Introduction

Imagine waking up one day feeling disoriented, unable to concentrate, or struggling to remember simple tasks from the day before. For many individuals recovering from COVID-19, this mental cloudiness, often described as "brain fog," is a persistent reminder of their illness. These cognitive challenges, along with fatigue and other lingering symptoms, 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 us to understand and interact with the world around us (Eysenck & Brysbaert, 2018). Cognition encompasses a range of mental processes such as the acquisition, storage, manipulation, selection and retrieval of information (Cambridge Cognition, 2015; Liu, Wang, Xin, Wang, Jiang & Meng, 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 impairment or decline refers to varying degrees of damage to cognitive function resulting from various causes (Birle et al., 2020; Liu et al., 2024). A systematic review found that 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 impairment, to mild cognitive impairment, where ….. (citation), to more severe forms like dementia, which significantly impact daily life ….. (citation). Cognition can be measured using a variety of methods, each varying in their level of objectivity and sensitivity (Cambridge Cognition, 2015). Understanding the importance of cognition undesorces the profound effects that impairments can have on an individual's independence an quality of life.

This thesis focuses on cognitive imapairment in individuals experiencing Post COVID-19 Syndrome, and their general well-being. By explaining … looking at …. Etc. In order to understand it is important to look at … … …

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Commented [JH8]: But what happens when these abilities begin to decline? Cognitive impairment refers to difficulties with memory, learning, concentration, or decision-making that are greater than typical age-related changes. This can range from mild cognitive impairment, where individuals notice subtle changes in cognitive function, to more severe forms like dementia, which significantly impact daily life. Understanding the importance of cognition underscores the profound effects that impairments can have on an individual's independence and quality of life.

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Commented [JH12]: This thesis focuses on cognitive impairment in individuals experiencing Post COVID-19 Syndrome (PCS), a condition characterized by the persistence of symptoms such as fatigue and cognitive dysfunction months after recovering from the acute infection. While subjective complaints of cognitive difficulties are common among PCS patients, objective measures often reveal discrepancies between what individuals report and their actual cognitive performance. The goal of this thesis is to explore these differences through a cluster analysis approach, aiming to better understand how objective cognitive measures relate to individuals' self-reported symptoms, their overall well-being, and their neural brain activity.
First, the dopaminergic system, closely related to the basal ganglia, is introduced, as it
is centrally involved in reward-based learning and movement generation. Then the concepts of reward, prediction, and ...

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.

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). 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. 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.

The discrepancies between self-reported cognitive difficulties and objective assessments highlight the complexity of measuring cognitive impairment. Before examining how these issues manifest in PCS, it is essential to understand the fundamental concepts of subjective cognitive impairment and objective cognitive impairment in a broader context. 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. The following sections provide an overview of both concepts, exploring their definitions, underlying mechanisms, and implications for research and clinical practice.

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Subjective cognitive decline

Several studies on subjective cognitive decline (SCD) do not differentiate between the terms *impairment* (subjective cognitive impairment, SCI) and *decline*. However, the term *impairment* does not inherently indicate a temporal course of subjective cognitive change, as it can be of a chronic and stable nature and therefore requires an additional definition of onset. In contrast, the term *decline* already includes the fact that an onset has occurred (Jessen et al. 2014). As this study focuses on cognitive difficulties in patients following infection with the SARS-CoV-2 virus, the term *decline* is more appropriate and will therefore be used throughout this thesis to ensure clarity and avoid confusion.

Subjective cognitive decline (SCD) describes self-reported cognitive difficulties despite normal performance on standardized cognitive tests (Jessen et al., 2014; Perez, Duque, Hidalgo & Salvador, 2024). The term SCD was first introduced by researchers and clinicians in the field of AD in 2012 and has since been widely accepted (Jessen et al., 2014).

To meet the diagnostic criteria for SCD, two conditions must be present (Jessen et al., 2014): (1) A self-perceived, persistent decline in cognitive capacity across various cognitive domains, compared to a previously normal status, which is not attributable to an acute event, and (2) normal performance on standardized cognitive tests used to classify mild cognitive impairment (MCI) or prodromal AD, adjusted for age, gender, and educational level. Additionally, several exclusion criteria must be considered when diagnosing SCD. Exclusion criteria are MCI, prodromal AD or dementia. Furthermore, cognitive complaints that can be

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Commented [JH19]: First introduced by researchers and clinicians in the field of Alzheimer’s disease (AD) in 2012, Subjective Cognitive Decline (SCD) has since been widely accepted as a key concept in cognitive impairment research. In recent years, it has gained increasing attention due to its potential role as a preclinical marker of cognitive impairment, particularly in neurodegenerative diseases such as AD (Jessen et al., 2014).

explained by psychiatric or neurological disorders (other than AD), medical condition, medication, or substance use do not qualify for an SCD diagnosis (Jessen et al., 2014).

As the aging population grows, the prevalence of individuals experiencing SCD continues to rise (Perez et al., 2024). Not only therefore has it gained increasing attention in recent years, but also due to its potential role as a preclinical marker of cognitive impairment, particularly in the context of neurodegenerative diseases such as Alzheimer's disease (AD) (Jessen et al., 2014). A meta-analysis of longitudinal studies on SCD with a follow-up period of at least four years estimated that 27% of individuals with SCD progressed to MCI of 27 %, while 14% developed dementia (Mitchell et al., 2014).

In conclusion, although individuals with SCD perform within normal ranges on neuropsychological tests they face an increased risk of objective cognitive impairment, such as MCI, AD, dementia (L i et al., 2022; Numbers et al., 2023; Rivas-Fern´andez et al., 2023). Therefore, it would be beneficial to investigate early and reliable biomarkers for the detection and treatment of SCD in an attempt to maintain cognitive health and delay or prevent the progression to AD (Abdulrab & Heun, 2008).

Objective cognitive impairment

Objective cognitive impairment (OCI) refers to measurable deficits in cognitive function that exceed normal age-related decline and can be observed in various neurological disorders, with dementia being one of the most prevalent (Knopman & Petersen, 2014). Among the different causes of dementia, AD is the most common and extensively studied (Kamatham, Shukla, Khatri & Vora, 2024; Karantzoulis & Galvin, 2011). However, OCI is not exclusive to dementia. Many individuals exhibit measurable cognitive deficits that exceed normal aging but do not reach the severity required for a dementia diagnosis. Mild cognitive impairment (MCI) has been identified as an early but abnormal state of cognitive decline (Petersen, 2004), representing a transitional stage between normal brain aging and dementia (Petersen, 2016; Petersen et al., 2018; Robert & Knopman, 2013). Noteworthy, not all patients with MCI progress to dementia (Petersen, 2016). Nevertheless, MCI is associated with a high risk of conversion to dementia within a relatively short period (Bischkopf, Busse & Angermeyer, 2002; Roberts & Knopman, 2013), and has therefore become a significant global public health concern (Petersen et al., 2018; Roberts & Knopman, 2013). The prevalence of MCI among individuals over 60 is estimated to be between 15% and 20% (Petersen, 2016).
Of these individuals with MCI, 10-15% develop dementia annually, compared to a 1-2% annual developing rate among healthy controls ((6–8).

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Commented [JH23]: In conclusion, individuals with SCD perform within normal ranges on neuropsychological tests, they exhibit varying trajectories, with some maintaining stable cognitive function (Sohrabi et al., 2019) while others face an increased risk of objective cognitive impairment, such as MCI, AD, dementia (L i et al., 2022; Numbers et al., 2023; Rivas-Fern´andez et al., 2023).

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The DSM-5 introduced Mild Neurocognitive Disorder (mild NCD) (as a predementia phase), which is conceptually similar to MCI (Petersen, 2016). The diagnostic criteria for NCD (and therefore also for MCI (Petersen, 2016)) are according to the DSM-5: (1) A decline in cognitive abilities in one or more cognitive domains. This decline must be identified through a combination of subjective concerns and objective assessment, as they complement each other in the diagnostic process. (2) Daily function remains preserved (also in MCI (Petersen, 2016)) and (3) the cognitive impairment cannot be better explained through a psychological disease.

However, MCI is not a homogeneous condition, as cognitive and functional severity can vary widely among individuals meeting the diagnostic criteria (Roberts & Knopman, 2013).

Something about why I'm writing about MCI here – relevance to my study.

Now transition to EEG as a tool to assess cognitive impairment

Given the challenges in detecting early cognitive decline, particularly in the preclinical and MCI stages of AD, there is a need for objective, reliable, and non-invasive assessment tools. While traditional neuropsychological testing provides valuable insights into cognitive function, it is often influenced by factors such as education, motivation, and testing conditions. Same with SCI that might be influenced by….. Neuroimaging techniques, such as MRI and PET, offer structural and metabolic insights but can be costly and less accessible for routine monitoring. In this context, electroencephalography (EEG) emerges as a powerful alternative due to its high temporal resolution, cost-effectiveness, and ability to directly measure brain activity. Unlike behavioral tests, EEG is not significantly affected by learning effects and can be repeatedly administered to track disease progression. Furthermore, research has demonstrated that EEG can detect subtle alterations in brain connectivity and neural synchronization associated with cognitive decline, making it a promising tool for assessing both subjective cognitive complaints and objective impairments in MCI and AD.

EEG as a Tool to assess cognitive impairment

Now we looked at the two concepts and now we are going to look at:

Given the clinical importance of detecting cognitive impairment as early as possible, electroencephalography (EEG) has been proven to be a valuable tool for assessing both SCI (Rossini et al., 2007) and MCI/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). EEG is a neurophysiological

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1. **A decline in cognitive abilities in one or more cognitive domains**, identified through a combination of **subjective concerns and objective assessment**, as both complement each other in the diagnostic process.
2. **Preserved daily functioning**, meaning that cognitive impairments do not significantly interfere with independent daily activities (also in **MCI**) (Petersen, 2016).
3. **Exclusion of other potential causes**, ensuring that the cognitive impairment cannot be better explained by a psychological disorder.

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Commented [JH44]: Given its intermediate position between normal aging and dementia, MCI is particularly relevant to this study, as it represents a stage where cognitive decline is measurable but not yet severe, making early identification and intervention crucial. Investigating MCI in individuals with Post-COVID-19 Syndrome (PCS) may provide valuable insights into whether COVID-19-related cognitive impairment follows a similar trajectory to neurodegenerative processes

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Commented [JH46]: EEG is a widely used, non-invasive, and cost-effective method for assessing brain activity, making it a valuable tool for detecting cognitive impairment (Babiloni et al., 2016; Neo, Foti, Keehn & Kelleher, 2023). Unlike traditional neuropsychological tests, EEG provides direct neurophysiological insights by measuring the electrical activity of neurons, primarily reflecting synaptic activity synchronized across large-scale cortical networks (Babiloni et al., 2016; Nunez et al., 2001). It has a high temporal ...

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Commented [JH54]: From Babiloni et al., 2016 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 (Jeong, 2004) and other neurodegenerative disorders (cite).

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). Babiloni et al. (2021) came to the conclusion, that EEG can serve as an supportive diagnostic tool for cognitive impairment, detecting brain dysfunction even before reaching pathological diagnostic criteria. 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).

Beginning in 1970, the clinical use of EEG for diagnosing abnormal brain aging progressively supplanted as more advanced neuroimaging techniques became available (Babiloni et al., 2011). Despite this (shift/transition), EEG remains a valuable and widely used tool in scientific research and (some) clinical settings due to its unique advantages over other neuroimaging techniques. 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;

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EEG signals are derived from electric activity of neurons in the cerebral cortex (Babiloni et al., 2016). Specifically, thes ...

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Neo, Foti, Keehn & Kelleher, 2023; Rossini et al., 2019). 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).

Additionally, 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 MRI procedures (Babiloni et al., 2016). Unlike MRI, EEG can be recorded while patients are seated or lying comfortably, making it a practical option for longitudinal monitoring of cognitive decline. Finally, EEG rhythms can be recorded in highly comparable experimental conditions in healthy subject, subjects with SCD, subjects with MCI and subjects with more progressed disease such as AD (Rossini et al., 2007).

This study will focus on analyzing resting state EEG (rsEEG) as an important approach within qEEG methodologies, 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).

RsEEG is typically recorded from subjects during brief periods under both eyes-open and eyes-closed conditions (Perez et al., 2024). Since the eyes-closed condition represents a simple, standardized procedure (Babiloni et al., 2016), it is the most commonly used (Babiloni et al., 2022) and will therefore be analyzed in this study to ensure comparability.

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

Eyes-closed rsEEG rhythms undergo gradual changes across physiological aging (Babiloni et al., 2011; Babiloni et al., 2016; Babiloni et al., 2006; Barry & De Blasio, 2017). A common method to characterize these rhythms is through spectral power analysis across distinct

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Commented [JH96R95]: In normal aging, there may be a gradual slowing of EEG rhythms and subtle changes in neu ...

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frequency bands, as it reflects the distribution of neural activity and its role in various cognitive processes (Babiloni et al., 2016; Perez et al., 2024; Ward, 2003). However, in pathological aging, as in AD, these alterations are often more pronounced and disruptive, with significant changes in frequency bands (Lejko et al., 2020).

Commented [JH98]: From Perez et al., 2024

Commented [JH99]: This sentence should somehow go in here

Commented [JH100]: From Perez