INVITED EDITORIAL

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LEADING TOPIC

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# Electrophysiological and neuroimaging tools to evaluate neurological symptoms, manifestations, and complications in patients with long COVID-19

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According to the latest literature, the SARS-CoV-2 virus is not confined to the respiratory tract, and can affect both the central (CNS) and the peripheral (PNS) nervous systems, leading to neurological symptoms, manifestations and complications after acute infection [1]. Systemic hematogenous or retrograde neuronal spreads are the main mechanisms contributing to short- and long-term neurological impairments after SARS-CoV-2 infection [2–4].

The main neurological symptoms include taste and olfactory dysfunction, myalgia, headache, altered mental status, confusion, delirium, and dizziness, which may present separately. Moreover, neurological manifestations and complications such as stroke, cerebral venous thrombosis, seizures, meningoencephalitis, Guillain–Barré syndrome, Miller Fisher syndrome, acute myelitis, and posterior reversible encephalopathy syndrome (PRES) have also been observed [5].

Clinical and structured assessments are critical to identify neurological impairments after COVID-19; however, several non-invasive neuroimaging techniques can be used to confirm findings on neurological examination, facilitate diagnosis, understand prognosis, and assist in long-term rehabilitation. Non-invasive brain imaging techniques can be classified into structure-based [e.g. computer tomography and magnetic resonance imaging (MRI)], metabolic-based (functional magnetic resonance imaging — fMRI, near-infrared spectroscopy — NIRS, etc.), and electrophysiological-based (mainly electro- and magneto-encephalography).

Structural and metabolic techniques are classically considered as having a very good spatial 'resolution' but a rather poor temporal one, while electrophysiological techniques are seen as having an excellent temporal resolution but a poor spatial one [6].

Among the neuroimaging techniques with high temporal resolution, electroencephalography (EEG) is mainly used in the evaluation of patients after COVID-19. EEG abnormalities are common in patients with COVID-19 and can be correlated with disease severity and pre-existing neurological conditions [7]. EEG studies focus on both cortical excitability (i.e. a qualitative study), and brain electrical activity patterns and their interference in cognitive behaviour (i.e. a quantitative study). Qualitative EEG studies have found frontal sharp waves in nearly all patients with COVID-19 who presented epileptiform discharges [8], bifrontal monomorphic diphasic periodic delta slow waves [9], diffuse background slowing, focal slowing, and frontal intermittent rhythmic delta activity (FIRDA) [10]. In addition, Gogia et al. [11] found that 50% of deceased patients had generalised diffuse severe slowing, indicating a global process. EEG abnormalities have been frequently observed in the frontal region and may serve as potential biomarkers of COVID-19 encephalopathy [7].

Concerning quantitative EEG studies, Cecchetti et al. [12] showed that patients with COVID-19 were characterised by a lower individual alpha frequency (power spectrum) compared to healthy subjects, and patients who showed stronger connectivity in the delta band at baseline concomitantly had better cognitive performance. Some authors have reported brainstem damage after COVID-19, mainly in the reticular activation system and cortical cholinergic projections, which have been previously related to changes in the tonic alpha rhythm in a healthy brain [13–16]. In addition, delta oscillations, especially in the anterior regions of the brain, have been associated with better performance on attention shifting and working memory tasks [17]. Based on nonlinear EEG features, Appelt et al. [18] observed a reduction in brain activity at rest

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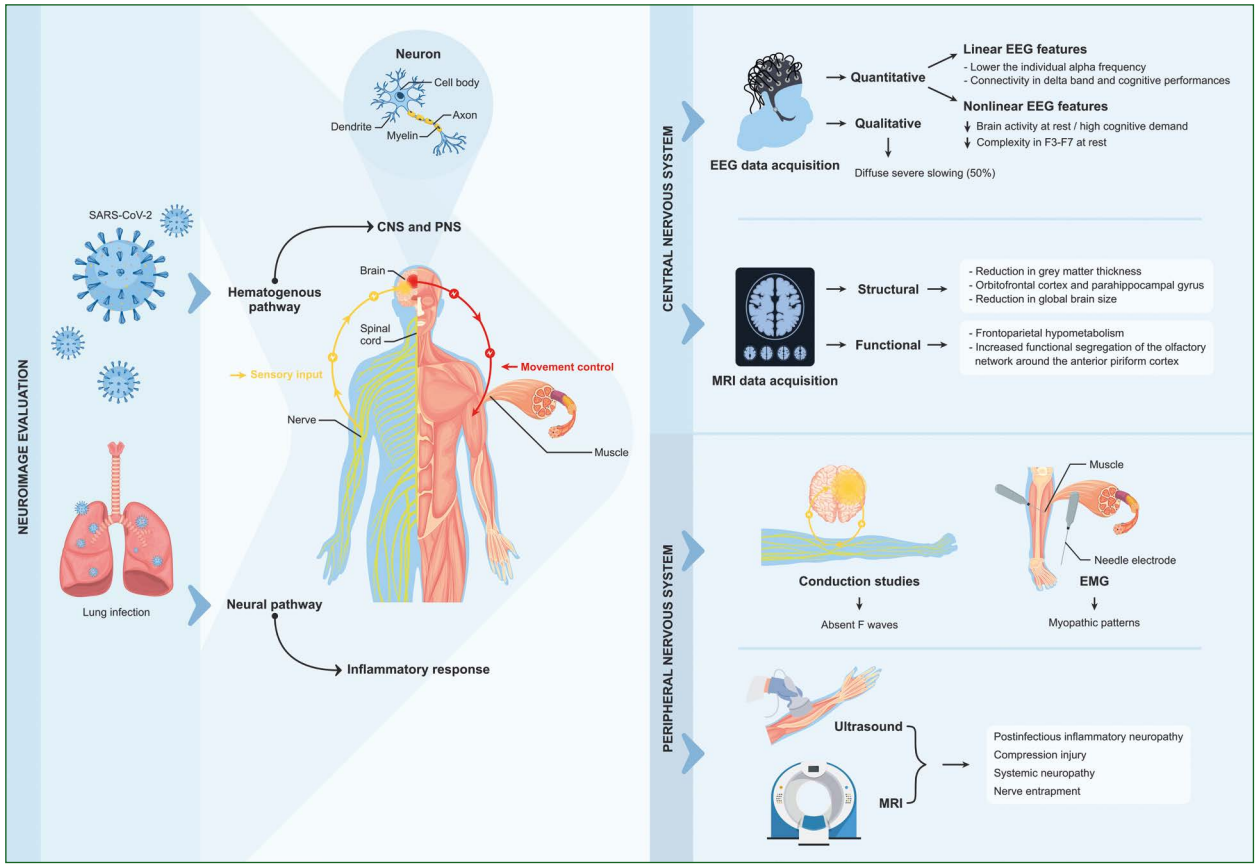


**Figure 1.** Mechanisms of CNS and PNS infection by SARS-CoV-2, and main neuroimaging tools used for evaluation

in the F2–F4 areas and during high cognitive demands in the F3–F7 areas. In the COVID-19 group at 6–12 months after acute infection, a reduction in signal complexity was found in F3–F7 areas at rest. During the same period, cognitive function worsened, and correlations between nonlinear EEG features and cognitive tests were also observed [18].

Structural and functional brain images have also been used in several studies to understand the impact of SARS-CoV-2 infection on the brain. At the structural level, images can be evaluated through visual or quantitative inspection (volumetry), and previous findings have revealed a lower cortical volume in the orbitofrontal, frontal, and cingulate regions of patients with COVID-19 compared to controls. In addition, cerebrospinal fluid analysis has shown that regional grey matter volume and thickness decrease were negatively associated with neuroinflammation [19]. Multimodal brain imaging data, obtained as part of the UK Biobank imaging study, showed three main changes in SARS-CoV-2 cases: (1) a greater reduction in grey matter thickness and tissue contrast in the orbitofrontal cortex and parahippocampal gyrus; (2) greater changes in markers of tissue damage in regions functionally connected to the primary olfactory cortex; and (3) a greater reduction in global brain size [20]. At the functional level, studies have shown frontoparietal hypometabolism based on 18F-fluoro-2-deoxy-D-glucose, positron emission tomography ($^{18}$FDG PET) analysis [21]. Esposito et al. [22] showed that an increased functional segregation of the olfactory network around the anterior piriform cortex node, besides calibrating the clinically observable olfactory impairment, might eventually trigger a counteracting reaction to a more widespread neurological involvement.

These findings support the idea that the PNS should be systematically evaluated after COVID-19, using electrophysiological and structural techniques. Patients with COVID-19 more frequently present absent F waves, which has been attributed to motor neuron hypoexcitability [23], and many authors have reported myopathic patterns on electromyography (EMG), suggesting a direct action of COVID-19 on muscular fibres [24, 25]. In addition, peripheral nerve injury can occur secondarily to post-infectious inflammatory neuropathy, prone positioning-related stretch and/or compression injury, systemic neuropathy, or nerve entrapment from haematoma. Considering these cases, structural imaging, such as high-spatial-resolution MRI of peripheral nerves and high-spatial-resolution ultrasound, can be an excellent diagnostic tool [26].

A summary of the mechanisms of CNS and PNS infection by SARS-CoV-2, as well as the main neuroimaging tools used for evaluation, are described in Figure 1. It must be underlined that clinical and neurological assessments are essential at any stage of COVID-19, and that neuroimaging is a complementary set of techniques with the aim of understanding

the clinical evolution and prognosis of patients, in addition to providing readouts that may serve as potential biomarkers for neurodegenerative diseases occurring after COVID-19.

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