

Theoretical Background

As of September 2024, over 760 million confirmed cases of coronavirus disease 2019 (COVID-19) have been documented by the World Health Organization (WHO) globally, leading to approximately 6.9 million deaths. The actual numbers are likely to be much higher due to underreporting. COVID-19 is an infectious disease caused by the SARS-CoV-2 virus (WHO, 2021). While most patients fully recover, some experience persistent symptoms such as fatigue, shortness of breath, cognitive dysfunction, and other symptoms that generally have an impact on everyday functioning (WHO, 2021). These remaining effects, referred to as Post-COVID-19 Condition or Syndrome (PCS), usually occur three months after the initial infection with the SARS-CoV-2 virus and last for at least two months with no other explanation. Approximately 10-20% of people infected with SARS-CoV-2 meet the criteria for PCS (WHO, 2021).

Cognitive Impairment in PCS

Cognitive impairment is one of the most frequent symptoms of PCS (Davids et al., 2021; WHO) and is therefore of high interest. These impairments are characterized by confusion, memory difficulties, disorientation, and trouble concentrating, which are referred to as experiencing “brain fog” by affected individuals (Bland et al., 2024; Kwan et al., 2024). Around 22% of individuals diagnosed with PCS experience COVID-related cognitive impairment, according to a meta-analysis by Ceban et al. (2022). This finding is based on data from 43 studies, 31 of which used subjective assessments and 12 that employed objective measures. Notably, studies using objective assessments of cognitive function reported significantly greater proportions of individuals with impairment (36%) compared to those relying on subjective modes of ascertainment, which identified 18% as cognitively impaired.

This shows, that subjective and objective measures of cognitive function represent two distinct approaches to assessing cognition. Subjective assessments rely on self-reported experiences and perceptions (Stewart, 2012), while objective assessments use standardized tests and tasks to evaluate cognitive performance in various functional areas. Several studies have illustrated these discrepancies between subjective and objective measures further. In fact, most studies have reported higher rates of cognitive impairment through subjective cognitive complaints than through objective test results (Schild, Scharfenberg, Kirchner et al., 2023). For instance, in a study by Schild, Goereci, Scharfenberg et al. (2023) among 52 patients who self-reported cognitive impairment after SARS-CoV-2 infection, objective cognitive screening tests confirmed impairment in only 25%, while extensive neurological assessment indicated impairments in 60% of these patients. Moreover, Schild, Scharfberg, Kirchner, et al. (2023)

reported that 88% of patients reported persistent self-reported cognitive impairment, with approximately a 40% discrepancy between the subjective reports and objective test results at both follow-up visits, underscoring the discrepancies between patients' self-reports and objective neuropsychological test results. Bland et al. (2024) observed that there was no significant relation between objective and subjective measures of cognitive function, implying that self-reports of "brain fog" may not be reflected by objectively measured cognitive dysfunction.

Subjective cognitive deficits in everyday situations are predicted by elevated anxiety and fatigue levels more than by objective cognitive performance (Zamarian et al., 2024). This lack of alignment highlights the complexity of cognitive impairment and raises questions about which additional factors may influence individuals' perceptions of cognitive difficulties. Recent research has addressed these questions by examining how psychological symptoms influence subjective cognitive and objective cognitive impairment. Zamarian et al. (2024) discovered that subjective cognitive deficits in everyday situations can be better explained by elevated anxiety and fatigue levels than by objective cognitive performance. In addition to anxiety (Almeria, Cejudo, Sotoca, Deus & Krupinski, 2020; Brück et al., 2019; Costas-Carrera et al., 2022; Hill et al., 2016; Zamarian et al., 2024) and fatigue (Bland et al., 2024; Delgado-Alonso et al., 2023; Zamarian et al., 2024), sleep disturbances (Zamarian et al., 2024) and depressive symptoms (Almeria et al., 2020; Brück et al., 2019; Costas-Carrera et al., 2022; Hill et al., 2016; Zamarian et al., 2024) have been found to be associated with subjective but not objective cognitive impairment (Henneghan, Lewis, Gill & Kesler, 2022). Objective cognitive function, on the other hand, was found to be related to perceived stress (Bland et al., 2024).

These findings highlight the intricate and often discordant relationship between subjective and objective cognitive performance, as well as their complex interactions with psychological factors such as anxiety, fatigue, sleep disturbances, and depressive symptoms. This complexity raises important questions about how these elements interact, particularly in the aftermath of SARS-CoV-2 infection. Understanding these dynamics is crucial for developing effective and personalized rehabilitation programs that aim to improve individuals' perceived cognitive function and assist in their recovery.

Cognition

Cognition is defined as "the mental action or process of acquiring knowledge and understanding through thought, experience, and the sense" (Cambridge Cognition, 2015).

Cognition is essential for everyday functioning and refers to a range of mental processes such as the acquisition, storage, manipulation, and retrieval of information (Cambridge Cognition, 2015).

Cognitive impairment. Mild cognitive impairment will be explained in this section.

When starting to talk about EEG: Why is EEG of interest? And why beta and delta frequencies?

EEG findings in MCI. Reduced delta power during resting state EEG has been identified in patients with MCI (Liddell et al., 2007). Furthermore, in the study, individuals with MCI demonstrated a significant positive correlation between delta power and immediate memory recall. Liddell et al. (2007) proposed that these findings suggest that delta power may be linked to memory decline in MCI, indicating that it could serve as a sensitive indicator of prodromal or early cognitive decline. However, other studies have shown increased delta power in MCI patients compared to healthy controls, particularly in frontal and centroparietall regions (Adler, Bramesfeld & Jajcevic, 1999; Moretti, Zanetti, Binetti & Frisoni, 2012). A decrease in beta power has been found in individuals with mild AD (Hogan, Swanwick, Kaiser, Rowan & Lawlor, 2003).

Fatigue

Fatigue, alongside cognitive impairment, is the most commonly reported symptom of PCS (WHO, 2021). As mentioned above, subjective perceptions of cognitive performance can be influenced by fatigue. Therefore, a closer examination of fatigue will follow to differentiate between the concepts of fatigue and subjective cognitive impairment.

EEG findings in Fatigue.

EEG findings in PCS patients. Electroencephalography (EEG) is a non-invasive, objective method for assessing neuronal activity and has proven to be a valuable tool in identifying neurophysiological dysfunctions in individuals with cognitive impairment (Koenig, Smailovic & Jelic, 2020; Kubota, Gajera & Kuroda, 2021). Because of this, EEG studies have become increasingly relevant for investigating individuals with COVID-19 and PCS, as they reveal changes in brain neural activity that correlate with fatigue and cognitive deficits in these patients (Antony & Haneef, 2020; Appelt et al., 2022; Cecchetti et al., 2022; Furlanis et al., 2023; Kopańska et al., 2022; Kubota, Gajera & Kuroda, 2021; Pasini et al.,

2020; Pastor, Vega-Zelaya & Abad, 2020; Roberto, Espiritu, Fernandez & Gutierrez, 2020; Wojcik et al., 2023).

Furlanis et al. (2023) found that two-thirds of the 20 participants presenting brain fog were characterized by unexpected abnormal EEG patterns. Ortelli et al. (2023) found that lower performance on cognitive tasks, particularly those assessing executive function, was associated with changes in brain activity in PCS patients.

There are different types of analyses used to evaluate EEG patterns of PCS patients, ranging from common power spectrum and event-related potentials (Cecchetti et al., 2022; Furlanis et al., 2023; Kopańska et al., 2022) to more sophisticated approaches, such as intrinsic mode functions and avalanche analysis (Appelt et al., 2022; Wojcik et al., 2023). However, in this thesis, a power analysis will be conducted, specifically examining delta and beta frequency.

Delta Power in PCS patients. Delta frequency (0.5-3 Hz) is typically absent during the waking state of healthy adults and is associated with deep sleep (Schandry, 2016). Ortelli et al. (2023) reported significant differences in the delta frequency band between PCS and healthy controls, with PCS patients displaying diminished activity compared to healthy controls. Lower delta power was associated with worse cognitive functioning. However, findings regarding delta power in PCS patients are not consistent. For instance, Kopańska et al. (2022) found a decrease in delta in the left hemisphere, similar to Ortelli et al. (2023), but also observed an increase in delta activity in the right hemisphere. In another study of 20 PCS patients, a delta-slowness pattern was revealed in nine of them (Furlani et al., 2022). Furthermore, the relative delta power values in this cohort were higher compared to those reported in the literature for healthy individuals. Similarly, Pastor et al. (2020) demonstrated a significant encephalopathic pattern in PCS patients characterized, among others, by an increase in generalized delta activity.

Beta Power in PCS patients. Beta frequency (14-30 Hz) is typically present when individuals are awake and mentally or physically active, or under psychological stress (Schandry et al., 2016). While Ortelli et al. (2023) found no significant differences in beta frequency bands, Kopańska et al. (2020) reported increased beta2 activity in both hemispheres and elevated beta1 activity in the left hemisphere in PCS patients.

EEG findings conclusion. Those EEG findings discussed above are mainly based on subjective perceived cognitive impairment rather than objective measures of impairment. To illustrate this, the findings of Ortelli et al. (2023) provide relevant insights. The PCS group had a significantly lower MoCA score and higher fatigue score (assessed with the self-

Commented [Janka Hau1]: Why beta and delta power?

Commented [Janka Hau2]: Other literature

Commented [JH3]: The predominant approach in the literature focuses on the analysis of broad frequency bands in the EEG power spectrum, from slow bands, delta (δ : 0.1–4 Hz) and theta (θ : 4–8 Hz), to faster bands, alpha (α : 8–13 Hz), beta (β : 14–30 Hz), and gamma (γ : >30–80 Hz) (Babiloni, et al., 2020).

Perez, Duque, Hidalgo & Salvador, 2024:
<https://doi.org/10.1016/j.biopsycho.2024.108823>

Commented [JH4R3]: These rhythms are replaced by fast oscillations in the range of beta (14–30 Hz).
[14] Steriade M (2003) The corticothalamic system in sleep. Front Biosci 8, d878–d899.
[15] Steriade M, Contreras D, Amzica F, Timofeev I (1996) Synchronization of fast (30–40Hz) spontaneous oscillations in intrathalamic and thalamocortical networks. J Neurosci 6, 2788–2808
Babiloni et al. (2011): <https://doi.org/10.3233/JAD-2011-0051>

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evaluation scale measuring perceived fatigue (FSS)), than the control group. However, the global cognitive score assessed with the MoCA was still considered normal, implying that, overall, PCS patients did not have clinically significant cognitive impairment.

Notably, there was no differentiation possible between EEG patterns associated with cognitive impairment and those related to fatigue. This raises an interesting opportunity to examine beta and delta power during resting state in two groups defined solely by objective cognitive measures, allowing for a clearer understanding of the relationship between EEG patterns and cognitive functioning in patients with PCS. This approach would allow potential abnormalities in EEG to be more directly linked to objective cognitive impairment rather than subjective cognitive impairment, which might be influenced by psychological factors, such as fatigue.

Aim of study

The study aims to explore the differences among groups that differ significantly in their objective cognitive performance levels following SARS-CoV-2 infection. This investigation is crucial given the widespread cognitive impairments reported in individuals with PCS and their profound impact on everyday functioning and quality of life. Due to the inconsistent findings in EEG patterns in beta and delta power in patients with PCS, but also in patients with MCI, there is a need for further investigation of this aspect. Specifically, the research will address the following research question: How do individuals with different cognitive performance levels differ in their self-reported limitations after SARS-CoV-2 infection, their well-being, and their resting state neural activity?

By examining the correlations between objective cognitive assessments and self-reported cognitive impairments, as well as the influence of psychological factors, this study aims to provide insights into the complex relationship between cognitive functioning and psychological health in individuals with, and without PCS.

Following SARS-CoV-2 infection, two distinct groups of individuals will be identified based on objective cognitive assessments, showing significant differences in performance levels between the groups. Suggesting, that one group performs significantly better or worse than the other group.

Hypotheses

Commented [JH6]: Setzen wir voraus, keine Hypothese

Commented [JH7]: Auf methodischer Ebene haben wir es geschafft zwei Gruppen - Auswertung, ob meine Methode funktioniert.

Commented [JH8]: Nehme ich vweg, wie als wenn ich Voraussetzungen teste. Wir wollen diese Verfahren verwenden. Shapiro Test.... Was kam dabei raus. Danach eigentliches Ergebnis. Ergeben die Gruppen sind, die wir erstellt haben (schon ankündigen in den Methoden) Habe vor zu gucken, ob meine Gruppen sinn ergeben. Ergeben sinn, da sie sich demografisch nicht unterscheiden aber kognitiv schon.

Commented [Janka Hau9]: Das sieht alles schon gut aus, aber versuch mal deine Hypothesen richtig hervorzuheben, du kannst ruhig richtig Abstand lassen und sagen

Hypothese 1:

Hypothese 2:

Hypothese 3a: Gruppe B hat weniger Fatigue als Gruppe A

Hypothese 3b: Gruppe B hat weniger Depression als Gruppe A

Hypothese 3c: Gruppe B hat weniger Angst als Gruppe A

und so weiter

WARUM du diese Hypothesen aufstellst, arbeitest du direkt vorher heraus, quasi als Übergang vom theoretischen Hintergrund in deine Fragestellung hinein. Und in den Methoden erklärst du dann WIE du die jeweiligen Hypothesen testest. Also die Hypothese, dass mehr Leute sich subjektiv eingeschränkt fühlen, in der Gruppe die objektiv schlecht abgeschnitten hat, müsstest du dann vielleicht mit einem Chi-quadrat Test überprüfen zum Beispiel

1. Individuals with objectively assessed lower cognitive performance will report higher levels of self-reported cognitive limitations compared to individuals who perform better.

2. Individuals who self-report cognitive impairment but do not exhibit lower performance in objective cognitive assessment may have higher fatigue, anxiety, and depression scores than all other individuals.

3. **Delta Frequency:**

a. Patients with lower objective cognitive performance will exhibit decreased delta power compared to better performers, suggesting that abnormal delta power is correlated with cognitive impairment.

b. Decreased delta power may also be related to fatigue, meaning that individuals with subjective cognitive impairment but without lower objective performance could also show reduced delta power. This would imply that their perceived cognitive limitations may be a symptom of fatigue rather than actual cognitive deficits.

4. **Beta Frequency:**

a. Patients with lower objective cognitive performance will exhibit increased beta power compared to better performers, suggesting that abnormal beta power is correlated with cognitive impairment.

b. Increased beta power may also be related to fatigue, meaning that individuals with subjective cognitive impairment but without lower objective performance could also show increased beta power.

Commented [JH10]: Do I need to go more into detail here?

How do individuals with different cognitive performance levels differ in their self-reported limitations after SARS-CoV-2 infection, their well-being and their resting state neural activity?