**Introduction**

Most of us have, at some point, experienced moments of disorientation, trouble concentrating, or forgetting simple tasks. For many individuals recovering from COVID-19, however, this mental cloudiness is more than a fleeting inconvenience. It is a persistent reminder of their illness. These cognitive challenges, along with fatigue and other lingering symptoms, continue to affect their daily lives long after the infection has passed.

Cognition is the most complex function of the brain (Birle et al., 2020) and is defined as “the mental action or process of acquiring knowledge and understanding through thought, experience, and the senses” (Cambridge Cognition, 2015). It is essential for navigating the complexities of everyday life (Cambridge Cognition, 2015; Eysenck & Brysbaert, 2018; Liu, Wang, Xin, Jiang & Meng, 2024), enabling individuals to comprehend and interact with the world around them (Eysenck & Brysbaert, 2018). Cognition encompasses a range of mental processes, including the acquisition, storage, manipulation, selection and retrieval of information (Cambridge Cognition, 2015; Liu et al., 2024), as well as core cognitive functions such as attention, perception, learning, memory, language, problem solving, thinking, and reasoning (Eysenck & Brysbaert, 2018). These cognitive abilities are vital for decision-making and adapting to daily challenges (Eysenck & Brysbaert, 2018).

But what happens when these vital cognitive abilities begin to decline? Cognitive decline refers to varying degrees of damage to cognitive function resulting from a range of causes (Birle et al., 2020; Liu et al., 2024). The global prevalence of cognitive impairment in adults over 50 years old ranges from 5.1% to 41%, with a median prevalence of 19% (Pais, Ruano, Carvalho & Barros, 2020). The prevalence increases with age (Liu et al., 2024; Pais et al., 2020). Cognitive impairment can range from subjective cognitive decline to mild cognitive impairment and more severe forms, such as dementia.

Cognition can be assessed using various methods, each differing in their level of objectivity and sensitivity (Cambridge Cognition, 2015). Recognizing the importance of cognition underscores the profound effects that cognitive decline or impairment can have on an individual’s independence and quality of life.

This thesis focuses on cognitive decline in individuals experiencing Post COVID-19 Syndrome and its impact on their general well-being. To fully understand this phenomenon, an overview of COVID-19 and its association with cognitive impairment in Post-COVID-19 Syndrome is first provided. Then, the distinction between subjective cognitive decline and objective cognitive impairment is explained. Next, the role of electroencephalography (EEG) as a neurophysiological tool for assessing cognitive function is introduced. Following this, existing EEG research on subjective and objective cognitive impairment, as well as its application in Post-COVID-19 Syndrome, is reviewed. Finally, the specific aim of this thesis is introduced, which is to explore how differences in objective cognitive performance after SARS-CoV-2 infection relate to self-reported cognitive impairment, general well-being, and EEG alterations in individuals with and without Post-COVID-19.

**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 Quelle. 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). It affects several cognitive domains, highlighting the diversity of cognitive deficits in PCS patients (Hasting et al., 2023; Widmann et al., 2023). Among the most frequently reported cognitive symptoms are lack of concentration, attention difficulties and memory loss (Amin-Chowdhury et al.; Buonsenso et al.; Cirulli et al.; Darley et al.; Elkan et al.; Fern´andez-de-Las-Pe˜nas et al.; Ferrucci et al; Garrigues et al.; Gonzalez-Hermosillo et al.; Leth et al.; Mattioli et al.; Morin et al.; Munblit et al.; Pereira et al; Pilotto et al.; Rass et al.; Rauch et al; Soraas et al.; Sykes et al.; Woo et al.). Patients also frequently report confusion, disorientation, mental slowness, trouble forming or finding words, increased in time needed to perform tasks and difficulties in learning new skills (Amin-Chowdhury et al.; Bland et al. 2024; Darley et al.; Ferrucci et al; Fortini et al.; Kwan et al., 2024; Morin et al.; Woo et al.). These symptoms are often collectively described by patients as “brain fog”, a non-specific re term used to express mental cloudiness, slowed thinking, and cognitive fatigue (Amin-Chowdhury et al., Bland et al., 2024; Fortini et al.; Kwan et al., 2024; Widmann et al., 2023).

Neuropsychological assessments have identified executive functions, attention, verbal learning, processing speed, episodic memory, visuospatial processing, psychomotor coordination as the cognitive domains most frequently impaired (Becker et al., 2021; Damiano et al., 2022; Delgado-Alonso; Ferrucci et al., 2021; García-Sánchez; Hasting et al., 2023; Mazza et al., 2021; Miskowiak et al. 2021).

To evaluate these domains, various assessment tools have been employed in the literature, including, for example, the Orientation-Memory-Concentration test (OMC), Montreal Cognitive Assessment (MoCA), Trail Making Test (TMT), Mini-Mental Status Examination (MMSE), Screen for Cognitive Impairment in Psychiatry (SCIP-D), and the Brief Repeatable Battery of Neuropsychological Tests (BRB-NT) (Leth et al., 2021; Mattioli et al.; Morin et al., 2021; Pilotto et al., 2021; Miskowiak et al., 2021; Becker et al., 2021; García-Sánchez, Evans et al., 2021; Ferrucci et al., 2021; Frontera et al., 2022; Rass et al., 2021).

While some studies have found that PCS patients perform worse on these assessment tools (Clemente et al., 2023; Cecchetti et al., 2022 Ortelli et al., 2023; Rahimi et al., 2024), others did not oberseve significant differences compared to healthy control (Appelt et al., 2022; Hasting et al. 2023). Importantly, even when group differences are found, patient scores often remain above the clinical cutoff for cognitive impairment (Hasting et al. 2023; Lynch et al., 2022). This shows, that despite the broad spectrum of neuropsychological assessment tools available, a considerable gap persists between subjectively reported cognitive difficulties and objectively assessed impairments. This gap highlights the complexity of measuring cognitive impairment.

**Subjective and Objective impairment**

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.

However, most studies have reported higher rates of cognitive impairment through subjective cognitive complaints than through objective test results (Schild, Scharfenberg, Kirchner 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. Similarly, Gomzyakova et al. (2022) found that objective cognitive decline, indicated by a MoCA score < 26, was detected in only 40 % of participants who reported subjective cognitive complaints. 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. In line with these findings, 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. This misalignment highlights the complexity of cognitive impairment and raises questions about the additional factors that may influence individuals’ perceptions of cognitive difficulties.

**Psychiatric and health-related symptoms influencing**

“[…] subjective cognitive deﬁcits in everyday situations are predicted by elevated anxiety and fatigue levels more than by objective cognitive performance” (Zamarian et al., 2004).

In addition to cognitive impairment, PCS patients often experience a range of other psychiatric and health-related symptoms, with fatigue being the most commonly reported alongside cognitive difficulties (Holdsworth et al., 2022; Premraj et al., 2022; WHO, 2021). Axiety, depression, and sleep disturbances are also frequently observed (Almeria, Cejudo, Sotoca, Deus & Krupinski, 2020; Badinlou et al., 2022; Damiano et al., 2022; Deng et al., 2021; Holdsworth et al., 2022; Premraj et al., 2022) However, results on how these symptoms are associated with cognitive impairment are inconsistent (Almeria et al., 2020; Schild et al., 2023). One study found that among ambulatory patients, objective cognitive test results were closely linked to anxiety, depression, fatigue and pain, a pattern that was not observed in hospitalized individuals (Blackmon et al., 2022). In contrast, a study using the MoCA reported no significant correlation between MoCA scores and levels of depression and anxiety (Gomzyakova et al., 2022), which aligns with findings from a separate study that also found no association between objective cognitive impairment and depression, anxiety, sleep disturbance, or fatigue (Henneghan et al., 2022). However, both studies identified significant associations between these symptoms and subjective cognitive complaints (Henneghan et al., 2022; Gomzyakova et al., 2022). These findings are supported by another study, showing that cognitive impairment and fatigue are significantly associated with depression, anxiety, and sleep disturbance (Badinlou et al., 2022).

Taken together, these findings support the assumption of Zamarian et al. (2024) that subjective cognitive deficits in PCS patients may be better explained by elevated anxiety and fatigue, and further complemented by depression and sleep disturbance (Henneghan et al., 2022; Gomzyakova et al., 2022) than by objective cognitive performance.

Although many individuals with self-reported cognitive difficulties perform within normal ranges on neuropsychological tests, they face an increased risk of developing mild cognitive impairment (MCI) and Alzheimer’s disease (AD) (Li et al., 2022; Numbers et al., 2023; Rivas-Fern´andez et al., 2023). In line with this, one study found that patients diagnosed with COVID-19 had a significantly increased risk of developing MCI compared to individuals with other acute upper respiratory infections (Bohlken, Weber, Heller, Michalowsky & Kostev, 2022). Interestingly, the prevalence of neurological and neuropsychiatric symptoms appears to be higher when assessed at or beyond six months following SARS-CoV-2 infection, compared to assessments conducted between three and sic months (Latronico et al., 2021; Premraj et al., 2022). In one study, 22% of participants exhibited cognitive impairment at three months post-infection, increasing to 26% at six months, as measured by the MoCA (Latronico et al., 2021).

Given the complexity of PCS symptoms and cognitive measurements identifying early and reliable biomarkers for the detection of subjective and objective cognitive impairment is crucial for maintaining cognitive health and prevent or delay its progression (Abdulrab & Heun, 2008).

**Biological factors**

The persistent symptoms may result from a combination of biological and psychological mechanisms (Premraj et al., 2022). For example, SARS-CoV-2 RNA may persist in brain tissue long-term, potentially contributing to progressive neuronal damage (Najjar et al., 2020; Singh, Chaubey, Chen & Suravajhala, 2020). Structural changes such as hippocampal atrophy, cortical thickening, and altered microstructural integrity have been associated with fatigue severity and cognitive deficits, particularly in attention and memory (Besteher et al., 2024; Díez-Cirarda et al., 2023; Heine et al., 2023). There as still many uncertainties how and to which extent the virus impacts the brain. To better understand the nature and extent of these changes, neurophysiological methods such as electroencephalography (EEG) may offer valuable insights.

**EEG**

Electroencephalography (EEG) has been proven to be a valuable tool for assessing both subjectiv cognitive difficulties (Rossini et al., 2007) and objective cognitive impairment such as MCI and AD (Babiloni et al., 2011; Dierks, Frölich, Ihl & Maurer, 1994; Jeong, 2024; Perez, Duque, Hidalgo & Salvador, 2024; Celesia et al., 1987, Rossini et al., 2007, Rossini, 2009, Yener et al., 2008, Yener et al., 2009). In fact, EEG can serve as a supportive diagnostic tool for cognitive impairment, detecting brain dysfunction even before reaching pathological diagnostic criteria (Babiloni et al., 2021).

A common method for characterizing rsEEG is to decompose oscillatory signal into spectral power across distinct frequency bands (Babiloni et al., 2016; Perez et al., 2024). Spectral power reflects the distribution of neural activity at specific frequencies and is associated with various cognitive processes (Babiloni et al., 2016; Perez et al., 2024; Ward, 2003).

* 1. EEG (alterations) in cognitive decline (specifically beta and delta, seperate points?)

Given this clinical importance of detecting cognitive impairment as early as possible,

1. Study Aim
2. Hypotheses