Impacts of COVID-19 on the brain and nervous system

HEALTH

COVID-19 was first described as a disease of the lungs, but it is now known that it has a far wider reach within the human body. The virus has also been implicated in disorders of the brain and the mind. ***Darius Rountree-Harrison*** *is an electroencephalogram analyst. This is an edited version of his presentation to STARTTS clinicians, adapted by* ***Sejla Murdoch****.*

The outbreak of the Severe Acute Respiratory Coronavirus 2 (SARS-CoV-2) disease – or as we know it, COVID-19 – was first reported in Wuhan, China, on 31 December 2019. The source of viral transmission to humans remains unclear, as does whether the virus became pathogenic before or after this date. A few weeks after this discovery, the pandemic was declared by the World Health Organization (WHO) in March 2020.

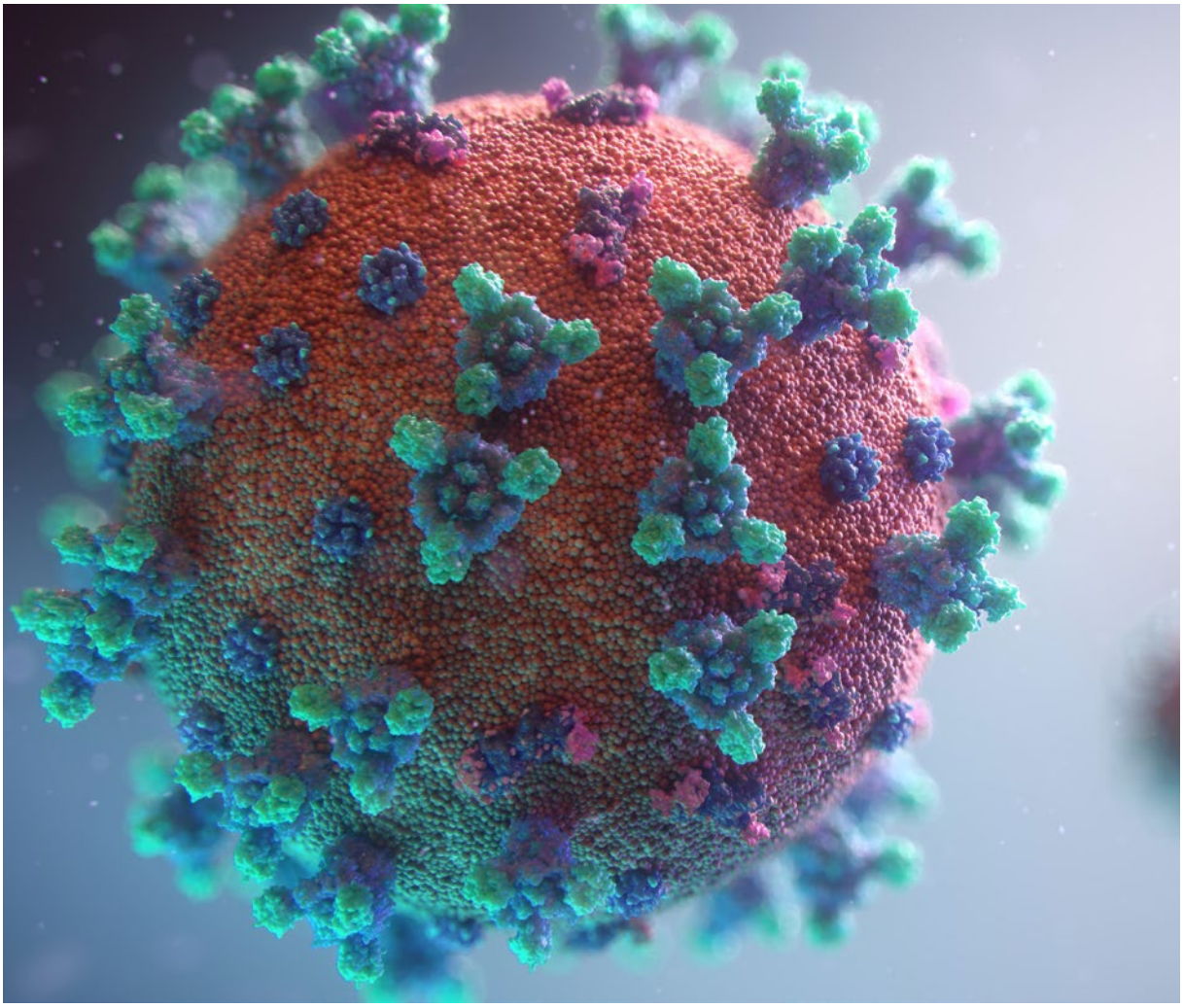
By the time this article is published, there will be more than 250 million people across the globe infected by COVID-19 with an expected death toll of more than 4 million. The severity of COVID-19 symptoms can range from very mild to severe. Some people may have only a few symptoms, and others may have no symptoms at all. Some people may experience worsened symptoms, such as shortness of breath and pneumonia, about a week after symptoms start.

In this article we focus on the findings that describe the impact of COVID-19 on the brain and nervous system.

Although most people with COVID-19 have mild to moderate symptoms, the disease can cause severe medical complications and lead to death. Older adults or people with existing medical conditions are at greater risk of becoming seriously ill.

Since last year doctors have described the impact of "long COVID", a term that refers to a wide array of physical and psychological impacts arising from infection with COVID-19. The virus has been reported to attack the nervous system directly, with non-direct impacts to organs and systems, such as elevated inflammation and blood pressure readings and immune responses also damaging the brain.

An electroencephalogram (EEG) can image these results and provides a valuable tool to guide and understand infection mechanisms and inform therapeutic intervention. The EEG is a non-invasive assessment method that records the brain's electrical activity in the form of wave patterns. It is also referred to as "brain



mapping." EEG assessments give a general indication of brain functioning, levels of alertness and self-regulation capacity, and can identify patterns associated with difficulties in cognition, sleep disorders and changes in mood and behaviour.

Although COVID-19 was first described as a respiratory disease affecting blood vessels as well as the lungs, it is now recognised as causing damage to multiple organs including the heart, kidneys, liver, intestines, muscles and skin, as well as being implicated in disorders of the brain and the mind – neurological and psychological impacts. Many of those affected report loss of smell, headaches, dizziness, anxiety, movement difficulties and cognitive problems. In some cases, disorientation, confusion and psychosis can occur.

Pathological processes can occur in the brain as a result of COVID-19 infection. The virus can invade the nervous system directly, damaging brain cells, and is implicated in conditions such as epilepsy, stroke and brain haemorrhage. The virus also can cause psychological symptoms by non-direct mechanisms including excessive inflammation, insufficient blood oxygen levels, organ failures, toxicity and blood clotting produced by the virus. In part, these neurological impacts contribute to the virus being so deadly, especially the stronger and more infectious Delta and Omicron variants.

COVID-19 can infect anyone, but as the pandemic goes on it is becoming increasingly clear there are groups more at risk of serious outcomes. From the outset, older individuals and those with pre-existing health conditions were considered the most vulnerable. Now it is becoming clear that individuals with pre-existing mental health conditions are also more likely to be hospitalised or die as a result of being infected by COVID-19. For those lucky enough to survive, its legacy can be lasting physical and mental challenges.

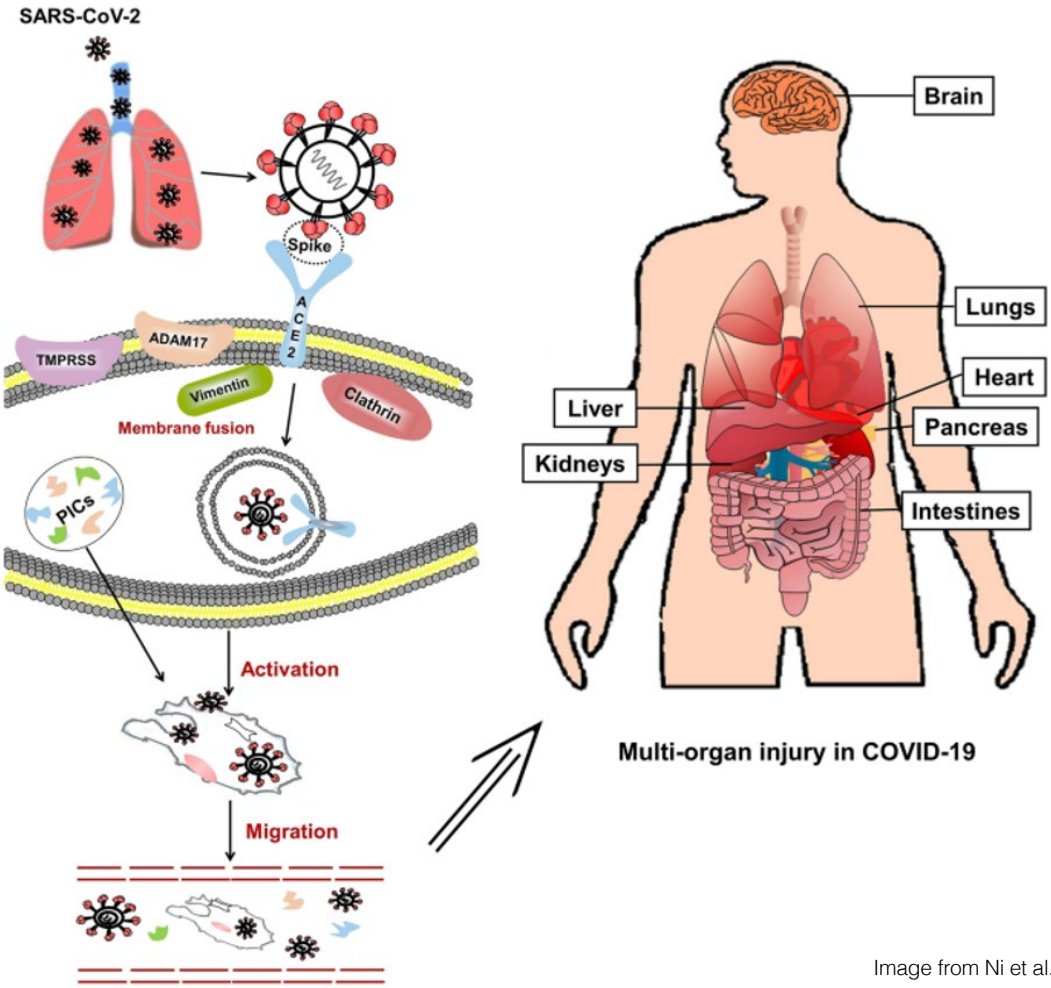


Image from Ni et al., (2020).

Covid-19 can infect multiple organs in the body

These longstanding mental health challenges are being referred to as "long COVID," which has been described as brain fog, memory issues, perceptual fuzziness, fatigue, a lack of clarity and confusion. Long COVID has been reported in 84.1 per cent of those people who needed ventilators, 12.2 per cent of those hospitalised, 9.2 per cent of those requiring assistance at home, 5.8 per cent requiring no assistance and 3.8 per cent without respiratory symptoms. This is 24.4 per cent of individuals who return positive biological test results for COVID-19. While these figures are from one study, it is reasonable to assume a substantial number of individuals may present with long-COVID given the World Health Organization (WHO) figures indicate there are 194,080,019 confirmed cases globally as of late July 2021.

Direct and non-direct mechanisms of COVID-19's nervous system impacts

The question of precisely how COVID-19 impacts the brain and mind is still being investigated, but several possibilities have emerged. They can be broadly classified as two main groups: direct viral damage, where the virus impacts brain cells itself; and non-direct damage, due to the virus causing blood clots, inflammation, toxins and starving the brain of oxygen and nutrients. For direct viral damage, how the virus gains entry into the nervous system is related to the locations and types of impairments caused.

Direct infection of the nervous system can occur through the nerves in the nose responsible for our sense of smell, optical nerves responsible for vision and other nerves of the face, mouth and throat that mediate taste and muscle movement. Additionally, nerves responsible for controlling the lungs and other organs, notably those of the digestive system, can also act as pathways for a viral attack on the brain.

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From these access points the virus can travel to specific locations in the spine and brain and cause direct impacts at those points. Direct infection of the nervous system can also be a result of infection of the blood. Blood carries the virus to the blood-brain barrier, a protective lining around the brain that usually controls what can enter the brain. It can be weakened by COVID-19 for several reasons, allowing the virus to directly attack the brain.

In contrast, non-direct nervous system damage does not involve the virus infecting the nervous system, but through infecting and damaging organs such as the heart, lungs and blood vessels (veins and arteries) that support the functioning of the brain, or as a consequence of overactive immune system responses. These direct and non-direct mechanisms may occur independently or together, which increases the diversity of symptoms experienced by individuals. With such a wide range of mechanisms and impacts, it is worth understanding the trick COVID-19 uses to enter the body in the first place.

Brain regions commonly impacted by COVID-19

The direct transmission of COVID-19 to the brain occurs through nerves connected to the eyes, nose, mouth, throat and lungs. Direct transmission results in the virus gaining access to brain stem centres that control breathing and heart rate, and areas involved in sensory perception and movement. Impacts to these regions may be associated with classic COVID-19 symptoms such as dry cough, difficulties breathing and more neurological symptoms such as the loss of taste, smell and vision issues.

However, some long COVID symptoms may also be linked to direct viral infection mechanisms because of COVID-19's impact upon neurotransmitters, molecules used by the brain to send signals between cells. Infection of nerves responsible for the sense of smell allows the virus to travel to the hypothalamus, a region responsible for maintaining the body's internal balance, which is known as homeostasis. The hypothalamus helps stimulate or inhibit many of the body's key processes, including heart rate and blood pressure, body temperature, appetite and body weight and sleep cycle.

Thus the presence of neurological symptoms, such as loss of smell or difficulties breathing, may suggest COVID-19 infection of the nervous system via a direct mechanism, which may be associated with changes to neurotransmitter levels. This information can guide mental health clinicians' therapeutic interventions.

COVID-19 infection of the brain via the blood-brain barrier

The other direct mechanism allowing COVID-19 to access the brain is through transmission in the blood to the blood-brain barrier. While the blood-brain barrier usually protects the brain from infection and toxins, in the case of COVID-19 the presence of ACE-II receptors in cells called pericytes within this barrier means it becomes susceptible to infection by the virus. Infection of pericytes acts as a stepping stone for COVID-19 to infect brain cells connected to pericytes, such as astrocytes and neurons. Additionally, pericyte infection makes the blood-brain barrier leaky, with microbleeds allowing COVID-19 to slip through gaps in the barrier directly into the brain.

In addition, COVID-19 can damage temporal lobe structures that have a role in processing affect, emotions, language and aspects of visual perception such as the hippocampus, which has a major role in learning and memory, and which is generally linked to depression, memory issues and cognitive decline.

The combined damage to the blood-brain barrier, frontal and temporal lobes leads to changes in the transmission of signals being sent around the brain, which could be associated with the disorientation, confusion and psychosis seen in COVID-19 patients. Making matters worse, microbleeds in the temporal lobes are associated with epilepsy, headaches and anger.

The takeaway is that when individuals experience symptoms such as headache, confusion and psychosis, it may be the result of direct impacts to the nervous system from damage to the blood-brain barrier. This points to the importance of considering the functioning of the whole body when addressing mental health issues, which may require any psychological interventions for long COVID to be combined with health interventions to heal non-direct mechanisms impacting the nervous system.

The main non-direct mechanisms through which COVID-19 impacts the nervous system are 1) by creating blood clots, which cause strokes, 2) impairing breathing, heart rate and oxygen supply to the brain, and 3) causing organ failure, which leads to imbalances in essential systems such as those that regulate fluid, salt levels and clear toxins. Each of these areas should be understood in principle to understand their effects upon the brain and deserve individual attention.

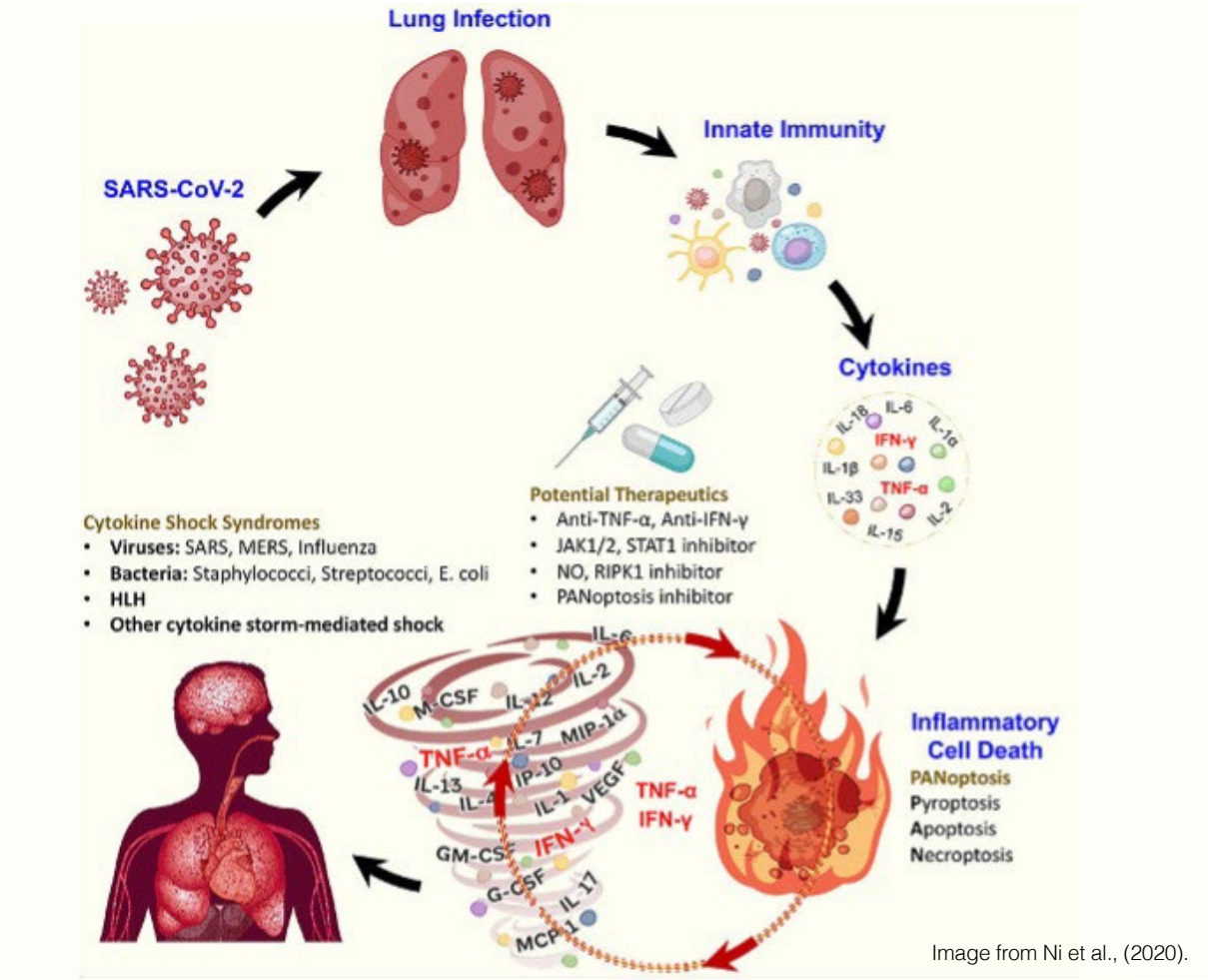


Image from Ni et al., (2020).

Cytokine storm and inflammatory cell death

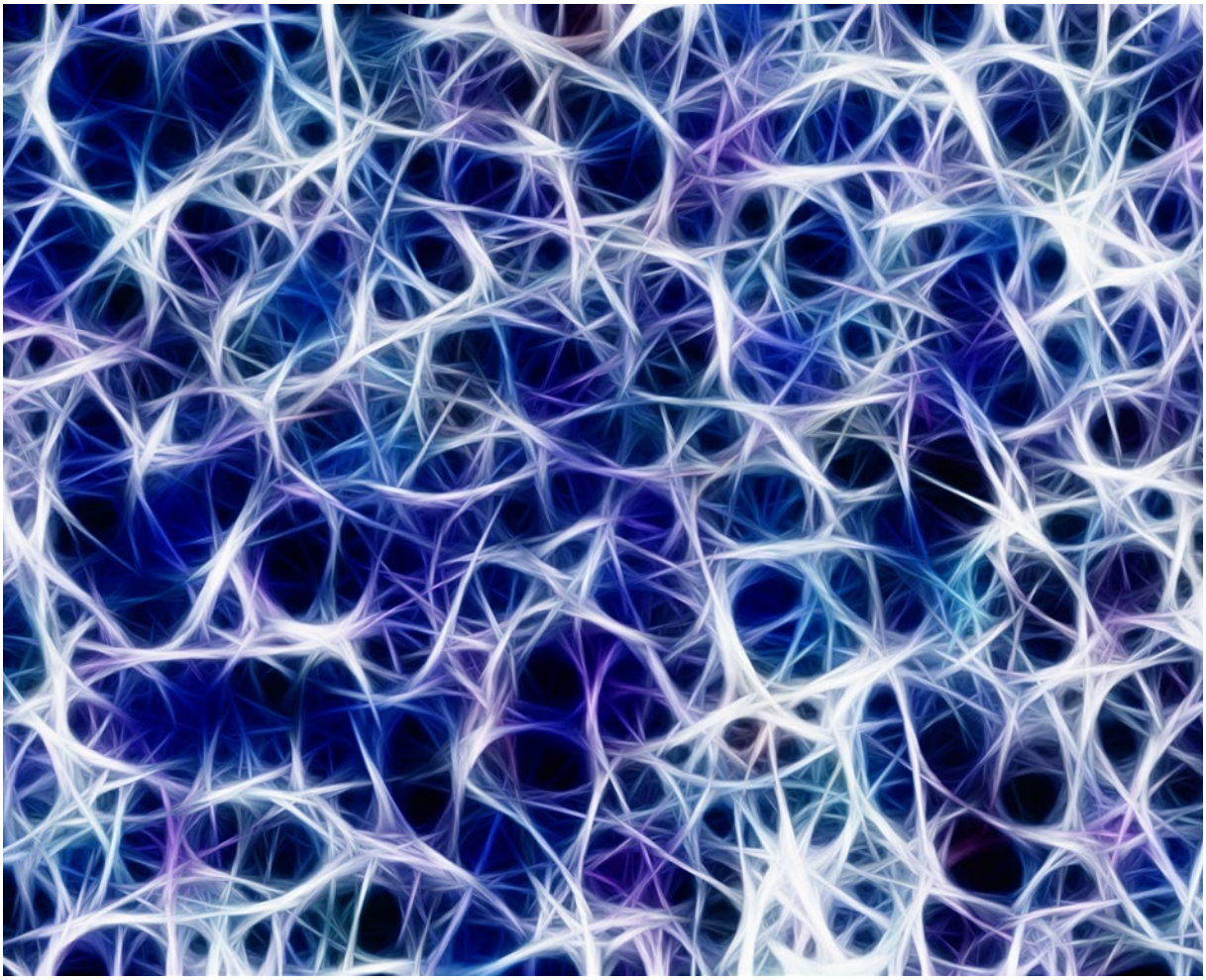
Through direct and non-direct mechanisms, COVID-19 promotes excessive immune activity, a so-called "cytokine storm", which has been implicated in both acute and long COVID symptoms. Cytokines are cell-signalling molecules that aid cell-to-cell communication during immune responses and stimulate the movement of cells towards sites of inflammation, infection and trauma.

This "storm" damages cells in the brain and other organs. During acute infection, cytokine storms have been implicated in brain cell disorders such as encephalitis, encephalopathy, endotheliitis and myelitis, as well as damage to the blood-brain barrier and organs. When the onset of psychological symptoms is delayed from the immediate period of infection, these symptoms are usually attributed to auto-immune related processes driven by cytokine storms.

Because of the damage to the brain, nerves and organs, these cytokine storms are a critical factor in the generation of many of the psychological symptoms associated with acute infection and long-COVID, and interventions to reduce inflammation should be considered.

Depending on the individual, vulnerabilities and direct and non-direct mechanisms of COVID-19 disease progression, myriad nervous system impacts and psychological symptoms can emerge. In the brain, these impacts on the nervous system and the associated psychological symptoms correspond to changes in "brain waves", or the patterns of electrical communication in the brain measured by an EEG.

A review of EEG changes observed in COVID-19 patients estimated that abnormal background activity was present in 96.1 per cent of patients, and generalised slowing was present in 92.3 per cent of cases. Electrical discharges similar to epilepsy, but not diagnostic of epilepsy, were seen in 22.4 per cent of individuals with no history of epilepsy or seizures, and 59.5 per cent of individuals with these conditions before they contracted COVID-19. Other common EEG findings included



changes in frontal lobe activity and irregular patterns of focal slowing, found on both sides or one side of the brain. The speed and shape of these patterns and their locations in the brain are likely to relate to the mechanisms by which COVID-19 has impacted the nervous system, which could hold clues to treating long COVID symptoms.

Unprecedented frontal slow activity associated with COVID-19

The myriad mechanisms by which COVID-19 can impact the nervous system mean it is still too early to draw definitive associations between reported cases, EEG patterns and causal mechanisms. When dealing with an individual experiencing acute or long COVID symptoms, it is necessary to consider their specific symptoms to understand the mechanisms by which the nervous system has been impacted, and to connect the resulting EEG patterns and psychological difficulties.

Once such considerations are made, the question is how to help these people recover. During acute and critical stages of the disease medical care with antivirals such as Remdesivir, steroids such as dexamethasone, the supply of oxygen and use of anticonvulsants might be recommended depending on the individual. However, addressing the psychological impairments of long-COVID often falls to psychologists and other health professionals outside emergency settings.

There is no doubt that we are still to see the long-reaching impact of COVID-19. As medical professionals collect more data and treat more patients with long COVID symptoms, science will be able to answer more questions and provide more treatment options.

Nevertheless, for those suffering now with psychological issues, help and support is available. If you or somebody you know is suffering from the long-term consequences of COVID-19, please speak to your doctor, seek a referral to see a psychologist or call a phone support service for immediate support.R