Updates on the neurological manifestations of SARS-CoV-2 infection

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Purpose of review
Since its emergence in 2020, the COVID-19 pandemic has created a global surge of survivors experiencing neurologic effects from SARS-CoV-2 infection. This review aims to provide an updated synthesis of the acute and chronic neurological manifestations of COVID-19, and to outline the current therapeutic strategies for these conditions.

Recent findings
Epidemiological studies have shown that COVID-19 patients with neurological symptoms during acute infection tend to have poorer hospital and functional outcomes. While the risk of adverse neurologic symptoms including cognitive dysfunction, headache, autonomic dysfunction, and chronic fatigue are thought to be greatest following infection with the original SARS-CoV-2 strain and its alpha variant, they remain prevalent after infection with subsequent less virulent strains as well. Some recent work has also found a link between SARS-CoV-2 and structural brain changes. However, ongoing trials show promising results for pharmacologic and nonpharmacologic treatments targeting the postacute neurological sequelae of COVID-19.

Summary
Lingering neurological manifestations after COVID-19 still pose considerable individual, healthcare system, and socioeconomic repercussions. Both preventive and multimodal treatment approaches are necessary to address these conditions. Further research is required to assess the lasting impacts of SARS-CoV-2 on the nervous system, particularly its potential contribution to the development of neurodegenerative diseases.

Keywords
coronavirus disease 2019, long COVID, neurological post-acute sequelae of COVID-19, post-COVID-19 conditions, SARS-CoV-2

INTRODUCTION

Coronavirus disease 2019 (COVID-19) was declared a pandemic by the WHO in March 2020. In the subsequent 5 years, it led to nearly 800 million confirmed cases and over 7 million deaths [1]. SARS-CoV-2, the virus responsible for COVID-19 disease, is an RNA virus that mainly impacts the respiratory system. However, it has become clear that neurological manifestations of COVID-19 can also occur at all stages of the illness, including during acute infection, the postacute phase, and chronic stages. This review presents the most recent findings related to the neurological symptoms associated with SARS-CoV-2 infection. Additionally, it highlights promising therapeutic strategies for the neurologic postacute sequelae of COVID-19 (neuroPASC).

ROUTES OF INFECTION AND PATHOPHYSIOLOGY OF SARS-CoV-2 IN THE CENTRAL NERVOUS SYSTEM

Although SARS-CoV-2 is not considered a classically neurotropic virus, there is some evidence that it has the potential for neurovirulence and may enter the central nervous system (CNS) [2,3▪] via several paths. In the neuronal route hypothesis, SARS-CoV-2 is carried to the CNS via retrograde axonal transport from the peripheral sensory neurons or via the cranial nerves encountered in the respiratory tract, such as the olfactory nerve. A second hypothesized route is the hematogenous pathway, in which viral particles in the systemic circulation traverse the blood–brain barrier (BBB) via a Trojan horse mechanism or directly through a compromised BBB.

Although SARS-CoV-2 viral RNA has been identified by PCR in the CNS on some postmortem studies supporting these theories, work to date has

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KEY POINTS

- SARS-CoV-2 infection has a myriad of neurological presentations both in the acute and postacute phases.
- These neurological manifestations include cerebrovascular disorders, immune-mediated disorders, cognitive dysfunction, constitutional symptoms, and peripheral and autonomic nerve disorders.
- The mechanisms underlying these conditions are not yet completely elucidated, but likely involve the interplay of neuroinflammation, immune dysregulation, endothelial injury, and viral effects on cellular homeostasis.
- Numerous studies are ongoing regarding pharmacologic and nonpharmacologic interventions to treat ongoing neurological symptoms of COVID-19, which can persist up to years after initial infection.
- The long-term outcomes of SARS-CoV-2 infection and its role in the pathogenesis of neurodegenerative conditions are not yet known.

failed to provide overt evidence of SARS-CoV-2 in neuronal cells using electron microscopy [2,4]. Thus, current evidence indicates the neurologic sequelae seen during COVID-19 infection are less likely a result of direct viral neuroinvasion. Instead, other pathophysiologic processes including cytokine storming, immune dysregulation, persistent neuroinflammation, and endothelial injury, are thought to play a more significant role in both the acute and postacute neurological sequelae resulting from SARS-CoV-2 infection [2] (Table 1).

ACUTE NEUROLOGICAL COMPLICATIONS OF CORONAVIRUS DISEASE 2019

Cerebrovascular disorders

Ischemic and hemorrhagic strokes

Epidemiological data show that there is a two-fold to three-fold increased risk of ischemic stroke in patients with COVID-19, with peak incidence observed within 1–2 weeks postinfection [5–7]. However, a study leveraging the UK Biobank found that COVID-19 patients, particularly those who were hospitalized, are at an elevated risk for developing major adverse cardiovascular events, including stroke, even up to 3 years following acute infection [8]. Compared with prepandemic stroke cohorts, patients with COVID-19-associated ischemic strokes have been shown to be younger with a higher number of modifiable cerebrovascular risk factors, such as diabetes, hypertension, dyslipidemia, atrial fibrillation, and congestive heart failure [9].

Concerning treatment, data from the Global COVID-19 Stroke Registry has shown that COVID-19 patients with ischemic strokes have higher rates of intracranial bleeding complications and worse clinical outcomes after revascularization therapy (intravenous thrombolysis and endovascular treatment) than non-COVID-19 patients [10]. However, there is no contraindication to revascularization therapy in patients with COVID-19 presenting with acute ischemic stroke. Inpatient mortality and morbidity of patients with COVID-19 and stroke are also higher compared with non-COVID-19 stroke patients or historical controls [11].

Table 1. Proposed mechanisms underlying the neurological sequelae of SARS-CoV-2

Neurological sequelae	Related diagnoses	Possible mechanisms
Cerebrovascular disorders	Ischemic stroke Hemorrhagic stroke Cerebral venous thrombosis	Microvascular endothelial dysfunction Hypercoagulable state
Immune-mediated and demyelinating disorders	Acute disseminated encephalomyelitis (ADEM) Autoimmune encephalitis Transverse myelitis Guillain–Barre syndrome	Autoimmune activation due to molecular mimicry
Neurocognitive Disorders	Brain fog Mild cognitive impairment	Persistent neuroinflammation, Structural alterations – decreased brain volume and cortical thickness in the orbitofrontal cortex, parahippocampal gyrus, hippocampus, and amygdala
Constitutional disorders	Fatigue Headache	Persistent neuroinflammation Endothelial dysfunction Oxidative stress
Nerve disorders	Neuropathy Autonomic dysfunction	Small and large fiber neuropathy

In contrast, studies have demonstrated a lower incidence of hemorrhagic strokes in COVID-19 patients [12], though intracerebral hemorrhage (ICH) patients with COVID-19 have higher odds of poor functional outcomes, discharge to hospice, and mortality [13].

Cerebral venous sinus thrombosis

Infection with SARS-CoV-2 can lead to a hypercoagulable state, increasing the likelihood of cerebral venous sinus thrombosis (CVST) in addition to arterial ischemic stroke [14]. Although the historical incidence of CVST is generally low, epidemiological reports early in the pandemic indicated that there is an increased risk of CVST among COVID-19 patients [14]. In contrast to classic CVST, which affects younger female individuals, COVID-19-associated CVST has a balanced sex distribution and can occur in individuals without traditional risk factors [15]. One study also found that COVID-19 patients with CVST have a higher incidence of altered mental status, higher baseline national institutes of health stroke scale (NIHSS) score, increased median thrombus load, higher rates of ICU admission, and longer duration of hospital admission [16]. COVID-19-related CVST is treated similarly to non-COVID-CVST, with immediate administration of parenteral unfractionated heparin or low-molecular-weight heparin, followed by conventional or newer oral anticoagulants [17]. Mortality and postacute outcomes are similar compared to pre-COVID CVT patients [16].

Immune-mediated and demyelinating disorders

Acute demyelinating encephalomyelitis

Acute demyelinating encephalomyelitis (ADEM) is an immune-mediated, monophasic, multifocal demyelinating disorder that affects the CNS. It is considered a para-infectious or postinfectious syndrome, usually occurring several weeks after infection and diagnosed through typical clinical and imaging (brain MRI) findings. A systematic review of ADEM cases secondary to COVID-19 showed a predominance of adult male cases, with a mean age of 50 years. The mean time for the development of ADEM was approximately 3 weeks (23 days) [18] from the onset of infection, and no association with COVID-19 severity was identified [19]. Intravenous corticosteroids are the recommended first-line treatment while intravenous immunoglobulin (IVIG) or plasma exchange are utilized in refractory cases [19]. ADEM in the course of COVID-19 contributes to higher rates of intensive care admission, long-term neurological sequelae, and mortality [20].

Autoimmune encephalitis

Autoimmune encephalitis is a rare but significant neurological sequela of COVID-19. Limited studies have demonstrated that patients can develop autoimmune encephalitis within a few days or up to 1 month after the onset of SARS-CoV-2 infection [21]. Clinical presentations vary, and may involve seizures, psychiatric symptoms, extrapyramidal movements, altered consciousness, neuromuscular symptoms, and cerebellar syndromes [22].

Similar to typical autoimmune encephalitis, CSF may be normal or show mildly elevated protein, elevated IgG levels, and the presence of oligoclonal bands [22]. Neuroimaging studies may also be normal or can demonstrate T2/FLAIR hyperintensities in several brain regions including the temporal lobes, white matter, insula, brainstem, cerebellum, and corpus callosum [23]. A systematic review found that the specific antibody is unknown in the majority of SARS-CoV-2-associated autoimmune encephalitis, though among those with identified antibodies, anti-NMDAR was the most common, followed by anti-LGI-1, and anti-MOG [22]. Other antibodies reported include Caspr-2, GAD-65, AMPA, CRMP-5, and GABA [22].

Autoimmune encephalitis after COVID-19 generally responds to immunotherapy. Successful treatment regimens have included high-dose corticosteroids, IVIG, plasma exchange, and rituximab [22]. Prognosis after treatment is favorable, with the majority of patients achieving complete recovery, although a small percentage of cases may experience residual neurological symptoms [22,23].

Guillain–Barre syndrome

Guillain–Barré syndrome (GBS) is an immune-mediated postinfectious syndrome that affects the peripheral nerves and has been associated with a variety of infectious agents including *Campylobacter jejuni, Haemophilus influenza*, and Epstein–Barr virus [24]. Multiple subtypes of GBS including acute inflammatory demyelinating polyneuropathy (AIDP), acute motor axonal neuropathy (AMAN), and Miller–Fisher syndrome (MFS) have since been reported following infection with COVID-19 [24,25].

Data indicate COVID-19-associated GBS has a male predominance with mean age of onset at 61 years [24]. Most cases present subacutely, with an average onset of 19 days post-COVID-19 infection [24]. Clinical presentation is similar to GBS due to other causes, including diminished strength of the distal limbs with ascending evolution, accompanying sensory changes,

hyporeflexia, and cranial nerve deficits [26]. The most common cerebrospinal fluid finding is albuminocytological dissociation [27], while electrodiagnostic studies indicated AIDP is the predominant subtype [27].

The most common treatment method for GBS following COVID-19 is IVIG, with plasma exchange also being trialed in case reports. Although there is a high prevalence of intensive care admissions in the context of COVID-19-associated GBS, most patients in published studies improved after treatment [25].

NEUROLOGICAL POSTACUTE SEQUELAE OF CORONAVIRUS DISEASE 2019

As the COVID-19 pandemic evolved, reports arose on various symptoms that persisted weeks or months after acute SARS-CoV-2 infection. Collectively, this group of chronic, debilitating conditions has been called post-COVID-19 conditions (PCC), PASC, or long COVID [28]. The detailed proposed mechanisms of neuroPASC are outside the scope of this review but include persistent neuroinflammation, immune dysregulation, autoimmune reactions, reactivation of latent infections, endothelial dysfunction, and alterations in gut microbiota [29]. Moreover, complex factors including viral biology (SARS-CoV-2 variants and reinfections), host biology (genetics and epigenetics), and external factors (vaccination and antiviral medications) play a role in the emergence and severity of neuroPASC.

Cognitive dysfunction or 'brain fog'

Accumulating evidence has shown that some individuals who previously had COVID-19 will experience lingering neurocognitive concerns, most strongly associated with original early alpha variants [30▪▪]. These cognitive symptoms include mental fatigue, memory impairment, slower processing speed, impaired attention, and difficulty concentrating [31]. Any combination of these symptoms can lead to 'brain fog' or post-COVID cognitive dysfunction (PCCD) [32]. Meta-analyses estimate the prevalence of PCCD at 7–59.2% [33]. Risk factors for PCCD include advanced age, preexisting mood and anxiety disorders, unemployment, poor baseline functional status, fewer years of education, APOE-e4 allele positivity, more severe COVID-19 infection, and pre-COVID cognitive impairment [30▪▪,33]. Vaccination may provide a slight cognitive benefit, and reinfection may lead to further cognitive decline; in one study, reinfection led to an additional decrease of 2 IQ points compared to those who did not experience reinfection [30▪▪].

Neuroimaging studies have reported structural and functional alterations in the brains of patients following COVID-19, including reduced grey matter volume in the parahippocampal gyrus, frontal gyrus, anterior cerebellar, occipital lobe, and bilateral superior temporal lobes [34]. These changes have been found to correlate with cognitive testing scores [34,35▪▪]. However, cognitive complaints are not necessarily associated with structural damage to the brain and may resolve. While established treatment guidelines are lacking, there are currently numerous trials investigating pharmacological agents and nonpharmacological approaches aimed at PCCD (Table 2).

Headache

The prevalence of persistent headaches post-COVID-9 ranges between 10 and 19% [36,37]. Post-COVID-19-associated headaches have a variety of clinical presentations and may have features of migraine and/or tension-type headaches [38]. One study showed that headache during acute infection was associated with the development of persistent headache post-COVID [39], though additional data is needed. Neuroimaging abnormalities in patients with persistent headache following COVID-19 infection include decreased grey matter and cortical thickness in the pars orbitalis, right fusiform gyrus, and frontal pole [40].

At present, there are no established protocols for managing headaches after COVID-19 and the choice of medication depends on the specific type of headache that patients exhibit [38]. Nonpharmacologic therapies, including physical therapy, lifestyle modifications, and regular exercise, along with identifying potential triggers, such as sleep patterns, dietary habits, caffeine consumption, and hydration, should be included in the treatment approach [38].

Fatigue and myalgic encephalomyelitis/chronic fatigue syndrome

Fatigue is one of the most commonly reported symptoms among patients post-COVID-19 with an estimated prevalence ranging from 40 to 60% [41]. There is evidence that female sex, older age, hospitalization or intensive care admission, co-morbidities such as hypertension and lung disease, and depression are risk factors for post-COVID-19 fatigue [42]. In most individuals, fatigue gradually improves over time without specific intervention. However, there is evidence that a subset of individuals with post-COVID fatigue will meet the standard case definitions of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) [43], including prolonged and severe fatigue, postexertional malaise, unrefreshing sleep, cognitive impairment, and orthostatic intolerance.

Table 2. Pharmacologic and nonpharmacologic agents for neurologic postacute sequelae of COVID-19

Neurologic manifestations	Intervention	Study details	Findings
Cognitive impairment	Donepezil 5 mg for 12 weeks [55]	Randomized controlled trial Donepezil: $n=10$ Control: $n=15$	Did not result in a significant overall increase in memory scales between the donepezil and control groups
	Guanfacine 1–2 mg + N-acetylcysteine 600 mg [56]	Case series $n=12$	Improved working memory, concentration, and executive function
	Palmitoylethanolamide (PEA) + Luteolin (LUT) [57] 700 mg PEA + 70 mg LUT for at least 2 months	Retrospective case control Co-ultraPEALut: $n=26$ Controls: $n=15$	Significant improvement in the Prospective Retrospective Memory Questionnaire (PRMQ) and MoCA raw scores after 10 months.
	Hyperbaric oxygen therapy [58] 40 daily sessions of HBOT	Randomized sham-control trial HBOT: $n=37$ Sham: $n=36$	Significant improvement in global cognitive function, attention, executive function, energy level, and neuropsychiatric symptoms
	Nirmatrelvir/ritonavir (Paxlovid) [59] Nirmatrelvir/Ritonavir 300/100 mg 2×/day for 15 days	Randomized controlled trial Nirmatrelvir/ritonavir: $n=102$ Placebo/ritonavir: $n=53$	No improvement in brain fog and fatigue in 155 patients experiencing moderate to severe long COVID
	Meditation, 30 min/session for 10 sessions over 5 weeks [60] Sound therapy and Coach-guided meditation with light stimulation	Randomized controlled trial Intervention: $n=17$ Control: $n=17$	Reduced cognitive impairment and improved physical and mental fatigue, pain, mood disturbances, and anxiety
	Photobiomodulation [61] Transcranial: 1070 nm Whole-body: 660/850 nm	Open-label observational study Transcranial: $n=7$ Whole-body: $n=7$	Significant improvements in MoCA, Digital Symbol Substitution Test, and Trails B
Fatigue	Low-dose naltrexone [62] Median 20 mg (range: 0.5–6 mg) for a median duration of 143 days	Retrospective cohort $n=59$	Lower number of symptoms and improvement in the severity of fatigue, PEM, unrefreshing sleep, and abnormal sleep pattern
	Amantadine for 2 weeks [63▪▪]	Open-label randomized controlled trial Amantadine: $n=30$ Control: $n=32$	Lower fatigue levels as measured by the visual analog fatigue scale (VAFS) and Fatigue Severity Scale (FSS)
	1.66 g L-arginine + 500 mg liposomal vitamin C for 28 days [64]	Single-blind randomized controlled trial L=Arg+Vit C: $n=23$ Control: $n=23$	Increased 6-minute walk distance and induced greater improvement in handgrip strength. Lower incidence of persistent fatigue in the treatment group.
	ImmunoSEB + ProbioSEB CSC3 [65] for 14 days	Double-blind randomized control trial Intervention: $n=100$; control: $n=100$	Resolution of fatigue in a greater percentage of subjects in the test vs. the control arm (91 vs. 15%) on day 14.
	High-definition transcranial direct stimulation (HD-tDCS) [66] 10 sessions (two sessions/week × 5 weeks)	Double-blind randomized sham-control trial HD-tDCS: $n=35$; Sham: $n=354$	Significantly greater reduction in fatigue, as measured by Modified Fatigue Impact Scale. Significant reduction in anxiety and improvement in quality of life.
	Transcranial magnetic stimulation (TMS) [67] 10 rTMS sessions	Retrospective observational study $n=14$	Significant improvement in all WAIS4 sub-items
	Rehabilitation Exercise and psycholoGical support After covid-19 InfectioN (REGAIN) [68▪]	Randomized controlled trial Intervention: $n=298$; control: $n=287$	Greater improvements in the PROMIS subscores for fatigue [2.50 (1.19–3.81), $P<0.001$], depression, and pain interference at 3 and 12 months
Postural orthostatic tachycardia syndrome (POTS)	Ivabradine [69] Ivabradine 5 mg 2×/day	Prospective observational study $n=55$	Improvement in heart rate and quality of life in small studies of patients with hyperadrenergic POTS

Despite this overlap, a recent study found that the prevalence of ME/CFS is similar in those who had COVID-19 vs. those who did not have COVID-19 [44▪]. In addition, it was found that SARS-CoV-2 infection does not confer a higher risk of developing ME/CFS compared to other infectious agents [44▪]. In terms of treatment, both nonpharmacologic and off-label pharmacologic therapy are being investigated to address post-COVID fatigue and ME/CFS (Table 2).

Sensory neuropathy

Sensory symptoms such as paresthesias, numbness, and pain may be experienced during or after acute SARS-CoV-2 infection [45] and can be categorized as sensory neuropathies. COVID-19-associated neuropathy can manifest as a large fiber neuropathy (LFN) predominantly affecting fibers responsible for vibration and proprioception [46] or a small fiber neuropathy (SFN), manifesting as pinprick sensory loss, hyperesthesia, allodynia, and neuropathic pain [47]. Nerve conduction studies and electromyography are useful tools to assess these sensory manifestations and are usually diagnostic in LFN but normal in SFN. SFN may be confirmed with a skin biopsy at a center with experience in this pathologic analysis [48]. Nonetheless, in some cases, these sensory manifestations may be present clinically without evidence of neuropathy on physical examination or electrodiagnostic studies [48].

There is a scarcity of clinical trials that evaluate the efficacy of any particular agent for post-COVID neuropathic pain. IVIG has been used for treatment in a few small cohorts [49▪], though the role of this and other immunotherapies remains unclear.

Autonomic dysfunction

Numerous studies have reported a range of autonomic dysfunction in individuals with PASC [50]. This group of symptoms includes lightheadedness, tachycardia, palpitations, exertional intolerance, presyncope/syncope, and hyperhidrosis, among others. Specifically, postural orthostatic tachycardia syndrome (POTS) is a multisystem disorder characterized by an abnormal autonomic response to upright posture, resulting in orthostatic intolerance and tachycardia without hypotension. POTS and POTS-like symptoms have been reported in some individuals as soon as weeks or months after acute SARS-CoV-2 infection [50,54]. Treatment of COVID-19-related POTS and non-COVID-19-related POTS are the same, and include nonpharmacological interventions, such as increased salt and fluid intake, waist-high compressive garments, and regular and graduate-supervised exercises [51]. When symptoms are severe, pharmacological agents, such as beta-blockers, ivabradine, fluodrocortisone, and midodrine, can be used [51].

TREATMENT STRATEGIES FOR NEUROLOGIC POSTACUTE SEQUELAE OF CORONAVIRUS DISEASE 2019

Managing NeuroPASC remains a substantial challenge for healthcare providers globally for a variety of reasons. Firstly, the manifestations and mechanisms of NeuroPASC are extremely diverse. Additionally, there is currently a paucity of validated, clinically accessible biomarkers or diagnostic tests making definitive diagnosis and targeted treatment more difficult. Finally, clinical trial data is lacking, with most studies consisting of small, observational cohorts. Thus, physicians must currently focus on an individualized and multimodal approach rather than a 'one-size-fits-all' approach to the treatment of these conditions [52].

Little is known about techniques to prevent the development of NeuroPASC. There is evidence linking the level of viral activity during early infection with the subsequent risk of NeuroPASC [53]. Thus, although vaccination and natural immunity from prior infections may not completely prevent the development of NeuroPASC, these measures can blunt the initial virus spread and may mitigate the development of both acute and chronic sequelae of COVID-19 [54].

Ongoing studies and clinical trials are investigating a variety of treatment options for the various symptoms associated with NeuroPASC, which are summarized in Table 2. It is important to emphasize that the limited scale and methodological differences of these studies restrict the generalizability of their findings, underscoring the need for larger and more rigorously designed randomized controlled trials to validate preliminary findings and expedite the development of treatment guidelines.

NEURODEGENERATIVE DISORDERS AS LONG-TERM SEQUELAE OF SARS-COV-2 INFECTION?

Previous studies have shown that viral infections are linked to the pathogenesis of neurodegenerative disorders, including Alzheimer's disease [70]. There is accumulating evidence that COVID-19 survivors are also at increased risk of dementia, including Alzheimer's disease [71–73]. It has been hypothesized that SARS-CoV-2-induced neuroinflammation drives microglial activation, impairs neurogenesis, and leads to loss of oligodendrocytes and neuronal

death [71]. The strongest evidence for COVID-19-related neurodegeneration comes from a UK biobank study, which demonstrated longitudinal cortical volume loss in limbic brain regions functionally connected to the primary olfactory cortex in approximately 60% of COVID-19 patients [74]. However, these volume losses were small, with minimal correlation to cognitive testing. Thus, the implications of the persistence of cognitive deficits and its link to the pathogenesis of neurodegenerative disorders remain unclear and warrant long-term surveillance.

CONCLUSION

COVID-19 continues to have enormous consequences in terms of morbidity and mortality worldwide. Although SARS-CoV-2 is primarily a respiratory virus, a large body of evidence indicates that it also affects both the central and peripheral nervous systems. The mechanisms of neurovirulence of SARS-CoV-2 appear to be largely due to neuroinflammation, immune dysregulation, endothelial injury, and persistent effects on cellular homeostasis, rather than direct viral invasion. As new SARS-CoV-2 variants emerge and infections occur despite vaccinations, lingering neurological manifestations will have a significant impact on healthcare systems and quality of life. Elucidating the underlying mechanisms of these conditions is vital in order to find the appropriate curative and preventive strategies. Additional studies are required to determine the long-term consequences of SARS-CoV-2 infection in the nervous system.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

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This study of more than 100 000 people showed that people who had recovered from COVID-19 had greater deficits in cognition than those who did not have COVID-19 in the past 12 weeks. Larger deficits were seen in those who had been infected by the original SARS-CoV-2 vriant or the B.1.1.7 variant.

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