Theoretical Background

Introduction to COVID-19 and Post COVID-19 Syndrome

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). 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. These remaining effects, referred to as Post COVID-19 Condition or Syndrome (PCS) or more commonly as long COVID, 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).

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. 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 et al., 2023). For instance, in a study by Schild et al.

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Commented [JH1]: 10-20% of people

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Commented [JH3]: Studies which objectively assessed cognitive impairment re-
ported significantly greater proportions of individuals with cognitive
impairment as compared to those employing subjective modes of
ascertainment (0.36 objectively assessed vs 0.18 subjectively assessed;

Commented [JH4]: In this systematic review and meta-analysis of 81 studies, we
established that approximatelt a third of the included individuals
experienced persistent fatigue and over a fifth of individuals exhibited
cognitive impairment 12 or more weeks following COVID-19 diagnosis

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(2022) 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 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).

Taken together, understanding the connection between subjective and objective cognitive impairment and the factors influencing them, is crucial for developing personalized rehabilitation programs that aim to improve cognitive function and assist in the recovery of PCS patients.

To understand the relationship between subjective and objective cognitive impairment, a

cluster analysis approach will be used to identify two groups of individuals infected with SARS-CoV-2 based on (only) objective cognitive measures, aiming for similar cognitive performance levels within each group and maximizing the difference between the two groups. After the cluster analysis was conducted, these groups will be compared not only in their cognitive performances, but also in their self-reported cognitive level, well-being and their resting state neural activity.

Objective cognitive measures

EEG findings in PCS patients
EEG findings in cognitive impairment

To understand the relationship between subjective and objective cognitive impairment, the focus will first be on defining cognition and cognitive impairment and how it is measured. Then the underlying factors (anxiety, depression, sleep quality, and fatigue) will be discussed, with special focus on fatique.

To understand the relationship between subjective and objective cognitive impairment, a cluster analysis approach will be used to identify two groups of different cognitive performance level, in a dataset of individuals infected with SARS-CoV-2, based on (only) objective cognitive measures.
Before the cluster analysis approach will be explained, a closer look into objective cognitive measures will be taken.

1. Introduction to COVID-19 and PCS
2. Cognitive impairment in PCS
3. Fatigue in PCS (not sure if I want that here. Or maybe just as part of Factors influencing cognitive impairment? Or later findings of Fatigue in PCS and then)
4. Factors influencing cognitive impairment
5. EEG findings in cognitive impairment
6. EEG findings in PCS

7. (maybe here fatigue?)
8. Cluster analysis approach
9. Research question
10. Hypotheses

Definition of cognitive impairment

How cognitive impairment is measured

Fatigue

EEG findings

Goal of this study (two objective cognitive groups, comparing them)

How to reach goal

EEG finding in PCS patients

EEG findings in cognitive impairment

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?

Hypotheses