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# Cognitive Sequelae of COVID-19

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**Cognition** includes memory, language, orientation, judgment, conducting interpersonal relationships, performing actions (praxis), and problem solving. **Cognitive disorders** reflect disruption in one or more of these domains and are frequently complicated by behavioral symptoms.

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**Cognitive disorders** exemplify the complex interface among neurology, medicine, and psychiatry in that medical or neurological conditions often lead to cognitive disorders that, in turn, are associated with behavioral symptoms.

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Several coronaviruses have shown to be **neuro-invasive**, including SARS and MERS.

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As of the 28th of June 2020, **SARS-CoV-2** has now infected over 10 million people worldwide and the pandemic continues to grow. The disease caused by SARS-CoV-2 is known as corona virus disease 2019 (COVID- 19), which manifests not just as a respiratory illness but also impacts the cardiovascular, renal, and the **nervous system** functions.

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Neuropsychiatric consequences are neurological, psychiatric, and cognitive problems due to **direct** brain damage, psychological stress, disease, or **indirect** effects on the CNS *via* an immune response or medical therapy . The **acute psychiatric manifestations** of COVID-19 reported in surveys are increased stress, anxiety, and depression . In the **long-term**, psychiatric presentations could also be affected by the outcome of their illness, stigma or memories, and amnesia associated with the critical care they receive .

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**Acute neurological symptoms such as headache, altered sensorium, acute cerebrovascular incidents, convulsions, and ataxia have been reported in more than a third of hospitalized patients .**

**Reports of acute cognitive complications such as attention and dysexecutive symptoms are also emerging .**

**However, we can just speculate about the long-term neuropsychiatric and cognitive consequences of COVID-19.**



## PATHOPHYSIOLOGY OF NEUROPSYCHIATRIC AND COGNITIVE CONSEQUENCES OF COVID-19

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SARS-CoV-2 is a novel virus and its pathophysiological mechanism on various physiological systems is yet to be **fully understood**. However, a lot can be learnt from other subtypes of coronaviruses.

Coronaviruses primarily affect upper respiratory tracts, but they have been detected both in the brain and cerebrospinal fluids of the infected individuals.

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There are **several mechanisms** through which coronaviruses can damage the nervous system. These may include **direct** infection injury, virus entering through blood circulation pathway, neuronal pathway, hypoxic injury, immune injury, and *via* binding to the angiotensin-converting enzyme 2 (ACE2). The neurotropic capacities of coronaviruses allow them to evade the immune response of the host and achieve latency.

# NEUROPSYCHIATRIC AND COGNITIVE EFFECTS OF CORONAVIRUS INFECTION

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## Acute Effects

In the short-term, **20–40%** of COVID-19 cases may present with neuropsychiatric complications, such as cerebrovascular events, headache, dizziness, encephalopathies, anosmia, ageusia, and mood problems.

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**The acute effect of CoV infections on the CNS is manifested in viral encephalitis, infectious toxic encephalopathy, and acute cerebrovascular disease. In a recent meta-analytic review, Rogers et al. (2020) reported the neuropsychiatric short- and long-term consequences of SARS and MERS infection.**

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They reported that during the acute illness, 27–41% of cases had neuropsychiatric symptoms such as confusion, depressed mood, anxiety, impaired memory, and insomnia. Steroid-induced mania and psychoses were also reported. The meta-analysis also looked at the available data related to COVID-19 infection and neuropsychiatric consequences and found that confusion and agitation were present in 65–69% of the **intensive care unit** patients.

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**Importantly, at discharge, 33% of the patients with COVID-19 had dysexecutive syndromes.**

**Over 30% of patients hospitalized with COVID-19 may exhibit cognitive impairment, depression, and anxiety that persist for months after discharge.**

## Long-Term and Chronic Neuropsychiatric Sequelae

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It is known that the neural and immune cells can host latent CoV which could contribute to **delayed** neurologic and neuropsychiatric complications (Desforges et al., 2019). However, long-term neuropsychiatric sequelae of COVID-19 are **currently unknown**.

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**We can speculate long-term effects from our understanding of the mechanisms of the COVID-19 on the CNS and evidence from long-term neuropsychiatric effects of SARS-CoV-1 and MERS. reported that 55% of survivors of SARS-CoV-1 had post-traumatic stress disorder (PTSD).**



## Long-Term Cognitive Sequelae

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From the emerging evidence and our understanding of the mechanism of CoV in the CNS, one can expect to have a range of cognitive consequences of COVID-19 infection. Attention and dysexecutive symptoms have commonly been reported with COVID-19 (Rogers et al., 2020; Varatharaj et al., 2020). Hypoperfusion in the frontotemporal region of the brain has also been reported (Helms et al., 2020) as well as structural brain abnormalities thalamic and temporal regions.

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Considering the demyelinating nature of the viral infection in the CNS, we can expect common cognitive problems that characterize **demyelinating illnesses** (such as MS).

Similarly, a link between loss of smell in COVID-19 patients and the prodromal phase of Parkinson's disease should be kept in mind while examining long-term cognitive consequences.

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**The short-term neuropsychiatric and cognitive complications following COVID-19 are varied and affect a large proportion of COVID-19 survivors. In the medium- and long-term period, there is going to be an influx of patients with psychiatric and cognitive problems who were otherwise healthy prior to COVID-19 infection.**

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**Increased neuropsychiatric manifestations could be observed in the form of an increase in cases of depression, anxiety, PTSD, and in certain cases severe mental illnesses. Early intervention for emerging cognitive problems will be critical for independent functioning and improved quality of life for many COVID-19 survivors.**

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Whereas residual or persistent neuropsychiatric symptoms are **not uncommon** in critically ill survivors following admission to an intensive care unit (**ICU**), post-COVID-19 follow-up studies reveal that **mild** and even **asymptomatic** infection may lead to cognitive impairment, delirium, extreme fatigue, and clinically relevant mood symptoms .

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Recent evidence suggests that psychiatric illness is **both** a risk factor for and consequence of COVID19.

In a large electronic health record (EHR)-based cohort study of over 60,000 COVID-19 cases, a documented psychiatric diagnosis in the **prior year** was associated with a 65% increased risk of COVID-19 when compared with a matched cohort of patients with physical health issues without psychiatric diagnoses.

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**Neurocognitive Disorders** There are few data regarding the long-term cognitive consequences of COVID-19. One study of 279 patients hospitalized with COVID-19 found that **34%** reported **memory loss** and **28%** described **impaired concentration** approximately 3 months after discharge.

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**Similar findings have been observed following infection with other coronaviruses, in which 20% reported cognitive deficits months to years after initial infection. In Taquet et al's large EHR study, new onset dementia following hospitalization for COVID-19 was 2–3 times more common than what was observed after hospitalization for other medical events.**



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**In more severe cases of COVID-19, long-term cognitive deficits are likely the sequelae of delirium experienced during the acute phases of illness. Particularly in older patients, delirium is one of the most common symptoms in COVID-19 patients presenting to the ED, and can be the only or primary symptom of SARS-CoV-2 infection.**

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Delirium occurs **in at least 30%** of patients hospitalized with COVID-19 and is substantially more common in those requiring **ICU admission** . The implications of delirium on long-term outcomes in these patients can be gleaned from the existing ICU literature.

Psychiatric and cognitive problems are more common in those requiring **ICU admission** .

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**Clinical trials are also urgently needed to clarify optimal treatment strategies for Neuropsychiatric and other potentially long-term impacts of COVID-19.**

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## **Delirium**

Increasingly recognized as commonly occurring during the COVID-19 pandemic, delirium has a higher prevalence than other conditions affecting the central nervous system (CNS) when compared with stroke, encephalitis, convulsions, or meningitis.

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Delirium in patients with COVID-19 has **many possible etiologies**, including metabolic, respiratory, and coagulation alterations that are consequences of the direct effects of SARS-CoV-2 on peripheral organs and systems.

Additionally, systemic inflammation that alters the blood-brain barrier leads to a CNS immune response.

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**The virus produces a direct effect in the brain in a minority of cases (encephalitis and meningitis), such that delirium could result from a CNS infection as well as brain inflammation.**

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Pathophysiological **mechanisms** for delirium in COVID-19 are **many**. Inflammatory response to systemic infections alters the blood-brain barrier, allowing a central inflammatory response leading to neuronal dysfunction of cholinergic circuits, among other alterations .

Pulmonary, cardiac, and renal insufficiency reduce CNS mitochondrial oxidation, **increase CNS dopamine**, and **decrease acetylcholine** production.

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There is also **no** evidence to suggest that the **covid-19 vaccines** would lead to neurocognitive issues.



