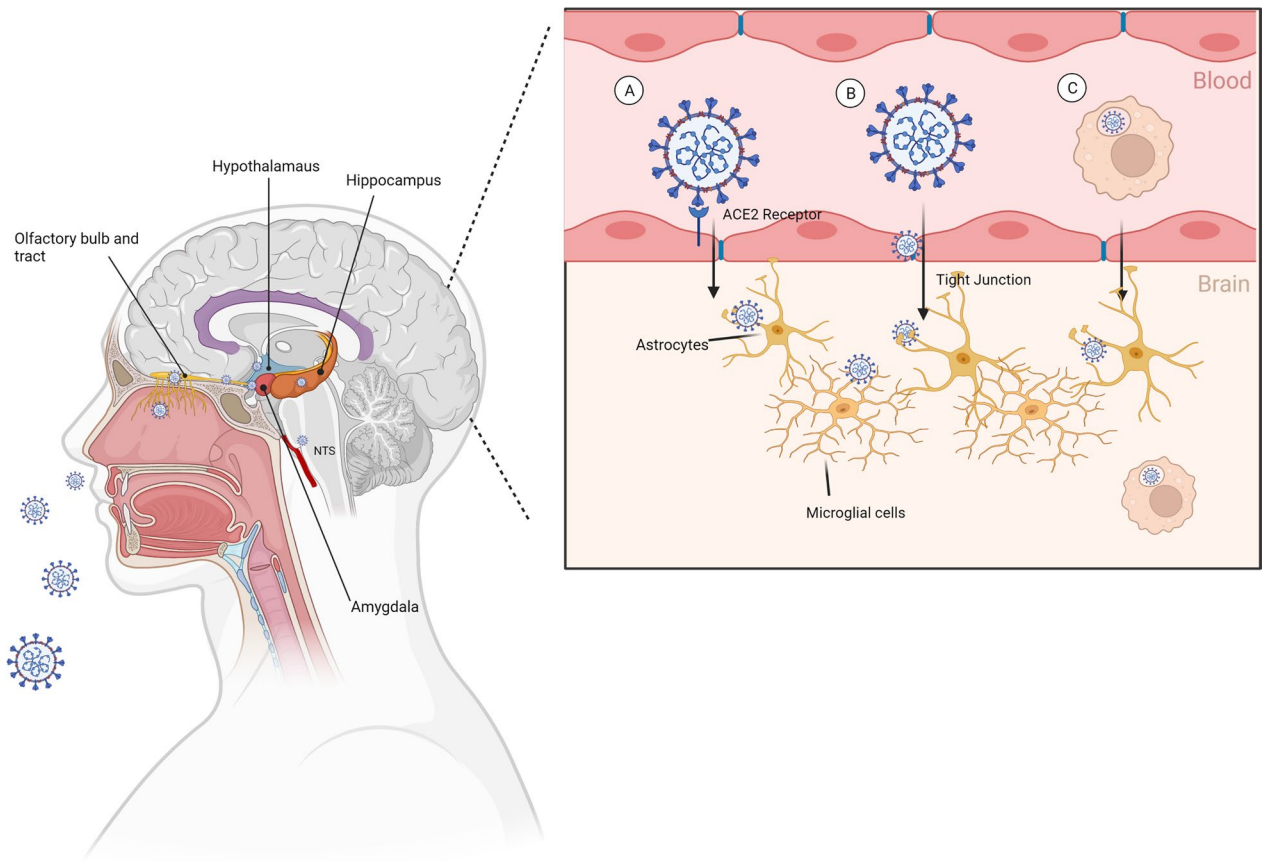

Fig. 1 Mechanisms of SARS-CoV-2 CNS dissemination. SARS-CoV-2 particles are first inhaled into the nasal cavity and begins CNS spread through active retrograde axonal transport along the sensory and olfactory nerves. The virus then enters systemic circulatory system and travel to the brain where the BBB prevents entry. Here the virus employs a combination of the three mechanisms to gain entry. Transcellular migration allows for the invasion of endothelial cells through interactions with the ACE2 receptors (**A**). The virus can also infect the tight junction for entry via paracellular transport (**B**). Lastly, the virus may also enter via a "Trojan horse" where viral particle becomes engulfed by a host phagocytic cell (**C**) [26]

[20]. Meinhardt et al. have identified the presence of intact SARS-CoV-2 particles and RNAs in the olfactory mucosa and in the neuroanatomical areas that receive olfactory tract projections. The above research findings provide early evidence for the use of axonal transport by the virus to find the trans-mucosal entry to the CNS via the regional nervous structures in the neural–mucosal interface [22, 23]. Other factors, such as systemic inflammation associated with COVID-19 infection, disrupt/weaken the BBB, which helps with easy entry into CNS cells. The SARS-CoV-2 virus in brain tissues is equivocal in patients presenting with neurological/neuropsychiatric symptoms. In a large study of 43 samples of postpartum brains of COVID-19 patients, neuropathology showed that only 53% of the brain tissue sample was positive for SARS-CoV-2 [24]. Another study, which analyzed cerebrospinal fluid of 7 patients with COVID-19 encephalopathy, found no traces of SARS-CoV-2 in the CSF in any patient but instead noted an increased CSF/serum quotient of albumin in 6/7 patients, suggestive of blood–brain barrier disruption. The authors suggest that COVID-19 encephalopathy may be due to indirect (or inflammatory) effects of the virus resulting in disturbed brain homeostasis and vascular dysfunction consistent with SARS-CoV-2-induced endothelialitis [25].

Cytokine network dysregulation and inflammatory systemic manifestation

In SARS-CoV-2 infection, inflammatory cytokines are overproduced by various tissues and immune cells due to the loss of negative feedback to the immune system [27]. The feedback failure leads to a hyper-reactive immune response and elevated levels of inflammatory cytokines, referred to as a "cytokine storm", a major hallmark of severe COVID-19 infections [28]. The disrupted inflammatory system causes an increased influx of neutrophils, macrophages, and T cells, causing damaging effects on the surrounding tissues at the site of infection. Current evidence supports the cytokine storm as the main pathological process causing lung injury, multiple organ failure, and ARDS [29]. Cytokines are produced when pattern recognition receptors (PRRs) recognize different surface molecules unique to each virus, known as pathogen-associated molecular patterns (PAMPs). This binding between PRRs and PAMPs initiates a series of events through downstream signaling pathways that activate transcription factors responsible for upregulating many immune molecules and pro-inflammatory cytokines. Different cells, such as tissue macrophages, mast cells, endothelial and epithelial cells, are major contributors to the production of pro-inflammatory cytokines such as IL-1, IL-6, and TNF-a [28]. Patients with SARS-CoV-2 exhibit significantly higher levels of IL-10 (anti-inflammatory cytokine) [30], potentially moderating the severe inflammatory response in COVID-19 patients. The contradictory argument is that the persistent elevation of IL-10 in severe viral infections may be harmful, as IL-10 has been shown to induce anergy of both CD4 + and CD8 + T cells, resulting in impaired humoral immunity (that is, inability to kill virus-infected cells) [30]. Clinical analysis and comparisons between COVID-19 patients admitted to the ICU versus those placed in the general ward have demonstrated that serum levels of IL-2R, IL-4, IL-6, IL-8, IL-10, ESR, CRP, Serum ferritin, PCT, IP-10, MCP-1, and TGF-B are correlated with the severity of the disease (see Table 1) [30–33]. It is noteworthy that IL-6 has always been an important central factor in "cytokine storm" and induces the differentiation of CD8 + T cells into cytotoxic T cells, which eliminate viruses by lysing the infected cells [27]. The utilization of cytotoxic T cells may cause a decrease in lymphocytes in most patients with COVID-19. Another recently conducted study collected plasma from 24 individuals follow-up at 1 and 3 months after the initial infection identified increased plasma cytokine IL-4 levels in all patients. The study also collected neuronal-enriched extracellular vesicles and demonstrated elevated levels of inflammatory and neurodegenerative proteins. In addition, in those volunteers who self-reported neurological problems, a positive correlation was observed between IL-6 and the severity of the different neurological sequelae. As a result, it was suggested that COVID-19 might cause ongoing peripheral and neuro-inflammation that may contribute to the onset of many neurological sequelae, which are discussed in detail in the next sections [34]. The typical serum profile of cytokines derangements in SARS-CoV-2 Infection are inappropriately elevated levels of TNF-α, IL-6, IL-1β, IL-2R, IL-8, IL-17, GM-CSF, inducible protein (IP)-10, D-dimer, CRP, and ferritin, which culminate as a cytokine storm [29, 35–40]. Ortelli et al. conducted a study on COVID-19 recovered patients and noted hyperinflammatory reaction to the virus as confirmed by elevated serum levels of C-reactive protein (CRP) and interleukin-6 (IL-6) during the acute phase of the infection. In addition, they found that compared to the healthy controls, these patients had significantly higher scores on the fatigue severity scale (FSS), poorer performance in the Montreal Cognitive Assessment (MoCA) battery, decreased motor speed, and increased reaction time to the computerized cognitive tasks (such as Vigilance Task, Stroop Interference Task, and Navon Task, a test for visual neglect). These findings elucidate the presence of long-term neuropsychiatric effects caused by COVID-19 [41] possibly mediated by the severe inflammatory response.

Along with this plethora of pro-inflammatory cytokines, patients with SARS-CoV-2 infection also

Table 1 Summary of the biological changes seen in COVID-19 infection

	Hematologic	Inflammatory biomarkers	Biochemical	Coagulation
Specific for early-stage infection		BLC [42] sCD30 [42] MCP-2 [42] IP-10 [33, 42] IL-8 [33] MDC [33]		
Increased	Total WBC count [31, 32] Neutrophil count [31, 32]	ESR [31, 32] CRP [32] Serum ferritin [31, 32] PCT [31, 32] IL-1RA [33, 36] IL-1β [31, 36] IL-2[31, 36] IL-2R [31, 32] IL-4 [31] IL-6 [31–33, 43] IL-7 [36] IL-8 [31, 32, 36, 40, 43] IL-9 [36] IL-10 [31, 33, 36, 43] IL-17 [31, 40] IL-18 [33] TNF-α [31, 36, 43] MIG [33] IP-10 [33, 36] MCP-1 [32, 36][a] MIP-1α [36] MIP-1β [36] GRO-a [33] IFN-γ [31, 36, 40] TGF-β [40] FGF2 [36] GCSF[36] GMCSF[36] PDGFB [36] VEGFA [36] SAA [31, 42]	ALT/AST [32] Bilirubin (total) [32] BUN [32] Creatinine [32] CK [32] CK-MB [32] LDH [32] Myoglobin[32] Cardiac troponin-I[32]	PT/aPTT [32] D-Dimer [32]
Decreased	Lymphocyte count [31, 32] Platelet count [32] Eosinophil count [32] Monocyte count [31] Hemoglobin [32]	IL-5 (late) [32] MDC (late) [32] FGF-2 (late) [32] MIP-1a (late) [32]	Albumin [32]	

ESR erythrocyte sedimentation rate, *CRP* C-reactive protein, *PCT* procalcitonin, *IL* interleukin, *TNF* tumor necrosis factor, *MIG* monokine-induced by gamma interferon, *IP-10* interferon-induced protein-10, *MCP-1* monocyte chemoattractant protein-1, *MIP* Macrophage Inflammatory Protein, *GRO-a* growth-regulated oncogene-alpha, *IFN-γ* interferon-gamma, *TGF-β* transforming growth factor beta, *FGF2* fibroblast growth factor 2, *GCSF* granulocyte colony-stimulating factor, *GMCSF* granulocyte–macrophage colony-stimulating factor, *PDGFB* platelet derived growth factor subunit B, *VEGFA* vascular endothelial growth factor A, *SAA* serum amyloid A, *MDC* macrophage-derived chemokine, *BLC/CXCL-13* B lymphocyte chemoattractant/chemokine ligand 13, *sCD30* soluble CD30, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *BUN* blood urea nitrogen, *CK* creatine kinase, *CK-MB* creatine kinase-MB, *LDH* lactate dehydrogenase, *PT* prothrombin time, *aPTT* activated partial thromboplastin time, *Red* correlated to disease severity

[a] MCP-1-predicted the duration of mechanical ventilation, highest NE dose administered, and length of ICU stay

express elevated expression of multiple chemokines and their receptors; most notable are the upregulation of neutrophil (CXCL17, CXCL8, CXCL1, and CXCL2) and monocyte (CCL2, CCL3, CCL7) chemo-attractants [35, 37, 44], which may lead to shock and tissue damage in the heart, liver, kidney, and progress to multiple organ failure [35]. The multi-systemic manifestations of COVID-19 are illustrated in Fig. 2.

SARS-Cov-2 related organic brain damage

As discussed above, multiple pathological processes can weaken the integrity of the blood–brain barrier and trigger an immune response with over-production of IL-6 (pro-inflammatory) and, in severe cases, *cytokine storm* (particularly IL-6). The subsequent increase in pro-inflammatory cytokines in the brain and a rise in IL-6 may be a useful marker for severe disease onset

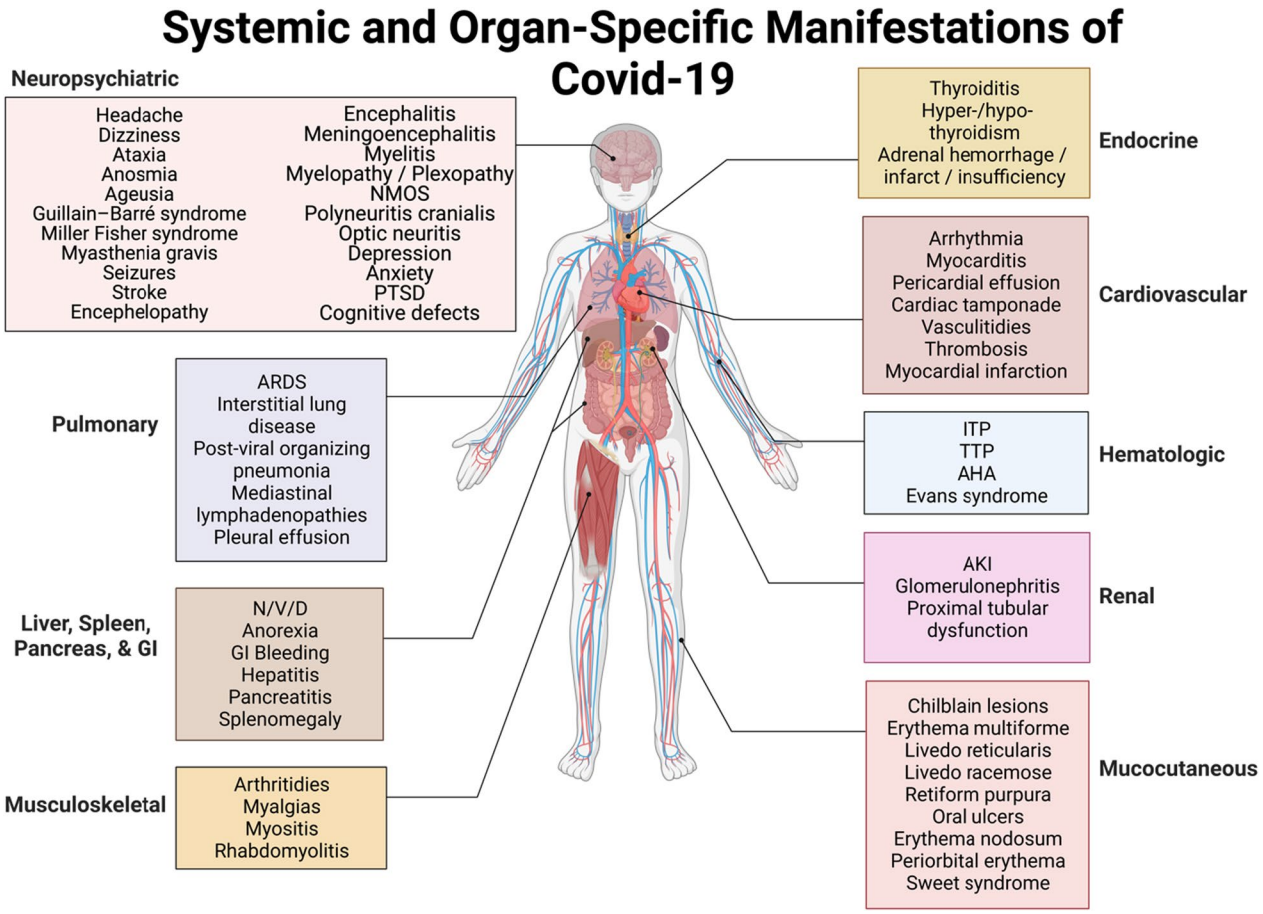

Fig. 2 Part of Fig. 2 is adapted from Burkert et al. [45]

[46]. IL-6 can induce a hypercoagulable state [47] that paves the way for acute necrotizing encephalopathy (ANE) [46, 48]. Such CNS-related pathological changes may be the cause of symptoms, including loss of smell (37.9%), loss of taste (41.37%), nausea/vomiting (31%), are of central origin and have been reported in more than one-third of COVID-19-positive patients [49, 50]. The evidences from studies on other SARS groups viruses, potentially SARS-CoV-2 infection of the CNS affects the brainstem (example, locus coeruleus) and the medullary structures involved in respiration (example, solitary tract nucleus, nucleus ambiguus), and has been speculated to partially mediate the high incidence of respiratory failure currently seen in COVID-19 [51]. Interestingly, dopaminergic neurons are particularly susceptible to SARS-CoV-2 infection [52–54], which may account for neuropsychiatric symptoms like brain fog, mild cognitive impairments (MCI), and lethargy that develop in the aftermath of COVID-19 infection. In addition, neurons and glial cells also express ACE2, which is the key receptor that SARS-CoV-2 exploits for intracellular invasion. Previous experimental studies of intranasally inoculated other strains of SARS-CoV Infection in ACE2 transgenic mice demonstrated neuronal death and upregulation of pro-inflammatory cytokine secretion (example, TNF-α, IL-1-β, IL-6) by neurons and astrocytes [55]. Even in the absence of SARS-CoV-2 infiltration into the CNS, peripheral cytokines involved in the host antiviral response may elicit neuropsychiatric symptoms by precipitating neuroinflammatory responses and/or compromised blood–brain interface (BBI) integrity, leading to peripheral immune cell transmigration into the CNS and disruption of neurotransmission [56]. Another important aspect of pathology is the COVID-19 downregulation of ACE 2 leads to excessive production of angiotensin II which can cause severe endothelial damage and dysfunction as well as oxidative stress and enhances thrombosis that may be one of the possible explanations of stroke occurrence which can increase the risk of psychiatric disorder such a depression and anxiety [57].

Role of SARS-CoV-2 on dopamine, serotonin, norepinephrine, and GABAergic pathway

It has been postulated that COVID-19 infections alter dopamine and serotonin synthetic pathways and might be involved in the development of neuropsychiatric symptoms [52]. DOPA decarboxylase (DDC) is a major enzyme in both the dopamine and serotonin synthesis pathways. It converts L-3,4-dihydroxyphenylalanine (L-DOPA) into dopamine and L-5-hydroxytryptophan (L-5-HT) into serotonin (5-HT). In fact, ACE2 and DDC co-express, suggesting that the defective expression of ACE2 induced by SARS-CoV-2 might impact DDC function and consequently alter levels of monoamine neurotransmitters such as DA and 5-HT [58], potentially playing an important role in etiology of neuropsychiatric disorders in SARS-CoV-2 infected patients. It is important to recognize that SARS-CoV-2 has demonstrated an impact on microglia and dopaminergic neurons in the CNS [52, 53, 59]. A prior in vitro study has shown midbrain dopamine (DA) neurons derived from human pluripotent stem cells (hPSCs) are selectively permissive to SARS-CoV-2 infection [60]. Parallelly, *ACE2 receptors are highly expressed in dopamine neurons*. SARS-CoV-2-related brain penetration and downregulation of ACE2, may cause additional harm and further alter dopamine levels and serotonin functioning [61]. This is evident in animal models with hypo-expression of ACE2, where decreased serotonin synthesis is observed [62] leading to an increased risk of depression and anxiety. Indeed, the downregulation of the ACE-2 receptor in COVID-19 also plays a crucial role in the pathological process in the body. It causes serious diseases [63] and also induces vulnerability to stressful conditions by influencing the neurotransmitter pathways as mentioned above [64]. Studies have shown that mice with downregulated ACE-2 expression demonstrate increased sympathetic activity [65] and decreased tryptophan uptake [66], which can lead to reduced brain 5-HT levels [62] and increased vulnerability to stress [67]. ACE-2 also acts as a neuroprotective factor and its downregulation by SARS-COV-2 has been speculated to be involved in neurodegeneration [68]. Moreover, SARS-CoV-2 induced hypercoagulable state, vasculitis, and micro-thrombosis in brain vessels locally exacerbate hypoxemia and hypoperfusion. These in turn increase oxidative stress and could lead to an elevated risk of cognitive impairment [69]. In addition, dopaminergic receptors modulate the innate immune response to a viral infection and some viruses even utilize the dopaminergic signal transduction pathway to increase neuronal susceptibility to infection [53, 70]. Since dopamine may downregulate the immune response during infection, increasing the life cycle of the virus, therapies targeting dopamine receptors may mitigate COVID-19 infection [53].

In SARS-CoV-2 infection, a high proportion of patients (up to 53.1%) experience mental and physical fatigue [41] frequently associated with executive dysfunction mainly involving attention deficits and impaired cognitive control [41]. In this context, it is noteworthy that the *brain expresses ACE_2 receptors on glial cells and neurons* most prominently in the brainstem, paraventricular nucleus (PVN), nucleus tractus solitarius (NTS), and the rostral ventrolateral medulla [71]. Consequently, ACE2 downregulation in COVID-19 infection may contribute to impairments in cognitive functions, which is possibly mediated by the associated enhanced oxidative stress and a decrease in the concentrations of the BDNF [72]. Being that depigmentation also occurs in the substantia nigra, it is reasonable to speculate that COVID-19 infection might affect dopamine (DA) levels in the CNS [73]. Based on the above evidence, it is logical to hypothesize that the predilection of SARS-CoV-2 for these key brain structures implicated in dopaminergic and noradrenergic homeostasis may result in pathologic alterations which may explain reported symptoms such as "brain fog", cognitive impairment, deficits of the executive functions (example, working memory, attention, concentration, and language tasks such as word-finding difficulties), confusion, sleep disturbances, mood instability, and lethargy. It is intriguing because these neuropsychiatric sequelae are seen in patients who demonstrated a mild form of COVID-19 and many were asymptomatic [74]. Furthermore, a study conducted by Versace et al. suggested a GABAergic mechanism by which COVID-19 might affect the CNS. They utilized trans-cranial magnetic stimulation (TMS) to investigate the integrity of intracortical GABAergic inhibitory circuits in the motor cortex in patients who have recovered from COVID-19 but had persistent fatigue and executive dysfunctions. They concluded that compared to healthy subjects, post-COVID-19 patients exhibited *reduced inhibition of the motor cortex* (M1) upon TMS application as evidenced by significant reductions of their short-interval intracortical inhibition (SICI) and long-interval intracortical inhibition (LICI) [75]. Of note, both SICI and LICI are paired-pulse mechanisms for modulating cortical excitability; they play an important role in the modulation of neural function during skill acquisition and prevention of neuronal fatigue during repeated stimulation [76]. SICI and LICI are conventionally measured as the relative reductions in the amplitudes of the motor evoked potentials (MEPs) in the hand muscle by the subthreshold conditioning stimuli. The $GABA_A$ receptors mediate SICI *and* the $GABA_B$ receptors mediate LICI. These impaired GABAergic mechanisms seen in post-COVID-19 patients may be attributed to the

symptoms such as fatigue and cognitive dysfunctions. Ortelli and colleagues. (2021) conducted another study that reaffirmed the presence of dysregulated cortical GABAergic circuits, as evidenced by a decreased duration of the *cortical silent period* (CSP, another measure of intracortical inhibition that is mediated by the cortical GABAergic neurons) in post-COVID-19 patients compared to controls, thus alluding to impairments of the corticomotor GABAergic neurons [41]. A long-term follow-up study reported a greater reduction in grey matter thickness and tissue contrast in the orbitofrontal cortex and parahippocampal gyrus and a greater reduction in global brain size in the SARS-CoV-2 cases. The participants who were infected with SARS-CoV-2 also showed on average a greater cognitive decline [77]. Thus, many of the long-term symptoms of COVID-19 ('long-COVID syndrome'), namely fatigue, cognition, apathy, and executive function, may be due to *cortical impairments of the GABAergic neurotransmission*.

SARS-CoV-2 and inflammatory hypothesis for depressive disorders

In SARS-CoV-2 infected patients, pro-inflammatory cytokines such as TNF-alpha and IL-6 in the plasma are significantly elevated. Of note, as proposed by the inflammatory hypothesis of depression, many of these pro-inflammatory cytokines are also implicated in major depressive disorder (MDD), especially treatment-resistant depression [78]. In a study, Taquet et al., reported that even after six months of a diagnosis of COVID-19, patients were still at high risk for developing psychiatric symptoms and neurological diagnoses [79]. Such risk of developing psychiatric disorders was even higher for those who had a severe and critical illness, required medical hospitalization, were admitted to the intensive care units, and had developed encephalopathy. These findings were consistent with a 3-month outcome, in the same retrospective cohort of COVID-19 positive patients [13]. COVID-19 infection undoubtedly acts as an etiological source of psychiatric symptoms. Furthermore, when compared to other acute health events, COVID-19 was found to have higher hazard ratios, indicating that it had a greater impact on mental health [11]. Although the etiology of these psychiatric outcomes is most likely to be multifactorial, a direct link to the viral infection may exist given the neurobiological mechanisms elaborated upon in the previous sections. In a prospective study by Mazza et al., the authors examined the mental state of COVID-19 survivors at one month and three months after their discharge from the hospital. The 3-month cohort demonstrated disorders in at least one psychopathological sphere in 35.8% of the respondents and a correlation was observed between COVID-19-associated inflammation and depression, in addition to other neurocognitive disorders [80].

Another immune molecule of interest is the C-reactive protein (CRP), a protein produced during an acute-phase response that is activated by infections/injuries. In the liver, hepatocytes recognize and bind to IL-6, leading to the secretion of acute-phase proteins (APP), particularly CRP. CRP levels act as an indicator of peripheral inflammation and correlate positively with the PHQ-9 total score of patients who presented symptoms of depression. This suggests a potential inflammatory pathway underlying these symptoms [81]. Although elevated levels of CRP are not normally described in viral respiratory infections, a significant increase of this protein has been reported in COVID-19 patients by several studies and suggests that CRP could potentially be used as an early prognostic biomarker for disease severity [82]. Similarly, MDD has been shown to have both cross-sectional and longitudinal associations with inflammatory markers including, CRP and IL-6 [83]. While studies have monitored the levels of these inflammatory biomarkers in the early and late phase of COVID-19 infection, no studies have evaluated these biomarkers in post-COVID, and more importantly, the relation of these biomarkers to severity of related psychiatric sequelae.

As discussed in earlier sections, COVID-19 can induce microglial activation as well as increase macrophage recruitment within the CNS; similar changes are also seen in the brains of depressed patients with completed suicide [84]. In addition, the activated microglia secrete inflammatory mediators, including glutamate, quinolinic acid, ILs, complement proteins, and TNF-α. Increased quinolinic acid results in higher glutamate and upregulation of NMDA receptors, possibly inducing altered learning, distorted memory, impaired neuroplasticity, hallucinatory experiences, and nightmares [85]. Historically, it has been found that central administration of IL-1 β and TNF-α to rats and mice will induce a full spectrum of behavioral changes and cause a depression-like "sickness behavior". Those mice/rats that were injected showed little interest in their physical and social environments while demonstrating decreased motor activity, and altered cognition [56]. More recently, it was discovered that the increase in pro-inflammatory cytokines could reduce the number of monoamines available in the synapse. This is in keeping with the monoamine hypothesis of depression that suggests that the underlying pathophysiologic mechanism of MDD is due to reduced levels of serotonin, norepinephrine, and /or dopamine in the central nervous system [86]. More specifically, elevated levels of IL-1β and TNF-α in the brain can stimulate the p38 mitogen-activated protein kinase (MAPK) and increase the activity of the serotonin transporter

(SERT). Increased activity of this transporter effectively reduces the amount of serotonin in the synapse and leads to depression-like behavior in animal models [87]. The increase in expression and function of the transporter is dependent on the expression of IL-1R as immobility was not observed in IL-1R knockout mice who received the same cytokine-inducer lipopolysaccharide (LPS) dosage [87]. Findings from similar studies are consistent with these results as injection of IL-1R antagonists blocked the effects of LPS [88]. Although these changes in SERT due to pro-inflammatory cytokines alone could not amount to the full spectrum of depression traits, it provides an interesting avenue for future research and a potential therapeutic target.

Impact of COVID-19 associated psychosocial stressors on neurobiology

Social factors also play an important role in the development of depression and other mood disorders. Due to the rapid spread of the virus, many safety measures were implemented in an attempt to decrease the rate of spread. These lockdowns and curfews that were implemented had an impact on both infected and uninfected individuals. The fear of infection with a potentially fatal new virus while being in lockdown may lead to feelings of anger, loneliness, and boredom. Social distancing measures have also been found to lead to frustration, aggression, mood disorders, insomnia, and psychosis. In addition, the presentation of mortality counts each day also has traumatizing effects on one's mental health [89, 90].

The important component in the perpetuation of the anxiety orchestra in the brain is the amygdala-mediated negative valence systems, which are particularly present in the limbic system, and are primarily responsible for responses to aversive situations or context, such as fear, anxiety, and loss [91]. The stress and anxiety during the COVID-19 pandemic resulted from imposed social isolation, resultant fear, loss, loneliness, and a negative impact on daily living [92]. The prolonged course of the COVID-19 illness may lead to chronic stress in turn causing strain on the limbic system [91]. The limbic region is quite sensitive to inflammatory processes (the various mechanisms of which are described below), and subsequently alters the neural circuits and regions associated with symptoms of generalized anxiety [93]. Also, acute fear/phasic anxiety is mediated by the amygdala, which releases corticotropin-releasing hormone (CRH), a stress hormone that acts on receptors on the bed nucleus of the stria terminalis (BNST), also called 'extended amygdala.' The BNST is an important structure of the limbic system sensitive to inflammatory process and it is implicated in chronic anxiety. The BNST also plays a pivotal role in the circuit from the hippocampus to the paraventricular nucleus of the hypothalamus. The paraventricular nucleus also releases CRH leading to downstream glucocorticoid release while also acting as a positive-feedback loop on the BNST, thus perpetuating the stress response leading to long-lasting anxiety. This circuit is known to play a crucial role in the stimulation of the hypothalamic–pituitary–adrenal (HPA) axis [92, 94]. From the pieces of evidence presented earlier, *ACE2 receptors are expressed on glial cells and neurons* within the brain, especially in the paraventricular nucleus of the hypothalamus [71]. In animal models, upregulation of ACE2 suppresses CRH synthesis, which alters the central processing of psychogenic stress, thereby blunting HPA axis activation and attenuating anxiety-like behavior. However, in COVID-19 the downregulation of the ACE2 receptor alters the corticosterone and HPA axis activation worsening anxiety-like behavior [95]. Moreover, the inflammatory cytokines from stress can specifically activate the anterior cingulate cortex (ACC) producing anxiety symptoms [93] while associated hypoactivity in the vmPFC results in impaired top-down regulation and hyperactivity of the amygdala; another mechanism of causing anxiety symptoms [93, 96]. In addition, insulin resistance disrupts the dopamine system which causes a cognitive decline, decrease in synaptic plasticity, decrease in neuronal survival, increase in cerebral degeneration, disruption of the HPA axis, and impairment of physiological mechanisms of reward, learning, and mood [97, 98]. From published evidence, one can hypothesize that stress associated with COVID infection can trigger a cascade of stress-triggered events resulting in stress-induced hypoglycemia-mediated insulin resistance, neuro-inflammation, and oxidative stress [97, 98].

Medical treatments in COVID-19 infection and neuropsychiatric symptoms

Although there are currently no specific medications with proven efficacy in treating the SARS-CoV-2 infection, some medications such as remdesivir, steroids, and other medications seem to have potential in SARS-CoV2, which has led to their off-label use. Corticosteroids are used in severe and critical SARS-CoV2 infections to control the hyperinflammatory responses. The intensity of the neuropsychiatric manifestations as side effects of corticosteroids is dependent on the dose and duration of the treatment. For example, steroids can cause mania, psychosis, delirium, depression, and cognitive impairment, especially in the elderly population [99]. However, authors recognize that the duration of corticosteroid treatment in COVID-19 infection is short and it is less likely an important cause of neuropsychiatric symptoms. Tocilizumab, a humanized monoclonal antibody that causes IL-6 blockade, seems to have preventive effects

on the cytokine storm. Inhibition of IL-6 has been shown to have beneficial effects in the treatment of rheumatoid arthritis [100] as well as for the cognitive symptoms in schizophrenia [101]. Remdesivir, an intravenously administered nucleotide prodrug of an adenosine analog that binds to the viral RNA-dependent RNA polymerase and inhibits viral replication through premature termination of RNA transcription, is proposed to reduce the viral load and thus the downstream effects of the virus; and as of yet, no neuropsychiatric side effects have been reported [102]. Immune checkpoint inhibition, such as PD-1 (such as nivolumab, pembrolizumab, cemiplimab) and CTLA-4 (such as Ipilimumab, tremelimumab) monoclonal antibodies, commonly used in the treatment of various malignancies, is another area being researched due to their potential to interrupt T cell exhaustion and depletion, thus improving lymphopenia and augmenting the humoral immune response to COVID-19 infection [103]. Though it must be noted there may also be an increased risk of cytokine release syndrome [103] as well as CNS side effects including fatigue, cognitive dysfunction, and memory loss [104]. The other antiviral medications molnupiravir and paxlovid (nirmatrelvir and ritonavir), have no reported psychiatric side effects. Other recent strains of the evolving SARS-CoV-2 viruses have variable neuropsychiatric disease outcomes but seem to have less severe post-COVID neuropsychiatric symptoms. It might logical to hypothesize such milder course could be due to the availability of the vaccine and/or new treatments ameliorating SARS-CoV-2 infection, though this needs to be evaluated further from the objective studies.

Conclusion

SARS-CoV-2 infection most important biological factor might be the virus's affinity and ability to downregulate the ACE-2 receptor to induce inflammation and cause direct damage to the various cellular systems, eventually causing the derangement of multiple neurophysiological systems. The impaired allostatic mechanism subsequently affects the early return of homeostasis within the neurotransmitter system, further increasing the risk of mental illness. Moreover, ongoing research evidence supports that SARS-CoV-2 infection compromises the HPA axis, induces oxidative stress, and skews the immune system by stimulating several excessive pro-inflammatory factors. Such diverse pathological processes of the COVID-19 infection may also indirectly alter the serotonin, dopamine, and GABAergic systems and lead to the manifestation of various psychiatric disorders. This interplay of various bio-psycho-social factors is critical in disrupting the neurophysiological system homeostasis, causing distinct neuropsychiatric symptoms that may be unique to the SARS-CoV-2 infections. Though SARS-CoV-2 is a novel disease, new strains of the virus are forming rapidly even before the emergence of research evidence. The above summary of evidence linking SARS-CoV-2 to psychiatric illness might be the tip of the iceberg representing the underlying viral neuropathology caused by SARS-CoV-2 infections.

Abbreviations

SARS- CoV-2	Severe acute respiratory syndrome corona virus-2
COVID-19	Coronavirus Disease 2019
CNS	Central nervous system
CDC	Center for disease control
NICE	National Institute Clinical Excellence
PTSD	Post-traumatic stress disorder
MRI	Magnetic resonance imaging
ACE2	Angiotensin converting enzyme-2
TMPRSS2	Transmembrane serine protease 2
ARDS	Acute distress respiratory syndrome (29).
PRR	Pattern recognition receptors
PAMPs	Pathogen-associated molecular patterns
IL	Interleukin
ESR	Erythrocyte sedimentation rate
CRP	C-reactive protein
TNF-a	Tumor necrosis factor-alpha
PCT	Procalcitonin
IP10	Interferon-inducible protein-10,
MCP1	Monocyte chemoattractant protein-1
TGF-B	Transforming growth factor-beta
GM-CSF	Granulocyte macrophage-colony stimulating factor
CCL	Chemokine ligand
CXCL	Motif chemokine ligand
ANE	Acute necrotizing encephalopathy
MCI	Mild cognitive impairments
BBi	Blood–brain-interface
hPSCs	Human pluripotent stem cells
DDC	Dopamine decarboxylase
L-5-HT	L-5-hydroxytryptophan
L-DOPA	L-3,4-dihydroxyphenylalanine
5-HT	5-Hydroxytryptophan
NE	Norepinephrine
FSS	Fatigue severity scale
MoCA	Montreal cognitive assessment
TMS	Trans-cranial magnetic stimulation
GABA	Gamma amino butyric acid
SICI	Short-interval intracortical inhibition
LICI	Long-interval intracortical inhibition
MEP	Motor evoked potentials
MDD	Major depressive disorder
PHQ-9	Physical Health Questionnaire-9
APP	Acute-phase proteins
MAPK	Mitogen-activated protein kinase
LPS	Lipopolysaccharide
CRH	Corticotropin-releasing hormone
BNST	Bed nucleus of the stria terminalis
HPA	Hypothalamic–pituitary–adrenal axis

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