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# COVID-19 and the Brain: Infection Mechanisms, Electroencephalographic Findings and Clinical Implications

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**Abstract**

The term *long-COVID* refers to a wide array of psychological impacts arising from infection with the Severe Acute Respiratory Coronavirus 2 (SARS-CoV-2). The virus has been reported to attack the nervous system directly, with nondirect impacts to organs and systems, such as elevated inflammation, blood pressure, and immune responses also damaging the brain. The electroencephalogram (EEG) has been used to image these insults and provides a valuable tool to guide understanding of infection mechanisms and, consequentially, therapeutic intervention. Due to the high likelihood of neurological complications, neurofeedback and other forms of neuromodulation may be particularly well suited to help long-COVID patients recover. However, clinicians providing neuromodulation interventions should be aware of, and take adequate steps to minimize, risks to themselves and others in providing face-to-face services. This review seeks to provide mental health professionals with an overview of the impacts of COVID-19 upon the nervous system, details current EEG findings, and outlines possibly relevant neurofeedback and neuromodulation interventions.

***Keywords***: COVID-19; long-COVID; electroencephalogram; neurofeedback; neuromodulation

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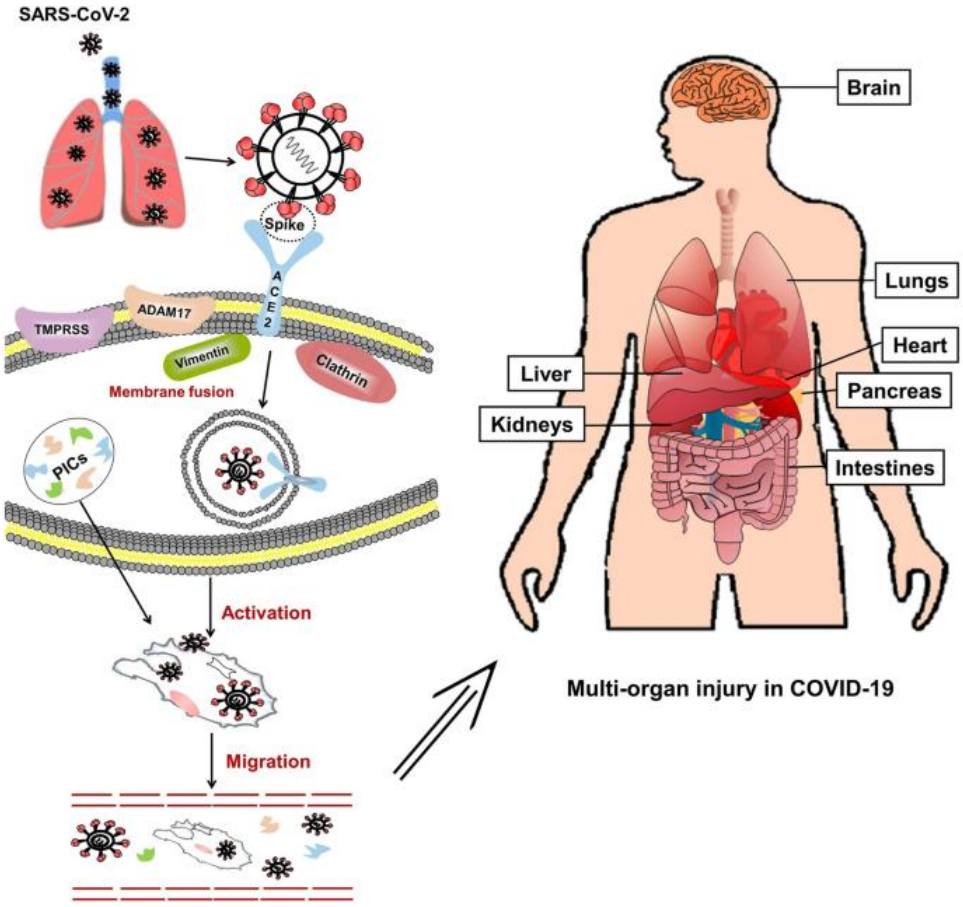
Although COVID-19 was first described as a disease-causing respiratory illness affecting the lungs, veins, and arteries, it is now recognized to have a far wider reach in the human body (Ni et al., 2020). As indicated in Figure 1, the virus can infect and damage multiple organs including the heart, kidneys, liver, intestines, muscles, and skin (Ni et al., 2020). It has also been implicated in disorders of both the brain (Bodro et al., 2021; Satarker & Nampoothiri, 2020) and the mind (Hampshire et al., 2021; Marshall, 2020).

Severe Acute Respiratory Coronavirus 2 (SARS-CoV-2), the virus that causes the Coronavirus disease of 2019 (COVID-19), is increasingly associated with neurological and psychological impacts. Many people affected have reported the loss of smell, headaches, dizziness, anxiety, movement difficulties, inattention, and cognitive difficulties (Hampshire et al., 2021). In a minority of cases, disorientation, confusion (Bodro et al., 2021; Satarker & Nampoothiri, 2020), and psychosis can occur (Marshall, 2020). However, regardless of the severity of psychological symptoms, 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 (encephalopathy, encephalitis, endotheliitis, and myelitis) and can be implicated in conditions such as epilepsy, stroke, and brain hemorrhage (Bodro et al., 2021). The virus also can cause psychological symptoms by nondirect mechanisms including

**Figure 1.** *COVID-19 Can Infect Multiple Organs in the Body.*




**Note.** Image reproduced with permission from Ni et al. (2020, CC BY-4.0).

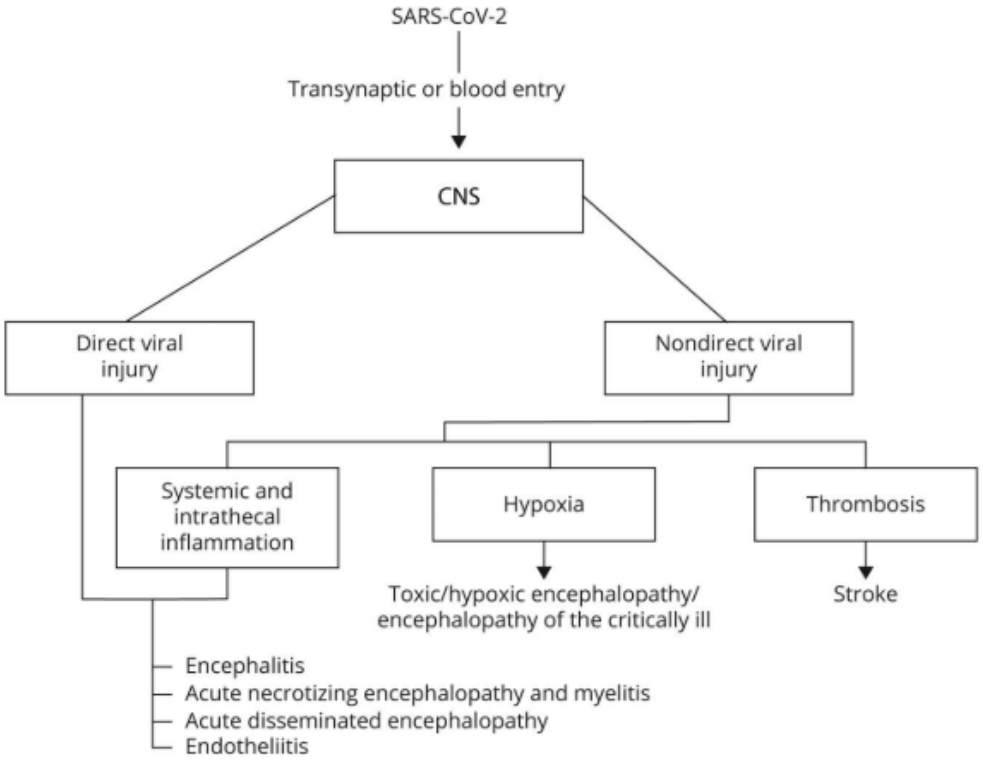
excessive inflammation, insufficient oxygen levels, organ failures, toxicity, and blood clotting produced by the virus (Panariello et al., 2020; Satarker & Nampoothiri, 2020). In part, these neurological impacts contribute to the virus being so deadly, especially the stronger and more infectious Delta variant (Davis et al., 2021; Farinholt et al., 2021; Roy et al., 2021). COVID-19 can infect anyone, but as the pandemic goes on it is becoming increasingly clear there are certain groups more at risk of serious outcomes from contracting it. From the outset, older individuals and those with preexisting health conditions were considered the most vulnerable (Australian Department of Health, 2021). Now it is becoming clear that individuals with preexisting mental health conditions are more likely to be hospitalized or die as a result of being infected by COVID-19 (Ceban et al., 2021). However, for those lucky enough to survive, the legacy of infection can leave lasting physical and mental challenges.

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 (Hampshire et al., 2021). Long-COVID has been reported in 84.1% of individuals who were ventilated, 12.2% of those hospitalized, 9.2% of those requiring assistance at home, 5.8% requiring no assistance, and 3.8% without respiratory symptoms (Hampshire et al., 2021). This is approximately 24.4% of individuals who return positive biological test results for COVID-19 (Hampshire et al., 2021). 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 figures indicate there are 194,080,019 confirmed cases globally as of late July 2021 (World Health Organization, 2021). In previous coronavirus outbreaks, neurological symptoms were seen in 0.04% of those infected with Severe Acute Respiratory Syndrome 1, and 0.2% of those infected

with Middle East Respiratory Syndrome (Marshall, 2020). Using these figures as an estimate and current WHO case estimates, approximately 7,763,200 to 38,816,003 people may have impacts on their nervous systems as a result of COVID-19. If we assume 24.4% of the 194,080,019 global COVID-19 cases will have long-COVID symptoms, this is approximately 46,579,204 individuals. These numbers suggest there will be a substantive mental health burden from the pandemic that mental health professionals will need to understand and find ways of addressing to help impacted individuals.

The question of how COVID-19 impacts the brain and mind is still being investigated, but several possible mechanisms have emerged (Ni et al., 2020; Satarker & Nampoothiri, 2020). As shown in Figure 2, these mechanisms can be broadly classified into two main groupings; direct viral damage, where the virus impacts brain cells itself, and nondirect damage, due to the virus causing blood clots, inflammation, and toxins, and starving the brain of oxygen and nutrients (Bodro et al., 2021). For direct viral damage, how the virus gains entry into the nervous system is related to the locations and types of impairments caused (Satarker & Nampoothiri, 2020). Direct infection of the nervous system can occur through the sensory nerves in the nose responsible for our sense of smell, nerves in the eyes responsible for vision, and other nerves of the face, mouth, and throat that mediate taste and muscle movement (Satarker & Nampoothiri, 2020). Additionally, nerves in the body 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 (Satarker & Nampoothiri, 2020). Via each of these access points, the virus is then able to travel to specific locations in the spine and brain and cause direct impacts at those locations (Satarker & Nampoothiri, 2020). 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 (Marcus et al., 2003; Whitley, 1990), which can become vulnerable to COVID-19 due to inflammation and infection of cells within this barrier that allow the virus to directly attack the brain (Satarker & Nampoothiri, 2020; Wang et al., 2021).

**Figure 2.** *Direct and Nondirect Mechanisms of COVID-19's Nervous System Impacts.*



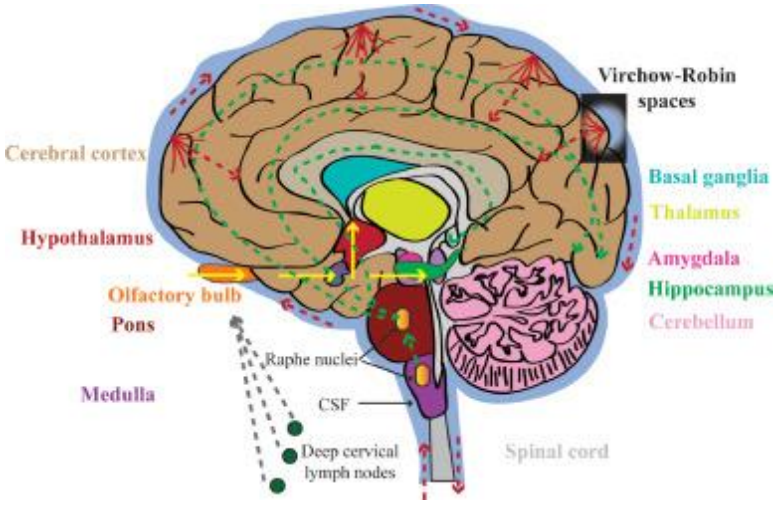

**Note.** Image reproduced with permission from Bodro et al. (2021, CC BY-4.0).

In contrast, nervous system damage via nondirect mechanisms does not involve the virus infecting the nervous system, but rather 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 (Bodro et al., 2021). These direct and nondirect mechanisms can occur independently or together which increases the diversity of symptoms between individuals (Bodro et al., 2021; Hampshire et al., 2021; Marshall, 2020; Satarker & Nampoothiri, 2020). With such a wide range of possible mechanisms and impacts of the virus, it is worth understanding the trick COVID-19 uses to enter the body in the first place.

COVID-19 is a trickster; it enters cells in the human body a bit like a thief picking a lock to open a door. In this analogy, the lock-picking tool used by the virus is called a “spike protein” and it can open the cellular lock because it mimics the shape of the real key, a protein produced by the body called Angiotensin-II (Ni et al., 2020). Angiotensin-II is a part of a complex system that regulates blood pressure and immune responses, the Renin-Angiotensin-aldosterone System (RAAS). The role of Angiotensin-II in the RAAS is to increase blood pressure and promote inflammation (Ni et al., 2020). Normally, it would bind to the cellular lock used by COVID-19, an ACE-II (Angiotensin Converting Enzyme 2) receptor, and would be converted into Angiotensin-I, which has the opposite effect, lowering blood pressure and reducing inflammation (Ni et al., 2020). However, when this lock has already been picked by COVID-19, Angiotensin-II isn’t able to use it and remains in circulation in the blood, increasing blood pressure and inflammation (Ni et al., 2020). Also, because Angiotensin-II is not converted into Angiotensin-I there is less of this protein to counterbalance the effects of Angiotensin-II. The consequence is very high blood pressure and inflammation that does damage to the linings of blood vessels, lungs, and tissue damage to organs (Ni et al., 2020). Critically, these ACE-II locks that COVID-19 uses to enter human cells are widely distributed in the body, with high concentrations in the lungs, heart, vasculature, liver, gastrointestinal tract, and kidneys (Ni et al., 2020). These receptors are also found in cells in the blood-brain barrier (Wang et al., 2021), sensory nerves of the nose and eyes, and in certain brain areas, such as the brainstem and hippocampus (Panariello et al., 2020; Zubair et al., 2020), that are respectively responsible for the control of breathing (Nattie & Li, 2012; Porges, 1995) and memory formation (DuBrow & Davachi, 2016; Fanselow & Dong, 2010). Because of the wide distribution of ACE-II receptors and the number of different organs they are associated with, the mechanisms by which COVID-19 impacts the nervous system (described in the paragraph before), are fundamentally important in identifying the causes of long-COVID and providing the appropriate interventions to help repair the associated damage.

The direct transmission of COVID-19 to the brain occurs through nerves connected to the eyes, nose, mouth, throat, and lungs (Cheng et al., 2020; Panariello et al., 2020); see Figure 3.

**Figure 3.** *Brain Regions Commonly Impacted by COVID-19.*




**Note.** Image reproduced from Cheng et al. (2020, CC BY-NC-ND 4.0).

Direct transmission results in the virus gaining access to brainstem centers associated with the control of breathing, heart rate, and areas involved in sensory perception and movement (Cheng et al., 2020; Panariello et al., 2020). 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 (Cheng et al., 2020; Panariello et al., 2020). However, some long-COVID symptoms may also be linked to direct viral infection mechanisms due to COVID-19's impacts upon neurotransmitters, which are 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 (Nampoothiri et al., 2020), a region responsible for coordinating many bodily functions such as regulating body temperature (Dampney, 2016; Lechan & Toni, 2016). Another brain region that can be impacted by direct transmission of COVID-19 is called the striatum (Cheng et al., 2020; Panariello et al., 2020), a structure that is involved in learning and movement (Nicola, 2007; Peters et al., 2016). In both the hippocampus and striatum, the presence of Angiotensin-I increases the concentration of dopamine and GABA, while decreasing norepinephrine concentrations (Panariello et al., 2020). These neurotransmitters are critical in a range of psychological processes. Dopamine is critical for learning and movement, with insufficient levels associated with attention deficit disorder (Arns et al., 2013; Arns et al., 2014) and Parkinson's disease (Benz et al., 2014; Przedborski, 2017). GABA is the main inhibitory or "OFF" signal in the brain and low levels are associated with anxiety disorders (Agorastos et al., 2015; Wilhelm et al., 2017) and epilepsy (Taubøll et al., 2015). Norepinephrine is a stimulating neurotransmitter, with low levels associated with depression (Chrousos, 2009) and alterations in consciousness (Berridge et al., 2012). There are also ACE-II receptors in the substantia nigra (Satarker & Nampoothiri, 2020), another structure closely associated with dopamine-related functions (Schultz, 2000). As described before, by COVID-19 binding to the ACE-II receptor, there is less Angiotensin-I produced, which in the brain may be linked to lower levels of dopamine, GABA and increased norepinephrine levels (Panariello et al., 2020). These neurotransmitter changes may relate to some of the psychological changes associated with long COVID (Bodro et al., 2021; Hampshire et al., 2021; Marshall, 2020; Satarker & Nampoothiri, 2020). Consequentially, 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 could help mental health clinicians guide their therapeutic interventions.

The other direct mechanism allowing COVID-19 to access the brain is through transmission in the blood to the blood-brain barrier (Satarker & Nampoothiri, 2020). 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 special cells called pericytes within this barrier means it becomes susceptible to infection by the virus (Wang et al., 2021). Infection of pericytes acts as a stepping-stone for COVID-19 to infect brain cells connected to pericytes such as astrocytes and neurons (Wang et al., 2021). Additionally, pericyte infection makes the blood-brain barrier leaky, with microbleeds allowing COVID-19 to slip through gaps in the barrier into the brain directly (Wang et al., 2021). Structures like the ventricles and temporal lobes are particularly affected by these microbleeds (Bodro et al., 2021). Subsequent transmission through the ventricles allows COVID-19 to reach the frontal lobes and posterior cingulate cortex (Panariello et al., 2020), which are core brain structures involved in executive and introspective processes and are implicated in most psychological disturbances (Menon, 2011). In addition, COVID-19 can damage temporal lobe structures such as the hippocampus (Bodro et al., 2021), which is generally linked to depression, memory issues, and cognitive decline (Panariello et al., 2020). The combined damage to the blood-brain barrier, frontal and temporal lobes leads to changes in the ability of brain signals to be sent around the brain, which could be associated with disorientation, confusion (Bodro et al., 2021; Satarker & Nampoothiri, 2020), and psychosis (Marshall, 2020) seen in COVID-19 patients. Making matters worse, COVID-19 causes microbleeds in the temporal lobes, which are associated with epilepsy (Bodro et al., 2021), headaches (Charles & Baca, 2013), and anger symptoms (Sugahara, 2004). The takeaway is when individuals experience symptoms like headache, confusion, and psychosis it may suggest direct impacts to the nervous system as a result of damage to the blood-brain barrier. Moreover, these symptoms are cause for great concern as they are thought to be associated with more severe neurological presentations, such as encephalopathy, encephalitis, endotheliitis, myelitis, and cerebrovascular disease (Bodro et al., 2021; Satarker & Nampoothiri, 2020). However, symptoms such as headache, confusion, and psychosis and

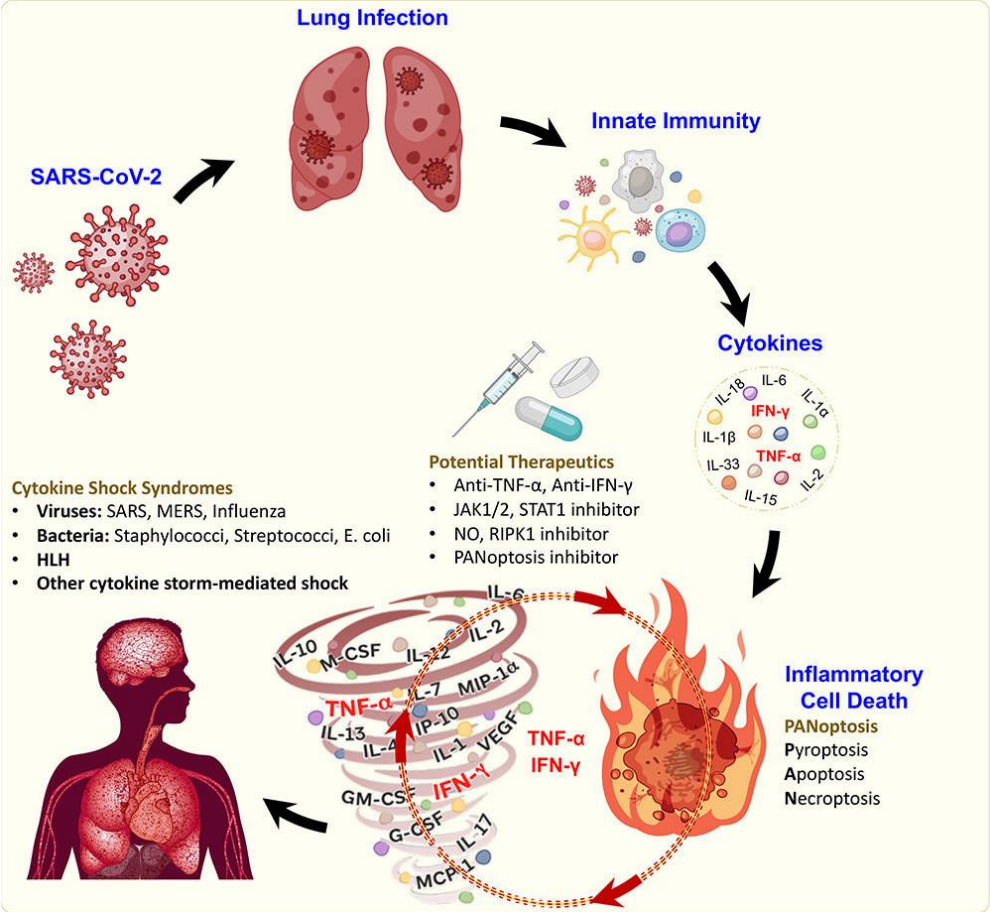
damage to the blood-brain barrier may be a result of nondirect mechanisms, including increased inflammation (Wang et al., 2021) and increased Angiotensin-II concentrations (Ni et al., 2020). This points to the importance of considering the functioning of the whole body when addressing mental health issues, which may require psychological interventions for long-COVID to be combined with health interventions to heal nondirect mechanisms impacting the nervous system. The main nondirect 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 (Satarker & Nampoothiri, 2020). Each of these areas should be understood in principle and deserve individual attention to understand their effects upon the brain.

In the body, COVID-19 damages blood vessels and organs, with the additional insult of increased Angiotensin-II levels promoting the formation of clots (Ni et al., 2020). Studies have estimated blood clots occur in 8% to 15% of individuals hospitalized due to COVID-19, which causes stroke in approximately 2.5% of these individuals (Bodro et al., 2021). Disturbingly, stroke is thought to be more frequent in COVID-19 patients under 50 years of age and is associated with a high probability of severe cognitive impairment or death (Bodro et al., 2021). Approximately 30–70% of intensive care patients develop blood clots in the veins and lungs, with one in four developing a clot in the heart that can cause a heart attack (Klok et al., 2020; Llitjos et al., 2020). COVID-19 can also infect heart cells directly, which may increase heart rates or cause heart failure (Ni et al., 2020). Elevated heart rates impair the supply of blood to the brain and are closely linked to reports of dizziness, while heart failure is associated with coma and death (Abdo et al., 2021; Klok et al., 2020). In combination with the damage to the heart and complications caused by blood clots, the linings of the lungs are also significantly damaged by the virus, which impairs their ability to function (Ni et al., 2020). The combined effects of all of these impacts can starve the brain of oxygen (Bodro et al., 2021). Low brain oxygen levels have been associated with symptoms of delirium, confusion, and psychosis, and have a high association with death in the acute illness and long-term cognitive dysfunction following the acute stage (Bodro et al., 2021). This may suggest breathing exercises and interventions to improve oxygen levels could be important in addressing long-COVID.

Organ failure is another nondirect mechanism by which COVID-19 can impact the brain (Satarker & Nampoothiri, 2020). Beyond the heart, lungs, veins, and arteries, COVID-19 can infect the digestive system, attacking organs such as the kidneys, pancreas, and small and large intestines (Ni et al., 2020). Approximately 6.7% of COVID-19 patients experience kidney damage (Ni et al., 2020) that impairs their ability to regulate salt and fluid levels and might be linked to some impairments of the nervous system (Cassia et al., 2021). In the pancreas, the virus can promote the development of insulin-dependent acute diabetes (Ni et al., 2020) and in some rare cases has been linked to widespread sensory neuropathy, where numbness to temperature, pain, vibration, and hot and cold is developed (Odriozola et al., 2020). Infection of the intestines (Ni et al., 2020) and gut microflora can also impair the absorption of molecules required to produce serotonin (Panariello et al., 2020). Consequentially, lower serotonin levels may reduce the ability of brain structures like the frontal lobes and hippocampus to function, which may be relevant for long-COVID symptoms (Panariello et al., 2020). This may suggest repairing gut health and gut microflora may be relevant in addressing long-COVID symptoms.

Through direct and nondirect mechanisms, COVID-19 promotes excessive immune activity, the so-called “cytokine storm,” illustrated in Figure 4, which has been implicated in both acute and long-COVID symptoms (Bodro et al., 2021; Karki et al., 2020). This “storm” damages cells in the brain and organs (Bodro et al., 2021; Karki et al., 2020). During acute infection, cytokine storms have been implicated in brain cell disorders such as encephalitis, encephalopathy, endotheliitis, and myelitis (Bodro et al., 2021; Karki et al., 2020), and damage to the blood-brain barrier and organs (Ni et al., 2020). 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 (Satarker & Nampoothiri, 2020). This is the case for the development of Guillain-Barré (Zubair et al., 2020) and Miller-Fisher syndrome (Panariello et al., 2020), which involve COVID-19 induced auto-immune damage to nerves that control movement producing paralysis symptoms like multiple sclerosis. Due to 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.

**Figure 4.** *Cytokine Storm and Inflammatory Cell Death.*




**Note.** Image reproduced with permission from Karki et al., (2020, CC BY-ND 4.0).

Depending on specific individual vulnerabilities and direct and nondirect mechanisms of COVID-19 disease progression, a myriad of 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 used by the brain that can be measured through recording an electroencephalogram (EEG). A review of EEG changes observed in COVID-19 patients estimated that abnormal background activity was present in 96.1% of patients, and generalized slowing was present in 92.3% of cases (Kubota et al., 2021). Epileptiform discharges that were not diagnostic of epilepsy were seen in 22.4% of individuals with no history of epilepsy or seizures, and in 59.5% of individuals with these conditions before they contracted COVID-19 (Kubota et al., 2021). Clinically relevant seizures, epileptic events that involve alterations in consciousness and uncontrollable movements, were seen in 2.05% of patients, while status epilepticus, a state where individuals are unresponsive due to epileptic activity, was seen in 0.80% of patients (Kubota et al., 2021). Other common EEG findings included changes in frontal lobe activity and irregular patterns of focal slowing found on both sides, and one side of the brain (Kopańska et al., 2021). 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.

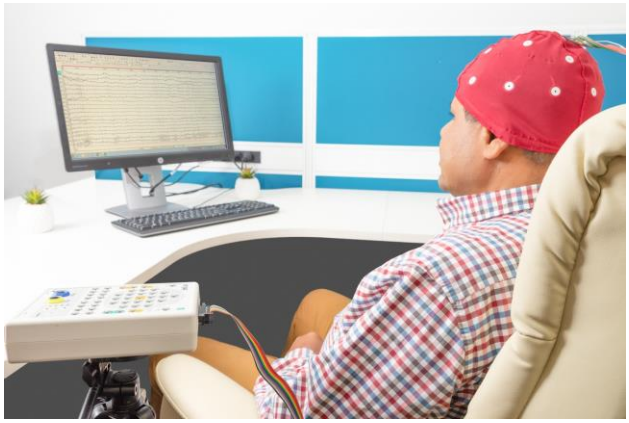
EEG patterns observed in the frontal lobes of COVID-19 patients included continuous and intermittent slow waves, which are thought to be related to insufficient oxygen; persistent theta activity, which is thought to relate to numerous microhemorrhage-related (blood-brain barrier damage) insults to brain cells that connect the frontal lobes (Kopańska et al., 2021); and frontal

sharp waves and sporadic epileptiform discharges that are associated with direct infection of the frontal lobes (via the sensory nerves for smell) and possibly also are involved with diminished organ functioning (Galanopoulou et al., 2020). Frontal patterns were also observed that developed a widespread sharp down-up-down pattern, suggesting organ failure related toxicity (Flamand et al., 2020). An irregular, unprecedented slow pattern, with a slight dominance to the right side of the brain, was also described in very severe COVID-19 patients with multiple organ failure, low brain oxygen levels, and possibly direct viral infection of the brain (Vellieux et al., 2020). Other patterns, commonly associated with encephalopathies, such as diffuse slowing and generalized or focal rhythmic slow content and epileptic activity were observed frequently (Kopańska et al., 2021; Kubota et al., 2021). In critical cases, when individuals were unresponsive or comatose, the EEG could have large bursts of activity followed by long periods of little activity at all (burst-suppression), or persistent epileptic activity (status epilepticus), or discontinuous suppression patterns (Kubota et al., 2021).

With the myriad of possible mechanisms by which COVID-19 can impact the nervous system, it is still too early to draw definitive associations between reported cases, EEG patterns, and causal mechanisms. Speculatively, there may be some association between frontal lobe EEG findings and direct viral infection mechanisms, most likely through nerves mediating smell and vision, in addition to the damage to the blood-brain barrier and low brain-oxygen levels. The presence of focal slowing or epileptiform activity to the sides of the head also suggests direct infection via the nerves mediating smell that eventually reach the temporal lobes close to the hippocampus, which is particularly prone to epilepsy due to synchronous firing properties of dendritically dense hippocampal pyramidal cell networks (Isokawa-Akesson et al., 1989; Nakahara et al., 2018), excessive neuroplasticity (Bartsch & Wulff, 2015), and the effects of stress (Dunkley et al., 2014; Gunn & Baram, 2017). The slow content in the temporal lobes may also be related to impairments in blood supply, such as blood clots, which may be more likely to show up in these locations. Slowing of the background activity and diffuse slowing suggests viral transmission to the brainstem, with changes in neurotransmitter levels possibly implicated. Although, brain cells that use these neurotransmitters, also target the frontal lobes, and may also be involved in the EEG patterns observed there. When accessing an individual experiencing acute or long-COVID symptoms it is necessary to consider their specific symptoms to understand possible mechanisms by which the nervous system has been impacted and to connect the resulting EEG patterns and psychological difficulties. Once these considerations have been made, the question of how to assist these individuals recover then arises. During acute and critical stages of the disease medical care, with antivirals such as Remdesivir or steroids such as Dexamethasone, supply of oxygen and use of anticonvulsants might be indicated depending on the individual (Zubair et al., 2020). However, addressing the psychological impairments of long-COVID often falls to psychologists and other health professionals outside emergency settings. The question then is “Are psychologists and other health services ready and able to provide these services in the middle of a pandemic?”

The emergence of new SARS-CoV-2 variants, such as the highly infectious Delta variant (Nunes-Vaz & Macintyre, 2021), poses existential questions about the future of face-to-face mental health service provision (Balcombe & De Leo, 2020). For many clinicians, services, and government agencies the immediate response involved a shift to greater use of telehealth services. At the peak of Australia’s first wave in April 2020, about 50% of mental health Medicare Benefits Schedule (MBS) subsidized were provided remotely, which gradually declined with COVID-19 case numbers to 20% of services being provided remotely in the equivalent period in 2021 (Australian Institute of Health and Welfare, 2021). Similar patterns were also observed for online mental health platforms (Australian Institute of Health and Welfare, 2021). While remote services can maintain support and assist many individuals with mental health difficulties, such as individuals that have been traumatized by the stress associated with the disease (Rajkumar, 2020) or the stress of self-isolation (Xia & Li, 2018), they are unlikely to be able to address the neurologically-based psychological impacts of COVID-19, including long-COVID. One potential intervention that may be able to address some of these issues is called neurofeedback. Neurofeedback, as shown in Figure 5, involves presenting a person’s EEG brain waves back to them in real time, allowing them to learn how to change these patterns. For neurofeedback to be effective, usually two face-to-face sessions a week are required. Given the higher levels of contact with clients associated and technology used in neurofeedback poses a greater infection risk (Hagedorn, 2014) it is critical to understand these risks and the behaviors required to reduce such risks.

**Figure 5.** *Image of Neurofeedback.*



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In enclosed spaces, normal to loud speech results in thousands of airborne fluid droplets per second, which remain airborne for 8 to 14 minutes depending upon their size, acting as a transmission mechanism for COVID-19 (Stadnytskyi et al., 2020). The wearing of a face mask prevents the majority of these airborne particles from entering the upper airways and lungs reducing airborne transmission risk (Xi et al., 2020). However, the mask itself, particularly at any folds, show increased concentrations of airborne material, which poses a possible transmission risk if hands are contaminated by touching the mask (Xi et al., 2020). In turn, this risk and the general risk of viral contamination from touching surfaces on which the virus is present can be minimized by hand washing and sterilization with 70–90% ethanol or 2-propanol (Noorimotlagh et al., 2021). Similarly, cleaning surfaces and equipment with sterilizing or disinfecting agents is also effective in reducing transmission risk (Noorimotlagh et al., 2021). Arguably, the most important behavior to reduce risk is being vaccinated against the virus. This is due to the reduced risk of infection or serious illness or death to yourself and the reduced risk of transmission to other individuals that vaccination against COVID-19 provides (Henry et al., 2021; Olliaro et al., 2021). Vaccination is still strongly recommended despite indications of reduced vaccine effectiveness against the Delta variant (Davis et al., 2021) and rare instances of infection despite vaccination (Farinholt et al., 2021). With the likely emergence of new variants in the future, booster vaccines are likely to be required (Rubin, 2021). Consideration of these risks and the implementation of risk minimization behaviors are required for a safe return to face-to-face service provision.

Neurofeedback and other forms of neuromodulation have been used to address many neurological and psychological issues that have similar origins, physiology, and patterns of brain activity to those occurring as a result of COVID-19. For instance, the origin of epilepsy is often linked to the activity of Angiotensin-II (Krasniqi & Daci, 2019), with the development of epileptic-like activity is thought to be one of the early EEG markers of COVID-19's impacts upon the nervous system (Bodro et al., 2021). A paper by Sterman and Friar in 1972 titled "Suppression of seizures in an epileptic following sensorimotor EEG feedback training" was the first account of neurofeedback being used clinically (Egner & Sterman, 2006; Sterman, 2010; Sterman & Egner, 2006). The "sensorimotor EEG feedback training" used by Sterman and Friar involved rewarding brain waves that occurred between 12 and 15 times per second near the crown of the head, with the reward being prevented whenever slower brain waves occurring between 4 to 8 times per second became too large (Egner & Sterman, 2006; Sterman, 2010; Sterman & Egner, 2006). This training was repeated two times a week over 2 years and resulted in the complete absence of seizures and greatly improved well-being (Egner & Sterman, 2006; Sterman, 2010; Sterman & Egner, 2006). Importantly, this account of seizure suppression worked when numerous medications had failed to achieve this outcome over 7 years before commencing neurofeedback (Yucha & Montgomery, 2008). In the subsequent 49 years since Sterman and Friar's pioneering work, numerous well-controlled research studies have replicated and supported this finding, with approximately 82% of individuals reporting seizure reductions greater than 50% (Sterman, 2010). Another review indicated 79% of individuals treated with neurofeedback had significant reductions in seizure size for a wide variety of epilepsy diagnoses, with these effects largely occurring in individuals that had not responded to antiepileptic medications (Tan et al., 2009). These improvements were seen from interventions as short as 3 weeks (Tan et al., 2009) and have also been documented in children and adolescents (Morales-Quezada et al., 2019) and the elderly (Reichert et al., 2016). Neurofeedback's ability to reduce epilepsy is one of the most well supported, understood, and efficacious applications of neurofeedback (Yucha & Montgomery, 2008). Importantly, the ability of neurofeedback to reduce epilepsy has been associated with increased GABA activity in the striatum and thalamus (Egner &

Sterman, 2006). As COVID-19, though its impact on Angiotensin-II levels, is thought to decrease GABA activity in these locations (Panariello et al., 2020), it is plausible that sensorimotor neurofeedback at central regions may address direct mechanisms by which COVID-19 impacts the nervous system. However, this is yet to be researched and no definitive recommendation can be made yet.

Another neurofeedback pioneer, Margaret Ayers, worked with stroke and closed head injury clients; her approach involved training one side of the head and then the other, focusing on the temporal lobes and locations towards the front and crown of the head.[1] Depending on the injury location, she rewarded brain rhythms between 12 and 15, or 15 and 18 times a second and prevented rewards for brain rhythms between 4 and 7 cycles per second (Evans, 2007; Hammond, 2005), which when reduced are associated with improved blood supply and stroke recovery (Ros et al., 2014). In a separate study, Ayres helped 250 individuals with closed head injuries to return to their preinjury levels of functioning by rewarding alpha activity (8–12 cycles per second). These stroke survivors also reported reductions in mood swings, anger outbursts, anxiety attacks, headaches, vertigo, light and sound sensitivity, as well as increased energy levels, concentration, memory, and cognitive performance as a result of the neurofeedback (Budzynski et al., 2009; Duff, 2016; Evans, 2007). Subsequent research has supported the premise of training both sides of the brain in stroke rehabilitation as it is thought compensatory processes in the opposite brain hemisphere lead to damaging overexcitation, which can be reduced with neurofeedback (Sitaram et al., 2017). These changes to the opposite side of the brain from the injury are associated with changes in functional connectivity and the synchrony of brain waves (Thatcher et al., 2020). In a series of case studies, training these connectivity patterns to resemble patterns observed in a group of healthy individuals led to clinical improvements (Koberda, 2015; Koberda & Stodolska-Koberda, 2014; Thatcher et al., 2020). Similarly, the reward of synchronous brain activity around 8 to 12 repetitions per second (alpha), between central brain regions involved in motor functions and the rest of the brain, has been linked to improved recovery and performance following stroke (Mottaz et al., 2015). This effect might be enhanced by coupling the audiovisual neurofeedback reward with simultaneous stimulation (Small et al., 2013), muscle biofeedback (Yucha & Montgomery, 2008), or simply imagining movement (Pichiorri et al., 2015) of the body areas with impaired movement. Importantly, rewarding either alpha activity or faster frequencies in stroke survivors is associated with improvements in verbal short- and long-term working memory; with alpha training specifically improving working memory, and training faster activity specifically improving short-term visual and spatial working memory (Kober et al., 2015), and visual acuity (Cho et al., 2015). These improvements were seen despite a wide variety of brain regions being impacted (Kober et al., 2015). Given the substantial overlap in brain regions impacted by COVID-19 related stroke (Bodro et al., 2021) and these studies, the improvements in cognitive performance are promising for long-COVID rehabilitation. However, it is unclear if improved mobility seen in the studies pairing neurofeedback and movement (Mottaz et al., 2015; Pichiorri et al., 2015; Small et al., 2013) occurred independently of the physiotherapy that was also provided (Sitaram et al., 2017). This uncertainty suggests a similar integrated rehabilitation program may be required for COVID-19 stroke survivors to regain function. Indeed, other forms of neuromodulation such as invasive stimulation (Elbaum & Benson, 2007; Moore et al., 2014) and noninvasive brain stimulation with electromagnets (Beck et al., 2017) or low-intensity lasers (Hamblin, 2016; Naeser et al., 2010) has improved motor control and cognitive functioning in stroke survivors and may be applicable in COVID-19 stroke rehabilitation. Although, at this point, no research has been undertaken to gauge the validity of these interventions in COVID-19 patients.

In the most severe COVID-19 cases, diffuse slowing and impairments in consciousness or coma may be seen (Abdo et al., 2021). While disorders of consciousness are not common presentations for neurofeedback, there are several case studies of note. Ayers, using similar methodologies as her work with stroke survivors, used neurofeedback to bring two individuals out of a level 2 coma (Ayers, 1995). Another study used neurofeedback to bring a five-year-old out of a chemotherapy-induced coma, with associated damage due to low oxygen levels in the brain (Fink et al., 2012). In two patients with unresponsive wakefulness, daily neurofeedback rewarding the ratio of fast to slow content over 3 weeks saw two of these patients increase the portion of fast brain activity and regain responsiveness and some functionality; there was no change in the third patient (Keller & Garbacenkaite, 2015). Several other case studies involving brain damage to deep and cortical

[1]Ayer's placement sites included T3-C3 & T4-C4, or C1-C5, or F8/T4.

structures that produced focal or diffuse slowing, which was associated with disorders of consciousness, have been remediated quite successfully with neurofeedback (Bearden et al., 2003; Hammond, 2011). Typically, these studies involve intensive interventions and it has been shown that the initial load of symptoms is correlated with the number of sessions required and the derived functional improvements (Bounias et al., 2002). The general prognostic recommendation for neurofeedback with diffuse slow patterns is to suppress slower activity, particularly at frontal locations, and to reward faster activity for increased effects (Johnstone et al., 2005). However, when a combination of slow and fast activity is present, it is likely the faster activity is compensatory and rewarding faster activity may paradoxically worsen symptoms (Ayers et al., 2000). In these instances, the best approach is to focus on the reduction of slow content with neurofeedback (Ayers et al., 2000). It is unknown if this heuristic and style of neurofeedback will remain true in COVID-19 rehabilitation and further evidence will be required.

In less severe COVID-19 cases there may still be an increase of slower brain waves in the frontal lobes (Bodro et al., 2021; Kubota et al., 2021). This may be a result of direct viral transmission to the frontal lobe along nerve fibers conducting the sensation of smell (Bodro et al., 2021; Hammond, 2007), or may be linked to low oxygen levels (Keller & Garbacenkaite, 2015) due to COVID-19's nondirect impacts upon the nervous system (Bodro et al., 2021; Ni et al., 2020). In COVID-19 patients who have lost their sense of smell, the frontal slowing pattern may be of particular relevance as similar patterns have been observed in individuals who have injured their olfactory nerves (Hammond, 2007). In two individuals with this presentation, neurofeedback to increase faster activity in the frontal lobes led to a reduction of slow content and the partial return of the sense of smell within 15 sessions and its full return in 22 sessions (Hammond, 2007). Beyond repairing damage to the sense of smell, frontal slowing may also be of relevance to the cognitive issues experienced by individuals with long-COVID (Hampshire et al., 2021). Frontal slow content is typically associated with cognitive difficulties at the beginning and later stages of life and is linked to the diagnoses of attention-deficit/hyperactivity disorder (Arns et al., 2013, 2014) and various forms of cognitive decline and dementia (Koberda, 2014; Saltmarche et al., 2017). In both instances, the type of neurofeedback used shares the common goal of reducing slow brain waves and increasing faster brain activity (Trammell et al., 2017; Wang & Hsieh, 2013), so-called "brain brightening" (Budzynski et al., 2009). Several forms of neurofeedback have been used for "brain brightening," including training the synchronicity of brain waves (Koberda, 2014; Simkin et al., 2014), rewarding particular frequency bands, typically faster brain waves (Arns et al., 2013, 2014; Wang & Hsieh, 2013), or the background rhythmicity of the brain (Arns et al., 2011; Sherlin et al., 2010) and adjusting the underlying base rhythmicity of the brain (Gevensleben et al., 2014; Kotchoubey et al., 2001; Strehl et al., 2017). In the context of COVID-19, its impacts upon dopamine levels in the brainstem (Schultz, 2000) and striatum (Panariello et al., 2020), areas that influence frontal lobe activity, may be linked to the cognitive issues experienced by individuals with long-COVID cognitive symptoms (Hampshire et al., 2021; Marshall, 2020) as these regions and neurotransmitters are also abnormal in attention-deficit/hyperactivity disorder (Arns et al., 2013, 2014) and cognitive decline (Koch et al., 2020; De Marco & Venneri, 2018). Indeed, it has been argued that damage to key brain regions such as the thalamus and striatum are the common origin for cognitive impairments in attention deficit disorders, traumatic brain injury, Down syndrome, autism, and stroke (Simkin et al., 2014). Consequentially, many of the neurofeedback protocols used in attention-deficit/hyperactivity disorder (Arns et al., 2013, 2014) can be applied in cases where the underlying processes are thought to be the same (Simkin et al., 2014). As these areas are impacted by COVID-19 (Bodro et al., 2021; Zubair et al., 2020), it is plausible, but not yet tested, that neurofeedback may also improve cognitive function in individuals experiencing long-COVID.

Beyond neurofeedback, a range of other neuromodulation interventions may be of relevance in addressing the neurological impacts of COVID-19. These include heart rate variability biofeedback, low-level laser therapy, audiovisual entrainment, and forms of relaxation interventions.

The impacts to veins and arteries caused by COVID-19 share some similarities to coronary artery disease. Heart rate variability biofeedback is a similar practice to neurofeedback, which focuses on the heart instead of the brain (Lehrer & Gevirtz, 2014; Shaffer et al., 2014) and may help address heart-brain physiology and associated pathologies such as hypertension, heart attack, and vascular issues caused by COVID-19. In outpatients who had been hospitalized due to an irregular heartbeat (ventricular fibrillation), this intervention lowered the risk of subsequent heart disorders and death by

86% (Yucha & Montgomery, 2008). Additionally, heart rate variability biofeedback has been shown to lower blood pressure and hypertension (Gilbert, 2003; Schroeder et al., 2003). These findings suggest heart rate variability biofeedback could be used to help offset COVID-19-related increases in blood pressure and heart rate (Ni et al., 2020). This is important for the nervous system functioning as one of the main impacts of high blood pressure, and heart rate is the reduced supply of blood and oxygen to the temporal lobes (Inui et al., 2001; Motomura et al., 2003). As mentioned before, this is associated with headaches and irritability (Bolay & Moskowitz, 2005; Charles & Baca, 2013; Drenckhahn et al., 2012; Sugahara, 2004). Prior research indicates biofeedback is efficacious and superior to many medications in reducing hypertension and headaches (Yucha & Montgomery, 2008), having been supported by the American Academy of Neurology for over 20 years to address these issues (Silberstein, 2000). By improving blood and oxygen supply to the brain, heart rate variability biofeedback can also improve connectivity patterns in the brain (Chang et al., 2013; Kumral et al., 2019), emotion regulation (Mather & Thayer, 2018), cognitive functioning (Chang et al., 2019; Liang et al., 2013) and overall mental health and resilience (Perna et al., 2019). Heart rate variability biofeedback has also been used successfully with a range of psychological disorders such as depression, anxiety, posttraumatic stress disorder, and substance use disorder (Moss & Shaffer, 2017). The mechanism underlying this wide range of applications and high effectiveness stems from the association between the control of breathing and the regulation of numerous other processes within the body (Cutsforth-Gregory & Benarroch, 2017; Shaffer & Venner, 2013; Smith et al., 2017; Thayer & Lane, 2000). In the context of COVID-19, this is highly relevant, as many of the brainstem regions damaged by the virus (Zubair et al., 2020) are activated by heart rate variability biofeedback and associated breathing practices (Jürgens, 2002; Kromenacker et al., 2018; Larsen et al., 2010; Vaschillo et al., 2002; Zelano et al., 2016), which may suggest this intervention could also help reduce the excitability of nerves targeting organs in the body (Stute et al., 2021), regulate body temperature (González-Alonso, 2012; Ramirez et al., 2019; Simon, 1974; Thayer et al., 1997), fluid and salt levels (Frank & Landgraf, 2008; Gilbert, 2003; Ranpuria et al., 2008) and angiotensin levels (Ardell, 2001; Persson & Kirchheim, 1991; Schroeder et al., 2003), which are disrupted by the virus. Moreover, it has been shown to limit inflammation (Huston & Tracey, 2015; Tracey, 2002) and improve organ functioning (Park & Thayer, 2014; Smith et al., 2017; Thayer et al., 2010). In particular, this may be of relevance to gastrointestinal symptoms caused by COVID-19 as bidirectional connections between the brain, heart, and intestines are thought to exist (Singh et al., 2014; Sundman et al., 2017), with gut microflora playing an important role in their functioning (Kazemian et al., 2020; Mayer et al., 2016; Petra et al., 2015; Tang et al., 2017). Together these findings may suggest heart rate variability biofeedback is particularly well suited to limiting direct and nondirect mechanisms by which COVID-19 attacks the nervous system and may offer a potential remedial intervention. Unfortunately, there seems to have been no research into the use of this promising intervention with COVID-19 related impacts on the body and mind.

A substantial body of research indicates that low-level laser therapy (also known as cold laser therapy or photobiomodulation), which typically uses near-infrared light frequencies to stimulate the brain (De La Torre, 2017) could help reduce inflammation, promote the repair of brain cells, and increase blood flow in the brain (Hamblin, 2016, 2019; Naeser et al., 2018). This intervention has been used to heal brain tissues damaged by low oxygen levels (Gonzalez-Lima et al., 2014; Moreira et al., 2011), traumatic brain injury (Naeser et al., 2014, 2016, 2018), Alzheimer's disease (Hamblin, 2019; Purushothuman et al., 2014), depression (Cassano et al., 2016), posttraumatic stress disorder (Naeser et al., 2014) and has been used for cognitive enhancement (De La Torre, 2017; Gonzalez-Lima & Barrett, 2014; Gonzalez-Lima et al., 2014). As many of the reported effects of this intervention target processes that are impacted by COVID-19, such as inflammation and blood flow (Ni et al., 2020; Panariello et al., 2020; Satarker & Nampoothiri, 2020), the wide range of disorders low-level-light therapy has been used for, and the reported cognitive enhancements associated with its use suggest it may be a valuable tool to address acute and long COVID. It is also worthwhile noting research involving audiovisual entrainment, where lights and sounds are used to stimulate the brain at particular frequencies, has been used to awaken comatose individuals and address a range of cognitive and psychological disorders (Budzynski et al., 2009; Evans, 2007). These interventions may be a useful inclusion amongst heart rate variability, neurofeedback, and other integrative health therapies to address long-COVID symptoms, but remain experimental interventions in the context of COVID-19 rehabilitation.

## Conclusion

COVID-19 can cause significant damage to the nervous system through direct and nondirect mechanisms (Bodro et al., 2021; Panariello et al., 2020), which can cause devastating acute (Abdo et al., 2021; Liotta et al., 2020; Llitjos et al., 2020) and long-lasting (Australian Institute of Health and Welfare, 2021; Hampshire et al., 2021; Rajkumar, 2020) psychological impacts. Current estimates suggest between 7,763,200 and 38,816,003 people worldwide may have cognitive difficulties and impacts to their nervous systems as a result of COVID-19. These impacts upon the nervous system can be detected with the EEG (Flamand et al., 2020; Kopańska et al., 2021; Vellieux et al., 2020). By comparing individual symptoms and EEG patterns it may be possible to determine the mechanisms by which the virus has impacted the nervous system and consequentially guide therapeutic intervention. Due to its ability to train the nervous system directly (Hammond, 2011; Sitaram et al., 2017) and target many structures impacted by COVID-19 (Zubair et al., 2020), neurofeedback may offer important therapeutic opportunities to address the psychological impacts of the virus. Given the wide range of psychological disorders neurofeedback can address (Niv, 2013; Omejc et al., 2019; Ros et al., 2014; Yucha & Montgomery, 2008) and the shared mechanisms underpinning many symptoms (Simkin et al., 2014) common to psychological disorders and COVID-19, there are strong grounds to include neurofeedback alongside other interventions to address the psychological impacts of the disease. An integrative approach to addressing psychological impacts of the COVID-19 should also consider heart rate variability biofeedback (Lehrer et al., 2014; Shaffer et al., 2014), low-level-light therapy (Hamblin, 2016, 2019; Naeser et al., 2018) and audiovisual entrainment (Budzynski et al., 2009; Evans, 2007), which also address many underlying processes, such as inflammation, associated with Long-COVID (Bodro et al., 2021). However, despite the support for the use of neurofeedback, heart rate variability biofeedback, photobiomodulation and other forms of neuromodulation in conditions similar to those seen with COVID-19 related presentations, and anecdotal clinical reports of their usefulness in addressing Long-COVID symptoms, there is yet to be research published on the use of these interventions with this client population. Clinicians and researchers should be cautious using the suggested forms of neuromodulation for COVID-19 rehabilitation, which should be considered experimental until further research supports their efficacy. In providing face-to-face services, clinicians should be aware of the risks and take appropriate preventative steps to reduce the risk of harm to themselves and their clients.

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