**Introduction**

At some point, most of us 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 examines cognitive decline and associated neuropsychiatric symptoms in individuals following SARS-CoV-2 infection. To fully understand this phenomenon, an overview of COVID-19 and its association with cognitive impairment in Post-COVID-19 Syndrome is first provided. The distinction between subjective cognitive decline and objective cognitive impairment is explained, followed by a discussion of the impact of neuropsychiatric symptoms on cognitive difficulties. 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 in individuals after SARS-CoV-2 infection relate to perceived cognitive functioning, associated neuropsychiatric symptoms, and EEG alterations.

**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 (WHO, 2023). 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., 2021, Buonsenso et al., 2021; Elkan et al., 2021; Ferrucci et al., 2021; Garrigues et al., 2020; Gonzalez-Hermosillo et al., 2021; Leth et al., 2021; Pilotto et al., 2021; Rauch et al., 2021; Soraas et al., 2021; Sykes et al., 2021; Woo et al., 2020). 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., 2021; Bland et al., 2024; Darley et al., 2021; Ferrucci et al., 2021; Fortini et al., 2021; Kwan et al., 2024; Morin et al., 2021; Woo et al., 2020). These symptoms are often collectively described by patients as “brain fog”, a non-specific term used to express mental cloudiness, slowed thinking, and cognitive fatigue (Amin-Chowdhury et al., 2021; Bland et al., 2024; Fortini et al., 2021; 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 et al., 2022; Ferrucci et al., 2021; García-Sánchez et al., 2022; 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., 2021; Morin et al., 2021; Pilotto et al., 2021; Miskowiak et al., 2021; Becker et al., 2021; García-Sánchez et al., 2022; 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 find 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.

**Subjective and Objective impairment**

Around 22% of individuals diagnosed with PCS experience COVID-19 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, et al., 2023). Among 52 patients who self-reported cognitive impairment after SARS-CoV-2 infection, the MoCA confirmed impairment in only 25%, while extensive neurological assessment indicated impairments in 60% of these patients (Schild, Goereci, et al., 2023). Similarly, Gomzyakova, Palchikova, Tumova, Kasyanov and Sorokin (2022) found that objective cognitive decline, indicated by a MoCA score < 26, was detected in only 40 % of participants who reported subjective cognitive complaints. This raises question about the sensitivity of the MoCA in detecting cognitive deficits, as it often yields results within the normal range (Hasting et al., 2023). 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, it was 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 (Bland et al., 2024; Brücket al., 2019). This misalignment highlights the complexity of cognitive impairment and raises questions about the additional factors that may influence individuals’ perceptions of cognitive difficulties.

**Influence of psychiatric and health-related symptoms on cognitive decline**

“[…] 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 symptoms, with fatigue being the most commonly reported alongside cognitive difficulties (Holdsworth et al., 2022; Premraj et al., 2022; WHO, 2021). Anxiety, depression and sleep disturbances are also frequently observed (Almeria, Cejudo, Sotoca, Deus & Krupinski, 2020; Badinlou, Lundgren & Jansson-Fröjmark, 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, Scharfenberg, 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, Lewis, Gill & Kesler, 2022). However, both studies identified significant associations between these symptoms and subjective cognitive complaints (Henneghan et al., 2022; Gomzyakova et al., 2022). Similar associations have been reported in several other studies (Badinlou et al., 2022; Brück et al., 2019; Costas-Carrera et al., 2022; Hill et al., 2016). Conversely, objective cognitive function has been found to be more closely related to perceived stress (Bland et al., 2024).

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) rather 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 six months (Latronico et al., 2020; 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., 2020).

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 are 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**

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).

EEG is a neurophysiological technique that records brain electrical activity via scalp electrodes (Babiloni et al., 2011; Babiloni et al., 2016), providing a direct, real-time view of human brain function in physiological and pathological conditions (Berger, 1929; Liu et al., 2024). The human brain consists of approximately 100 billion neurons, forming intricate synaptic networks that support cognitive function (Babiloni et al., 2016). As the brain ages, these synaptic networks weaken due to synaptic pruning, neuronal apoptosis, and the loss of cortico-cortical connections, leading to a decline in cognitive function (D'Amelio and Rossini, 2012). Pathological processes can accelerate this process of brain aging (Babiloni et al., 2016). EEG allows the analysis of cortico-cortical connectivity and neuronal synchronization of firing, and coherence of brain rhythmic oscillations at various frequencies, providing insights into the functional alterations associated with synaptic network weakening and cognitive decline (Babiloni et al., 2011; Nunez et al., 2001).

The value of EEG in studying cognitive impairment has been recognized for decades. Hans Berger introduced EEG in humans in 1924 and was the first to observe pathological EEG patterns in a verified AD patient (Berger, 1931; Berger, 1932; Jeong, 2004), laying the foundation for numerous studies on EEG in AD and other neurodegenerative disorders (Jeong, 2004).

Several studies have found a strong correlation between the degree of EEG abnormality and cognitive impairment (Brenner et al., 1988; Erkinjuntti et al., 1988; Johannesson et al., 1979; Kaszniak et al., 1979; Liddle, 1958; Merskey et al., 1980; Obrist et al., 1962; Rae-Grant et al., 1987; Roberts et al., 1978; Soininen et al., 1982; Wiener and Schuster, 1956). Quantitative EEG (qEEG) and event-related potentials (ERPs) have been explored as potential clinical markers for detecting early stages of AD and monitoring disease progression (Celesia et al., 1987, Rossini et al., 2007, Rossini, 2009, Yener et al., 2008, Yener et al., 2009). In fact, rsEEG rhythms have been shown to reflect distinct patterns of cortical neural synchronization that can distinguish patients with Parkinsons’s disease dementia from those with AD (Babiloni et al., 2011)

EEG is a direct, non-invasive, safe, cost-effective, and portable method making it a simple and convenient tool for assessing brain function (Babiloni et al., 2016; Babiloni et al., 2021; Biasiucci, Franceschiello & Murray, 2019; Meghdadi et al., 2021; Neo, Foti, Keehn & Kelleher, 2023; Rossini et al., 2019). EEG’s portability enables recordings to be performed in various settings and individuals such as vulnerable elderly or those with advanced disease who may struggle with magnetic resonance imaging (MRI) procedures (Babiloni et al., 2016). Furthermore, EEG offers high temporal resolution (Meghdadi et al., 2021; Rossini et al., 2004; Rossini et al., 2019) (time resolution of ≤ 1 ms), enabling it to provide neurophysiological data that cannot be obtained from other neuroimaging techniques (Biasiucci et al., 2019).

Another advantage is its repeatability. EEG markers remain largely unaffected by meta-learning relative to task progression, allowing for repeated assessments throughout disease progression (Babiloni et al., 2016).

This study will focus on analyzing resting state EEG (rsEEG), as it is a promising tool for measuring quantifying brain neurophysiological dysfunction (Babiloni et al., 2011; Babiloni et al., 2016; Perez, Duque, Hidalgo & Salvador, 2024). Unlike the measuring of ERPs, rsEEG captures spontaneous brain activity independently of cognitive tasks or stimuli (Babiloni et al., 2016; Babiloni et al., 2021; Mantini, Perrucci, Del Gratta, Romani & Corbetta, 2007; Perez et al., 2024), making it resilient to factors such as fatigue, movement, anxiety, or meta-learning (Babiloni et al., 2016; Babiloni et al., 2021; Perez et al., 2024).

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).

**Now about frequency bands in general before looking at abnormalities in frequeny bands in MCI and covid patients**

EEG signals are commonly categorized into five distinct frequency bands: Delta (1-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta (13-30 Hz), and gamma (>30 Hz) (Babiloni et al., 2011; Babiloni et al., 2016). These frequency bands provide specific physiological insights into the brain’s functional state during sleep and wake periods (Babiloni et al., 2011; Nunez et al., 1999). However, there is no universal consensus on their exact frequency ranges, as definitions vary across studies. While Babiloni et al. (2016) define the delta band as 1-4 Hz and the beta band as 13-30 Hz, this study will consider delta as 0.5-4 Hz (Bachman & Bernat, 2018; Gunasekaran, Azizi, Van Wassenhove & Herbst, 2023; Uchida, Maloney & Feinberg, 1992) and beta as 14-30 Hz (Brovelli, Ding, Ledberg, Chen, Nakamura & Bressler; 2004; Liang, Zhang, Liu, Lou, Liu & Wang, 2020; Pesonen, Hämäläinen & Krause, 2007; Poppelaars, Harrewijn, Westenberg & Van der Molen, 2018; Tzagarakis, West & Pellizzer, 2015).

Attar (2022) defines the frequency bands as follows: Delta waves are typically absent during wakefulness in healthy adults and is primarily associated with deep sleep. Theta waves are associated with the transition between wakefulness and sleep. Alpha waves are characteristic of relaxed wakefulness. And beta waves are typically present when individuals are awake and mentally or physically active, or under psychological stress.

During normal aging, eyes-closed rsEEG rhythms undergo gradual changes, including a shift in power distribution across frequency bands (Babiloni et al., 2011; Babiloni et al., 2016; Babiloni et al., 2006; Barry & De Blasio, 2017; Liu et at., 2024). However, in pathological aging, such as AD, these alterations become more pronounced and disruptive (Claus et al., 2000; Lejko et al., 2020; Liu et at., 2024).

A key feature of pathological aging is EEG slowing, which has been linked to cognitive impairment, where greater slowing is associated with worse impairment (D’Atri et al., 2021; Farina et al., 2020; Finnigan & Robertson, 2011; Lejko et al., 2020). This slowing is characterized by increased power in low-frequency band (delta, theta) and reduced power in high-frequency band (alpha, beta) (Farina et al., 2020; Lejko et al., 2020; Liu et al., 2024).

In AD, these EEG alterations are well-documented, with a consistent pattern of increased delta and theta power alongside reduced alpha and beta power compared to healthy older adults (Babiloni et al., 2011; Claus et al., 2000; D’Atri et al., 2021; Dringenberg, 2000; Elmståhl, Rosén & Gullberg, 1994; Farina et al., 2020; Fröhlich et al., 2021; Hogan, Swanwick, Kaiser, Rowan & Lawlor, 2003; Jelic, Shigeta, Julin, Almkvist, Winblad & Wahlund, 1996; Jeong, 2004; Lejko et al., 2020; Musaeus et al., 2018; Özbek, Fide & Yener, 2021; Wada, Nanbu, Jiang, Koshino, Yamaguchi & Hashimoto, 1997).

However, findings in MCI and self-reported CD remain less consistent (Fröhlich et al., 2021). While some studies report EEG slowing similar to that seen in AD, albeit to a lesser extent, others show greater variability in frequency band alterations (Fröhlich et al., 2021;

Notably, theta and gamma bands are recognized for their involvement in memory (Klimesch, 1999; Nyhus & Curran, 2010), whereas delta bands play a role in maintaining focused attention (Harmony, 2013). The alpha band has been associated with attention and memory processes (Klimesch, 1999, 2012). Although the role of beta oscillations in the cognitive process has been explored less, some evidence suggests that they are related to the state of attention (Güntekin et al., 2013).

Given the inconsistencies in EEG alterations in MCI (and SCD), this study focuses on delta and beta frequency bands, as …. (something about MCI/cognitive impairment, maybe also PCS, fatigue).

In this study delta and beta frequency bands are primarly considered, since ….

**Delta power in MCI**

Findings on delta power in MCI remain inconsistent. Several studies have observed increased delta power (Adler, Bramesfeld & Jajcevic, 1999; Babiloni et al., 2006; Babiloni et al., 2010; Farina et al., 2020; Jelic et al., 2020; Koenig et al., 2005; Moretti, Zanetti, Binetti & Frisoni, 2012; Ya, Xun, Wei, Ting, Hong & Yuan, 2015), while others found no significant differences between MCI and healthy individuals (Fröhlich et al., 2021; Jelic et al., 1996), and yet others reported a decrease in delta power during rsEEG (Kwak, 2006; Liddell et al., 2007). Additionally, Liddell et al. (2007) observed a significant positive correlation between delta power and immediate memory recall in MCI, suggesting that delta power may be linked to memory decline and could serve as a sensitive indicator of prodromal cognitive decline.

These findings suggest that….

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).

In MCI, delta power alterations have been observed primarily in the frontal (D’Atri et al., 2021), left temporo-parietal (Farina et al., 2020), and temporal-occipital regions (Jelic et al., 2020).

**Beta power in MCI**

Finding on beta power in MCI are inconsistent. Several studies found no significant differences in beta power compared to healthy control (Babiloni et al., 2006; Fröhlich et al., 2021; Jelic et al., 1996; Kwak, 2006(?); Ya, Xun, Wei, Ting, Hong & Yuan, 2015). However, Jelic et al. (1996) noted a tendency toward higher beta values in frontal regions in individuals with objective memory disturbance, through this difference was not statistically significant. Conversely, other studies have reported a decrease in beta power (Babiloni et al., 2015; Jelic et al., 2020; Koenig et al., 2005), particularly in the temporal and occipital regions (Jelic et al., 2000). These findings suggest that ….

**Delta and beta power in SCD**

Perez et al. (2024) reviewed studies on rsEEG frequency bands in SCD and observed that findings for the delta and beta bands were inconsistent across research. Of the nine studies included in the review, five did not find alterations in the rsEEG delta frequency band in individuals with SCD. The remaining four reported an increase in delta power in individuals with SCD compared to healthy controls, as well as in individuals with MCI compared to those with SCD. Sibilano et al. (2023) identified the delta (and theta) bands as the most effective in distinguishing SCD from MCI.

Three studies reported notable changes in beta band activity. While two found increased beta activity in individuals with SCD compared to healthy controls, and in individuals with MCI compared to those with SCD, the third study observed a tendency toward decreased beta power in MCI compared to SCD.

* 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