Lower temporal and parietal rCBF were significantly associated with lower parieto-occipital alpha activity, while presence of leukoaraiosis was significantly associated with lower relative beta activity and higher absolute delta and theta activity (Claus et al., 2000). The preclinical finding that beta activity is found in subcortical or lower cortical structures [51–53] may either suggest that neuronal function of these brain structures is compromised by the presence of leukoaraiosis or that leukoaraiosis results in disconnection of subcortical and cortical structures. Thus, the results suggest that leukoaraiosis in AD patients is related to slowing of the EEG, evidenced mainly by increase of theta and loss of beta activity (Claus et al., 2000).

Topographic analyses of the resting EEG showed a significant increase in delta band power at the frontal regions. This finding is consistent with that of previous EEG studies both with visual inspection (Liddell 1958; Swain 1959) and with significant probability mapping (Miyauchi et al 1989, 1994), in which delta activity was observed predominantly at the frontal areas (Wada, Nanbu, Jiang, Koshino, Yamaguchi & Hashimoto, 1997).

The generalized slowing of the neocortical EEG is a characteristic symptom in AD and refers to a reduction in desynchronized, activated EEG patterns that are replaced by deactivated, synchronized activity (Dringenberg, 2000).

What is the physiological significance of the changes observed in the spectral power of delta, theta, alpha, and beta rhythms in individuals with SCD? The alterations in the high and low components of the delta rhythms, indicative of a healthy brain, are thought to be influenced by inhibiting oscillators within the reticulo-thalamic (7–14 Hz), thalamo-cortical (1–4 Hz), and intracortical (<1 Hz) neural circuits (Steriade, 2006). Moreover, it has been proposed that thalamo-cortical circuits play a role in the generation and modulation of theta rhythms. Thus, it is plausible to hypothesize that diminished activation of neurons, possibly due to acetylcholine reduction or synaptic damage, can impact inhibitory and excitatory cortical feedback interactions that are crucial for generating cortical rsEEG rhythms. This disruption may influence the regulation of overall brain arousal, the balance of cortical inhibition/excitation, and vigilance, potentially resulting in a decrease in spectral power across the delta and theta bands.

Beta rhythms may be associated with the regulation of thalamocortical flow, encompassing commands, images, and motor plans through the basal ganglia and motor thalamus (Oswal et al., 2013). As mentioned previously, Iliadou et al. (2021) found distinct alpha and beta rhythm patterns from those found in other studies reviewed. These authors suggested that the psychophysiological changes observed in the SCD in their study may reflect an initial compensatory process in response to early cognitive impairment. from Perez, Duque, Hidalgo & Salvador, 2024.

Ortelli et al., 2023:

Introduction: Cognitive impairment is very often associated with fatigue, associated with a plethora of symptoms that could be interpreted as “brain fog”. No “universally accepted” definition of “brain fog” has yet been established [[4](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B4-biomedicines-11-02228)]. In PCS patients (PCS-pts), previous studies reported specific deficits in sustained and selective attention, abstraction, inhibition, set shifting, learning and long-term memory [[3](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B3-biomedicines-11-02228),[5](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B5-biomedicines-11-02228),[6](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B6-biomedicines-11-02228)]. Part of these deficits may be related to intrinsic aspects of fatigue; in fact, lack of energy, muscle weakness, as well as global slowing in reaction times, could ultimately impact executive functions [[3](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B3-biomedicines-11-02228),[7](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B7-biomedicines-11-02228),[8](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B8-biomedicines-11-02228),[9](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B9-biomedicines-11-02228)].

Currently, the neural basis underlying cognitive deficits and fatigue in PCS is not yet fully understood. Previous studies have indicated that the neural basis of cognitive impairment and fatigue in PCS may involve a combination of factors, including neuroinflammation, immune system dysfunctions and dysregulation of the autonomic nervous system [[10](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B10-biomedicines-11-02228),[11](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B11-biomedicines-11-02228),[12](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B12-biomedicines-11-02228)]. Neuroinflammation, triggered by the binding of the SARS-CoV-2 virus to angiotensin-converting enzyme 2 (ACE2) receptors in the brain, leads to a cytokine storm and activation of microglia, astrocytes and oligodendrocytes. This inflammatory response can result in a reduction in myelinated axons, impairment of hippocampal neurogenesis and overall disruption of neural circuit functions, thereby contributing to cognitive impairment.

It is known that an imbalance between pro-inflammatory and anti-inflammatory factors could represent a possible basis for understanding the pathophysiology of cognitive impairment, together with alterations in brain activity, in several chronic diseases (as has been demonstrated, for example, in migraine and neuropathic pain). Therefore, it is conceivable that chronic inflammation in PCS-pts “stresses” the neuronal activities, leading in turn to brain network dysfunctions and cognitive impairment [[19](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B19-biomedicines-11-02228)]. Additionally, functional abnormalities have been observed in various brain regions, including the frontal lobe structures, olfactory cortices, limbic system and prefrontal cortex [[13](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B13-biomedicines-11-02228),[14](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B14-biomedicines-11-02228),[15](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B15-biomedicines-11-02228),[16](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B16-biomedicines-11-02228),[17](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B17-biomedicines-11-02228),[18](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B18-biomedicines-11-02228)]. These regions are known to be involved in attention, memory, executive functions and emotional processing.

Electroencephalography (EEG) studies have also provided insights into the neurophysiological impact of SARS-CoV-2 infection, revealing changes in brain electrical activity that correlate with cognitive deficits in PCS patients [[17](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B17-biomedicines-11-02228),[20](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B20-biomedicines-11-02228),[21](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B21-biomedicines-11-02228),[22](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B22-biomedicines-11-02228),[23](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B23-biomedicines-11-02228),[24](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B24-biomedicines-11-02228),[25](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B25-biomedicines-11-02228)].

Investigating the neural substrates of cognitive deficits and fatigue in PCS patients can provide valuable insights into the pathophysiology of this condition and open the way to the development of targeted interventions for affected individuals. The EEG patterns of PCS-pts were evaluated with different types of analyses, from common power spectrum and event-related potentials (ERPs) [[17](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B17-biomedicines-11-02228),[20](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B20-biomedicines-11-02228),[22](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B22-biomedicines-11-02228)] to more complex brain dynamic analyses, such as intrinsic mode functions (IMFs) and avalanche analysis [[21](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B21-biomedicines-11-02228),[23](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B23-biomedicines-11-02228)].

Results: The statistical analysis of current source density revealed significant differences between PCS-pts and HCs in the delta frequency band (mean CSDs: PCS-pts: 1.18, HCs: 5.86; 142 voxels), with PCS-pts exhibiting reduced activity compared to HCs (log-F-ratio threshold = −2.156, p-corrected = 0.0006, one-tailed). No other significant differences in source localization were found between PCS-pts and HCs. In PCS-pts, reduced delta activity was distributed bilaterally over the frontal–parietal lobe and in the left temporal lobe, with the postcentral gyrus showing the highest current density difference.

In the present study, we demonstrated changes in brain source activity at rest in PCS-pts complaining of cognitive deficits and fatigue In line with previous studies, we found that executive functions, memory and language were defective in PCS-pts as compared to HCs [[3](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B3-biomedicines-11-02228),[5](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B5-biomedicines-11-02228),[6](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B6-biomedicines-11-02228),[7](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B7-biomedicines-11-02228),[9](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B9-biomedicines-11-02228)]. Interestingly, the global cognitive score was normal [[27](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B27-biomedicines-11-02228)], thus implying that, overall, PCS-pts did not have clinical, significant cognitive impairment. Lower performance in cognitive tasks, especially in those evaluating executive function, was associated with brain activity changes in PCS patients, both in classical EEG analyses (power spectra and ERPs.

Moreover, Appelt and colleagues [[23](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B23-biomedicines-11-02228)] found an abnormal modulation of EEG activity in PCS-pts during the Trail Making Tests (TMT), associated with an increase in the time of execution. In particular, they found EEG changes over frontal regions, which are involved in executive function.

Indeed, we found a reduction in brain source activity at rest in the frontal, parietal and temporal brain regions when PCS-pts were compared to HCs. Of note, the main finding of our study is the reduction in brain source activity for the delta band (0.5–3.5), distributed bilaterally in the frontal–parietal lobe, and in the left temporal lobe, with the postcentral gyrus having the highest current density difference.

Similarly, Kopanska and colleagues [[20](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B20-biomedicines-11-02228)] found a decrease in delta activity in the left hemisphere of PCS-pts compared to pre-COVID EEG activity in the same subjects. On the other hand, Cecchetti and colleagues [[17](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B17-biomedicines-11-02228)] found lowered delta activity at baseline (2 months after acute infection) in PCS-pts, related to a lower performance in executive function tasks (i.e., TMT and FAB), predicting worse cognitive performances at follow-up (10 months). Coherently, among all cognitive processes related to delta oscillations (e.g., spatial navigation), it has been suggested that delta activity in the anterior regions of the brain, especially in the frontal cortex, may be related to the inhibition of interferences during attentional shifting tasks. Thus, fine tuning of delta activity in the frontoparietal network is essential to reach better performance in attentional cognitive tasks [[33](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B33-biomedicines-11-02228)]. Higher GABA concentration in frontal cortex was associated with more efficient suppression of distractors [[34](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B34-biomedicines-11-02228)]. In line with these findings, in the elderly, higher GABA concentration in the frontal regions has been associated with better cognitive performance on the MoCA [[35](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B35-biomedicines-11-02228)]. We do not have direct evidence of a link between reduced delta activity and GABAergic dysfunction. Nevertheless, recently, a transcranial magnetic stimulation (TMS) study in PCS-pts complaining of fatigue found a link between impairment in executive function and GABAergic inhibition [[36](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B36-biomedicines-11-02228)]. Specifically, PSC patients showed an alteration of short- and long-interval intracortical inhibition (SICI and LICI), which may reflect a reduction in intracortical GABAergic activity in the primary motor cortex (M1). These neurophysiological findings highlight the presence of central motor and cognitive fatigue associated with GABAergic circuit dysfunction in PSC-pts [[7](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B7-biomedicines-11-02228),[8](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B8-biomedicines-11-02228),[9](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B9-biomedicines-11-02228),[36](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B36-biomedicines-11-02228)]. GABAergic neurons are known to have a high expression of ACE2 receptors [[37](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B37-biomedicines-11-02228),[38](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B38-biomedicines-11-02228)], known to be SARS-CoV-2 targets [[12](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B12-biomedicines-11-02228),[39](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B39-biomedicines-11-02228)]. Therefore, in PCS-pts, the neuroinflammation may induce central GABAergic impairment, representing a common denominator for motor and cognitive fatigue and executive deficits.

Taken together, these results support the hypothesis that a dysfunction in the GABAergic system is involved in the pathophysiology of “brain fog” in PCS-pts [[7](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B7-biomedicines-11-02228),[8](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B8-biomedicines-11-02228),[9](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B9-biomedicines-11-02228),[36](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B36-biomedicines-11-02228)]. In this study, “brain fog” was investigated by both FSS and PDCS. To our knowledge, this is the first study that investigated the relationship between EEG features and an objective measure of perceived cognitive difficulties. Intriguingly, PDCS scores were negatively correlated with delta source power. As previously explained, a reduction in delta activity has been associated with executive attentional deficits [[34](https://pmc.ncbi.nlm.nih.gov/articles/PMC10452696/#B34-biomedicines-11-02228)].

In conclusion, mild PCS-pts could manifest specific neuropsychological and neurophysiological features. They show objective, although subclinical, reductions in cognitive performance and higher fatigability as compared to HCs. These patients, at the same time, showed a reduction in delta source power. This finding is very intriguing. We hypothesize that PCS-pts, complaining of cognitive deficits, do not have a cognitive dysfunction so defective as to lead to clinical impairment. Nevertheless, these alterations affect their cognition. In line with these observations, the reduction in delta source activity at rest in PCS patients was found bilaterally in the frontal–parietal lobe network, and in the left temporal lobe; these are brain regions involved in the central executive network (CEN), default mode network (DMN), salience network (SN) and sensorimotor network (SMN).

Ortelli et al., 2021:

Based on neuropsychological data, post-COVID-19 patients presented with [cognitive deficits](https://www.sciencedirect.com/topics/neuroscience/cognitive-disorders), particularly in the executive domain, in comparison with HC. MoCA scores were on average borderline compared to the Italian normative data cut-off [[26](https://www.sciencedirect.com/science/article/pii/S0022510X20306079" \l "bb0130)], but they were lower than in the control group, concurring with a reduction in global cognition following COVID-19 with respect to HC. Moreover, three post-COVID-19 patients developed such a severe cognitive impairment that they were unable to participate in the computerized tests. In line with previous data [[67](https://www.sciencedirect.com/science/article/pii/S0022510X20306079" \l "bb0335)], the abnormally low FAB scores we found in more than half of our post-COVID-19 patients clearly demonstrate evidence of a [dysexecutive syndrome](https://www.sciencedirect.com/topics/medicine-and-dentistry/dysexecutive-syndrome). The neuropsychological pattern we found, which is characterized by both [dysexecutive syndrome](https://www.sciencedirect.com/topics/neuroscience/dysexecutive-syndrome) and dysregulation of certain emotional-motivational aspects, often anticipates the development of dementia in patients suffering from neuroinflammatory and [neurodegenerative diseases](https://www.sciencedirect.com/topics/medicine-and-dentistry/degenerative-disease) [[68](https://www.sciencedirect.com/science/article/pii/S0022510X20306079" \l "bb0340),[69](https://www.sciencedirect.com/science/article/pii/S0022510X20306079" \l "bb0345)].

In our sample of patients, the reduced activity of intracortical GABAergic circuits, reflected in post-exercise shortening of SP, was previously demonstrated by means of paired-pulse TMS techniques (data submitted). Patients presented, as compared to HC, markedly reduced short-interval intracortical inhibition (SICI), and disruption of long-interval intracortical inhibition (LICI) assessed in the FDI at rest. SICI is thought to represent GABAA-receptor-mediated fast inhibitory post-synaptic potentials (IPSPs) in corticospinal neurons [[81](https://www.sciencedirect.com/science/article/pii/S0022510X20306079" \l "bb0405)] and LICI is considered to be dependent on slow IPSPs mediated through GABAB-receptors [[81](https://www.sciencedirect.com/science/article/pii/S0022510X20306079#bb0405)]. Moreover, short-latency afferent inhibition (SAI) was slightly diminished in these patients. SAI evaluates [motor cortex](https://www.sciencedirect.com/topics/medicine-and-dentistry/motor-cortex) inhibition induced by sensory afferents (through inhibitory connections from the primary somatosensory cortex to M1). SAI is modulated by excitatory cholinergic thalamocortical projections to the inhibitory GABAergic network in M1 and is reduced by muscarinic and GABAA [agonist](https://www.sciencedirect.com/topics/neuroscience/agonist) administration [[81](https://www.sciencedirect.com/science/article/pii/S0022510X20306079#bb0405)]. SAI was decreased during repetitive non-fatiguing movements inducing MEP depression [[82](https://www.sciencedirect.com/science/article/pii/S0022510X20306079" \l "bb0410)] and was significantly activated during cognitive tasks [[83](https://www.sciencedirect.com/science/article/pii/S0022510X20306079" \l "bb0415)]. Taken together, these findings point out to a general reduction of cortical GABAergic and - to a lesser extent - [cholinergic activity](https://www.sciencedirect.com/topics/neuroscience/cholinergic-activity) in COVID-19 patients. This could underlie both the reduced cognition and the abnormal fatigue perception and could represent one of the possible mechanisms of COVID-19-related [neurotoxicity](https://www.sciencedirect.com/topics/neuroscience/neurotoxicity).

Previous studies from animal models suggest that IL-6 hyperinflammatory-induced state may decrease the density of functional [GABA receptors](https://www.sciencedirect.com/topics/neuroscience/gaba-receptor) and shifts the balance between [synaptic inhibition](https://www.sciencedirect.com/topics/medicine-and-dentistry/synaptic-inhibition) and excitation [[84](https://www.sciencedirect.com/science/article/pii/S0022510X20306079" \l "bb0420)]. This imbalance could be responsible for alterations of neurophysiological responses [[85](https://www.sciencedirect.com/science/article/pii/S0022510X20306079" \l "bb0425)] and for the misprocessing of information that largely regulate emotionally salient information and cognitive functions [[86](https://www.sciencedirect.com/science/article/pii/S0022510X20306079" \l "bb0430),[87](https://www.sciencedirect.com/science/article/pii/S0022510X20306079" \l "bb0435)]. [Neuroinflammation](https://www.sciencedirect.com/topics/medicine-and-dentistry/neuroinflammation) may induce central GABAergic impairment, representing a common denominator for neuromotor and cognitive fatigue, executive deficits, and apathy in post-COVID-19 patients.

Northoff & Sibille, 2014:

Molecular studies in MDD demonstrate changes in specific GABA interneurons, namely

SST-positive and to a lesser extent PV-positive neurons, affecting the regulation of input/

output of excitatory signals from and onto pyramidal neurons. We here hypothesize that

such dysbalance at the local cell circuit affects the processing of information as it transits

through cortical layers, translating, through multiple steps described here, to a dysbalance

between the PACC and DLPFC as core regions of the DMN and executive network, and in

turn leading to a dysbalance between internal and external mental contents in awareness in

MDD as clinically observed.

Ferrucci et al., 2023:

his examination showed significant Aβ deposition in the superior and middle frontal cortex, and in the posterior cingulate cortex extending mildly in the rostral and caudal anterior cingulate areas. Although some other reports have already suggested that brain hypometabolism may be

associated with cognitive impairment at shorter intervals from SarsCov-2 infection, our study is the first to assess cognitive functions, brain metabolic activity and in a patient also amyloid PET one year after COVID-19, demonstrating that cerebral effects of COVID-19 can largely outlast the acute phase of the disease and even be followed by amyloid deposition. Given growing consensus that MDD patients have a decrease in GABA levels in the brain and the revolutionary discovery that NMDA receptors antagonists.

Neuropsychological assessment: At T1, 6/7 patients (86%) showed main impairment in verbal

memory, processing speed, and visual attention; 5/7 patients (71%) showed impairment in visuospatial learning and 4/7 (57%) delayed visuospatial recall. At T2, patients’ visuospatial learning had completely recovered, but 5/7 still presented verbal memory deficits (71%, 3 with stable profile, 1 worsened and 1 improved), 4/7 patients still exhibited processing and visual attention

deficits (57%, all improved), 2/7 still had attention deficits (28%, both worsened), and 3/7 patients still had visual-spatial memory deficits (43%, 2 with a stable profile, 1 worsened).

Our findings confirm that cognitive abnormalities can detect 12 months after patients have COVID-19 and in many cases (42.8% in our sample) these are associated with abnormal brain metabolism. Brain hypometabolism patterns differed, and selectively involved the left temporal mesial area, pontine area, and bilaterally the prefrontal and parietal areas.

Our results suggest that, in addition to cognitive changes, SarsCov-2 infection can also induce abnormalities in brain metabolism and possibly amyloid deposition that persists

one year after infection.

Neurological sequelae, including the cognitive impairment leading to Alzheimer’s disease might in the future be a major feature complicating COVID-19. Further studies need to explain the pathophysiological mechanisms underlying the long-term neurological consequences of SarsCov-2 infection and its possible correlation with amyloid-related cognitive impairment.

Monje & Iwasaki, 2022:

We highlight a number of possible underlying disease mechanisms that could contribute to CNS dysfunction, including neuroinflammatory effects of distal inflammation, autoimmunity, direct CNS infection, herpesvirus reactivation, neurovascular disease, and hypoxia. What accounts for the persistent nature of cognitive dysfunction in neuro-COVID remains to be fully elucidated. Continuing neuroinflammation could reflect a lasting state change in CNS immune and glial cells that perpetuates neural pathophysiology, ongoing endotheliopathy with microvascular disruption and blood-brain-barrier breakdown, autoimmunity, response to ongoing peripheral inflammation.

Hugon, Msika, Queneau, Farid & Paquet, 2021:

In brain fog and cognitive deficits. Previous experimental and clinical studies have shown that the anterior and posterior cingulate cortex are implicated in emotions, memory, depression, and decision of action [7, 7]. The anterior cingulate cortex receives inputs from the orbitofrontal cortex in the outcome rewards. The posterior cingulate cortex has outcomes towards the hippocampus. These deficient brain connections could explain the cognitive signs observed in these patients and characterized by episodic memory deficits and abnormal executive and attentional functions. Hypometabolisms of the cingulate cortex have been observed in several neurological and psychiatric diseases including mild cognitive impairment due to Alzheimer’s disease, severe depression and internet gaming disorder [1, 3, 6, 10].

Cecchetti et al., 2022:

However, up to date only few studies have explored cognitive involvement through structured neuropsychological assessments. Concerning brain alterations, a recent British MRI study of 394 patients with available scans before and after COVID-19 revealed a loss of grey matter (GM) in limbic cortical areas directly linked to the primary olfactory and gustatory systems, possible hallmark of the cerebral spread of the virus [16]. Since neuropathology excluded irreversible neocortical damage and highlighted a pronounced microglia activation within white matter (WM), cortical hypometabolism has been interpreted as a consequence of remote WM or brain-stem damage [17]. Moreover, in our previous EEG study on 18 acute COVID-19 patients, we suggested that EEG alterations might represent a useful tool to evaluate early cerebral involvement in COVID-19; a frequent finding in our cohort was an anterior prevalence of slow waves, correlating with metabolic and hypoxic alterations [18–20].

Considering the lack of longitudinal studies with long follow-up and with structured neuropsychological and EEG assessments, we aimed at exploring longitudinal cognitive and concomitant EEG features in a population of adult COVID-19 survivors up to 10 months after hospital discharge.

Neuropsychological assessments -> A battery of tests investigating the main cognitive domains (global cognition, executive functions, memory, visuospatial functions, language) was implemented. At each timepoint, the presence of cognitive impairment was defined by a performance lower than the normal values in at least two tests within the same domain.

Patients also showed a greater CSD at delta frequency band in bilateral frontal and central-temporal regions when compared to healthy controls.

In this study, we did not explore neuroinflammation, which has been previously demonstrated to play a certain role in the development, maintenance or recovery of cognitive and neuropsychiatric symptoms [8, 11]. Pathological cortical deafferentation, thus, does not entirely explain findings at delta band. We hypothesize that some sort of compensatory mechanisms might have been triggered in high-performing patients. Delta oscillations, especially in anterior regions of the brain, have been indeed related to a better performance in attention shifting and working memory tasks [49Harmoney]. Consistently, we observed a significant positive correlation of delta CSD with TMT and FAB, which investigate the same skills.

Yong, 2021: It is widely known that SARS-CoV-2 is a neurotropic virus with the capacity to infect and replicate in neuronal cell cultures, brain organoids, and murine brains.21−23. This is in line with the high rate of neuropsychiatric or neurological symptoms (e.g.,cognitive and mood impairments, headache, smell and taste alterations, fatigue, and myalgia) among cases of COVID-19 and other pathogenic human coronaviruses. 24−26 Even mild COVID-19 cases exhibit these neurological signs, indicating that brain involvement may occur in the early phase of COVID-19. 27. However, in other instances, brainstem neuropathology was observed despite the absence of SARS-CoV-2 RNA in brain autopsy of deceased COVID-19 patients. 38−40 This suggests that COVID-19 may induce brainstem damage through methods besides SARS-CoV-2 invasion, such as pathological immune or vascular activation. For example, leukocyte infiltration, activation of resident microglia and astrocytes, and microthrombosis have been observed in brain autopsies of COVID-19 victims, particularly at the brainstem. 37,39,41,42

Indeed, the brainstem is known to be highly vulnerable to acute and chronic damage from various sources, including inflammation, trauma, metabolic alterations, or vascular injury. 43 Taken together, SARS-CoV-2 may damage the brainstem through viral invasion, inflammation, and vascular activation44. Taken together, it can be hypothesized that brainstem dysfunction may be involved in the pathology of long-COVID.

Notably, long-COVID resembles and is closely associated with myalgic encephalomyelitis or chronic fatigue syndrome (ME/CFS), characterized by fatigue, myalgia, and cognitive and sleep impairments.115,116 Interestingly, brain imaging research has found that symptom severity of ME/CFS associates and correlates with brainstem dysfunction, particularly at the

RAS.11 7−12.

This review emphasized that the brainstem may be an overlooked aspect of long-COVID. In acute COVID-19, brainstem damage has been widely documented in autopsy studies. A few autopsy reports have even found SARS-CoV-2 genes and proteins in the brainstem, indicative of viral tropism and invasion. Indeed, the brainstem has a relatively high expression of ACE2 receptor, and possibly neuropilin-1, that SARS-CoV-2 exploits for cell infection. As neurological manifestations appear even in mild cases of COVID-19, the brainstem could be affected in the early disease phase. Since neurons rarely regenerate, the brainstem damage from COVID-19 may be long-lasting. Indeed, brainstem dysfunction has also been

implicated in other chronic disorders, such as chronic pain and migraine and ME/CFS. Therefore, it can be hypothesized that long-COVID may stem from persistent brainstem

dysfunction.

Versace et al., 2021: TMS study. The present findings provide neurophysiological evidence of

severe impairment of GABA-ergic intracortical circuits in patients

who recovered from COVID-19 with various central and peripheral

neurological manifestations and who presented fatigue and

impairment of executive functions. Compared to HS, post-COVID-19 patients exhibited reduced

inhibition within the M1 as evidenced by disruption of GABAA

mediated SICI, at ISI 2 ms and 3 ms, and of GABAB mediated LICI,

at ISI 50 ms and 100 ms.

Theoharides, Cholevas, Polyzoidis & Politis, 2021: Long‐COVID syndrome symptoms, especially brain fog, are similar to those experienced by patients undertaking or following chemotherapy for cancer (chemofog or chemobrain), as well in patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) or mast cell activation syndrome (MCAS). The pathogenesis of brain fog in these illnesses is presently unknown but may involve neuroinflammation via mast cells stimulated by pathogenic and stress stimuli to release mediators that activate microglia and lead to inflammation in the hypothalamus.

Perez et al., 2024:

However, findings for the alpha, delta, and beta bands were inconsistent, demonstrating variability across studies and highlighting the need for further research. Although the rsEEG of frequency bands emerges as a promising early biomarker, there is a noteworthy need to establish uniform standards and consistent measurement approaches in order to ensure the reliability and comparability of the results obtained in the research

Güntekin, Emek-Savaş, Kurt, Yener & Başar, 2013:

The role of beta oscillations upon cognitive stimulation is least studied in comparison to other frequency bands. The study included 17 consecutive patients with MCI. The experiments used a visual oddball paradigm. In MCI patients, there were no differences in evoked beta power between target and non-target stimuli. Furthermore, upon presentation of visual oddball paradigm, occipital electrodes depict higher beta response in comparison to other electrode sites. The increased beta response upon presentation of target stimuli in healthy subjects implies that beta oscillations could shift the system to an attention state, and had important function in cognitive activity. This may, in future, open the way to consider beta activity as an important operator in brain cognitive processes.

eta oscillatory responses are considered to be related to [sensorimotor functions](https://www.sciencedirect.com/topics/neuroscience/sensorimotor-function) ([Engel and Fries, 2010](https://www.sciencedirect.com/science/article/pii/S2213158213000909" \l "bb0045)), and were decreased by voluntary movement ([Pfurtscheller and Berghold, 1989](https://www.sciencedirect.com/science/article/pii/S2213158213000909" \l "bb0305), [Pfurtscheller et al., 1996](https://www.sciencedirect.com/science/article/pii/S2213158213000909" \l "bb0055)) and also by motor imagery ([Neuper et al., 2009](https://www.sciencedirect.com/science/article/pii/S2213158213000909" \l "bb0310)). [Traub et al. (1999)](https://www.sciencedirect.com/science/article/pii/S2213158213000909" \l "bb0315) showed that when the stimulation was intense the action potential burst depicts a transition from gamma frequency to beta frequency. [Traub et al. (1999)](https://www.sciencedirect.com/science/article/pii/S2213158213000909#bb0315), [Haenschel et al. (2000)](https://www.sciencedirect.com/science/article/pii/S2213158213000909" \l "bb0320), [Kisley and Cornwell (2006)](https://www.sciencedirect.com/science/article/pii/S2213158213000909" \l "bb0325) concluded that beta band activity is closely related to stimulus-driven salience. [Leventhal et al. (2012)](https://www.sciencedirect.com/science/article/pii/S2213158213000909" \l "bb0330) suggested that beta oscillations reflect a post-decision stabilized state of cortical–basal ganglia networks, which normally reduces interference from alternative potential actions.

Illiadou, et al., 2021: During resting state condition, the MCI group showed increased delta band power compared to the SCD group.

Theta and delta band powers tended to increase in selected scalp regions as cognitive impairment progressed, whereas alpha and beta 2 band powers showed a decreasing tendency. Differences in spectral power among subjects were most prominent for the theta band, followed by the beta 2 and alpha bands.

Spectral power differences in the delta band were less prominent. Theta, alpha, and beta 2 powers were found to be significantly correlated with memory function

The lack of correlation between delta frequency and neuropsychological test results may be due to the mild disease status of the AD patients recruited in this study. Previous QEEG studies that used cognitive tasks revealed an increase in alpha and beta bands with memory performance, including registration, recall, and recognition (; Palva and Palva, 2007).

Palva & Palva, 2007: We propose that simultaneous α-, β- (14–30Hz) and γ- (30–70Hz) frequency band oscillations are required for unified cognitive operations, and hypothesize that cross-frequency phase synchrony between α, β and γ oscillations coordinates the selection and maintenance of neuronal object representations during working memory, perception and consciousness.

D’Rozario et al., 2020: Findings show that compared to healthy controls, those with MCI have pronounced changes in sleep macro-architecture with greater wake after sleep onset, reduced total [sleep time](https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/sleep-time), lower sleep efficiency, longer [sleep onset latency](https://www.sciencedirect.com/topics/medicine-and-dentistry/sleep-onset-latency), longer [rapid eye movement sleep](https://www.sciencedirect.com/topics/neuroscience/rapid-eye-movement-sleep) (REM) latency, reduced REM sleep, greater N1 sleep, and worse severity of [hypoxemia](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/hypoxemia)

Gennaro et al., 2007: Sleep deviation, rsEEG after sleep deviration. Increase in delta power.

Corsi-Cebrera et al., 1992: Study in sleep deprivation. Beta higher after sleep deprovation than after normal sleep. rel and abs power

Gorgoni et al., 2014: Sleep deviation, higher level of subjective sleepiness and increase of delta and beta EEG activity.

Wang et al., 2025: Studies on EEG in patients with axiety few and scattered. Significantly increased beta band activity (power spectrum). Suggested that increased power of beta rhythm is related to high levels of anxiety in healthy participants and patients with social anxiety.

How ever symptoms. These studies indicated increased beta-band activity in patients with anxiety

disorders or healthy participants experiencing an induced anxiety state. Suggest abnormal hyperarousal of brain alertness.

Li et al., 2020: Fatigue, no significant difference/changes in delta power.

Jap, Lal, Fischer & Bekiaris, 2009: fatigue. Stable delta activity over time. Significant decrease of beta activity.

(Newson & Thiagarajan, 2019):In a reviwe of restung state frequency bands in psychiatric disorders. Aggregating across all reported results we demonstrate that characteristic patterns

of power change within specific frequency bands are not necessarily unique to any

one disorder but show substantial overlap across disorders as well as variability

within disorder. Increase in absolute delta power in depression. Depression: 8 studies were identified for the review. Dominant result was increase in the absolute beta power. However, these increases were no longer visible when considering relative power, where most studies failed to find any significant differences across any band. To few studies on anxiety for the inference of any trends or for calculation of consistency scores.

Sibilano et al., 2023

A deep learning approach

While MCI refers to a well-defined, intermediate stage between normal ageing and pathological status [9], many patients experience a subjective cognitive decline (SCD) in memory and other cognitive domains prior to demonstrable impairment.

SCD is not linked to a particular disease status itself [10]. However, it has been proved that the subjective decline, even at the stage of normal cognitive performance on mental tests, is associated with an increased risk of positive biomarkers for Alzheimer’s and later conversion to dementia [11–14]

Since EEG signals reflect functional changes in the cerebral cortex, EEG-based biomarkers can be used to assess neuronal degeneration caused by AD progression long before actual tissue loss or behavioral symptoms appear.

On the same band, the model reached good sensitivity and specificity values, respectively of 73.3% and 78.6%, showing it is capable of discriminating SCD and MCI subjects when

they have that specific condition.

Indeed, changes in relative power in the lower frequencies (δ and θ) indicate a diffuse slowing of brain oscillations, which is a hallmark feature in the progression of AD [33].

In this context, EEG spectral analysis revealed that higher delta and theta powers are associated with clinical progression of SCD patients towards MCI and dementia, mainly when considering EC resting-state activity.

Our results uphold this evidence, showing that changes in delta are particularly useful in characterizing the brain activity of subjects affected by SCD or MCI, both when compared to other common EEG rhythms and to the all-band dataset.

“Brain fog” furlanis et al., 2022

central nervous system (CNS)

For individuals with PCS, understanding whether their subjective cognitive difficulties or fatigue could be linked to biological or neurological alterations could be valuable. However, identifying these links is not trivial. Finding group differences in these frequencies can be at least an indicator for somewhat abnormal functioning of the brain. Some studies seek to use the EEG for discovering so called biomarkers, hoping they will facilitate diagnosing, monitoring and treatment of the respective disease. In differential diagnoses, for example, the location and frequency of restingstate oscillations could distinguish patients with Parkinson’s dementia from those with Alzheimer’s (Babiloni et al., 2011).

In the PCS context, it would be for example interesting to evaluate, whether the EEG patterns of Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) that has symptoms similar to PCS (Wong andWeitzer, 2021) align with the EEG patterns of PCS. One study tried this already, comparing Fybromyalgia, ME/CFS, and PCS, but came to the conclusion that for PCS the evidence is still too scarce (Silva-Passadouro et al., 2024). Therefore, one value of this studies lies in adding to the number of EEG studies in PCS. While EEG literature in PCS might be scarce, EEG literature in general is plentiful. Here, it could be insightful to draw on results from EEG studies that investigate similar symptoms, such as cognitive impairment and fatigue.

The complexity of cognitive and emotional disturbances following SARS-CoV-2 infection cannot be fully captured by diagnostic labels such as "Post-COVID Syndrome." A symptom-centered approach is crucial for uncovering the **individual differences** in neural functioning that may underlie persistent complaints like “brain fog,” attention difficulties, or fatigue. **Resting-state EEG**, particularly in the **delta and beta frequency bands**, provides a non-invasive window into the brain's functional status at rest, offering insights into how symptom profiles may correspond to **neural activation patterns**

**Literature**

Birle et al., 2020

Bland et al., 2024

Cambridge Cognition, 2015

Ceban et al., 2022

Eysenck & Brysbaert, 2018

Kwan et al., 2024

Liu, Wang, Xin, Jiang & Meng, 2024

Pais, Ruano, Carvalho & Barros, 2020

Schild, Scharfenberg, Kirchner et al., 2023).

WHO, 2021

Davids et al., 2021

Therefore subjective cognitive complains need to be taken seriously

[Gomzyakova](https://pubmed.ncbi.nlm.nih.gov/?term=%22Gomzyakova%20N%22%5BAuthor%5D): Cognitive impairment is one of the main factors that disrupt daily social functioning and quality of life.

Blackmon et al. (2022): emphasize the importance of assessing both subjective and objective complaints in determining prevalence of cognitive impairment in recovering patients and research participants.

Therefore, identifying early and reliable biomarkers for the detection of SCD is crucial for maintaining cognitive health and delay or prevent its progression to AD (Abdulrab & Heun, 2008).

There is agreement that subjective impairments should be taken seriously, and that changes in experience and behavior not apparent to the clinician should be examined, evaluated, and documented.

. EEG studies can play a role in identifying

abnormal brain signals and linking them to changes in behavior and perception.

Discussion: Cecchetti: n alternative explanation for mental disorders after

COVID-19, and in particular for PTSD, might be searched

in being clinically treated at home and in isolation. We were

indeed surprised to observe that, in our cohort, executive

dysfunctions and psychopathological disturbances were pre-

sent in most of patients under 50 years of age. These patients

were those clinically milder and that received medical care

at home for most of the disease time, not requiring mechan-

ical ventilation. Facing a disease like COVID-19 isolated

at home, fearing possible complications in the absence of

direct medical control and without a structured mental health

intervention, could have had an impact on their psychiatric

and cognitive functioning, as previously suggested [40]

For the purposes of this study, subjective cognitive decline is defined as a self-perceived cognitive decline in cognitively normal people [[31](https://pmc.ncbi.nlm.nih.gov/articles/PMC11262122/#b31-2712-7672_2022_3_3_45)]. In line with this definition the sample was divided in two subgroups: those who complained about decreased cognitive functions and those who had no cognitive complaints.

This study analyzed the congruence of subjective and objective cognitive performance in a cohort of patients initially presenting with SCC or fatigue as part of PCS. To our knowledge, this is the first study to report domain-specific findings. Other factors that might influence subjective perception of cognition, such as depression, anxiety, sleep, quality of life, demographic variables, and personality factors, were taken into account (stolen from Schild et al. 2023).

Hasting et al. (2023): Cognitive screening using the MoCA failed to reliably detect the presence of cognitive deficits, as it mostly yielded results within the normal range. Moreover, elderly patients with mild cognitive impairment may have an increased risk of converting to dementia status ([Liu et al., 2021](https://econtent.hogrefe.com/doi/full/10.1024/1016-264X/a000376#c34)).

t “long/post-COVID syndrome” (hereinafter jointly referred to as PCS)