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, 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 us to comprehend and interact with the world around us (Eysenck & Brysbaert, 2018). Cognition encompasses a range of mental processes, including 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 decline refers to varying degrees of damage to cognitive function resulting from a range of 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 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)

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Commented [JH12]: 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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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. 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 cognitive assessments highlight the complexity of measuring cognitive impairment. Before examining how these issues manifest in PCS, it is essential to understand the concepts of subjective cognitive decline 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 domains. The following sections provide an overview of both concepts, exploring their definitions, underlying mechanisms, and implications for research and clinical practice.

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

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Commented [JH21]: 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).

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 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 developing objective cognitive impairment, such as MCI and AD (L i et al., 2022; Numbers et al., 2023; Rivas-Fern´andez et al., 2023). Therefore, identifying early and reliable biomarkers for the detection of SCD is crucial for maintaining cognitive health and delay or prevent its 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,

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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 (Petersen, Stevens, Ganguli & Tangalos, 2001; Shah, Tangalos & Petersen, 2000).

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 varies widely among individuals meeting the diagnostic criteria (Roberts & Knopman, 2013).

Research suggests a link between PCS and increased risk of MCI. Bohlken, Weber, Heller, Michalowsky & Kostev (2022) found that patients diagnosed with COVID-19 had a significantly increased risk of MCI – referred to as mild cognitive disease (MCD) in their study – compared to those with other acute upper respiratory infections. Additionally, Schild et al. (2022) objectively confirmed NCD in around 60% of individuals with PCS with SCD in their study. This is why the context of MCI is discussed here.

As described, SCD and MCI are distinct measures of cognitive difficulties, yet they are interconnected and can both be observed in patients with PCS. Since SCD can progress to MCI, and MCI can further advance to AD, identifying early and reliable biomarkers for both conditions is crucial for maintaining cognitive health and delaying or preventing disease progression (Abdulrab & Heun, 2008). Given this 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 as a Tool to assess cognitive impairment

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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 [JH43]: This variability highlights the complexity of MCI as a clinical syndrome and underscores the importance of early and accurate assessment.

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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 (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.,

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EEG signals are derived from electric activity of neurons in the cerebral cortex (Babiloni et al., 2016). Specifically, these signals are mainly produced by post-synaptic ionic currents of synchronously active cortical pyramidal neurons reflecting the integrative information processing of signals coming from thalamus, brainstem, and other cortical modules (Babiloni et al., 2016).

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2016; Babiloni et al., 2021; Biasiucci, Franceschiello & Murray, 2019; Meghdadi et al., 2021; 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

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;

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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 0.5-3 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).

Delta frequency is typically absent during wakefulness in healthy adults and is primarily associated with deep sleep (Attar, 2022). Theta frequency is associated with the transition between wakefulness and sleep (Attar, 2022). Alpha frequency is characteristic of relaxed wakefulness (Attar, 2022). And beta frequency (14-30 Hz) is typically present when individuals are awake and mentally or physically active, or under psychological stress (Attar, 2022).

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 (beta, 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, Rosen & 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).

Commented [JH97]: From Babiloni et al., 2016

Commented [JH98]: @article{bachman2018independent, title={Independent contributions of theta and delta time-frequency activity to the visual oddball P3b}, author={Bachman, Matthew D and Bernat, Edward M}, journal={International Journal of Psychophysiology}, volume={128}, pages={70--80}, year={2018}, publisher={Elsevier} }

Commented [JH99]: https://doi.org/10.1016/j.ijpsycho.2018.03.010

Commented [JH100]: @article{gunasekaran2023characterizing, title={Characterizing endogenous delta oscillations in human MEG}, author={Gunasekaran, Harish and Azizi, Leila and van Wassenhove, Virginie and Herbst, Sophie K}, journal={Scientific Reports}, volume={13}, number={1}, pages={11031}, year={2023}, publisher={Nature Publishing Group UK London} }

Commented [JH101]: https://doi.org/10.1038/s41598-023-37514-1

Commented [JH102]: @article{uchida1992beta, title={Beta (20--28 Hz) and delta (0.3--3 Hz) EEGs oscillate reciprocally across NREM and REM sleep}, author={Uchida, Sunao and Maloney, Tom and Feinberg, Irwin}, journal={Sleep}, volume={15}, number={4}, pages={352--358}, year={1992}, publisher={Oxford University Press} }

Commented [JH103]: https://doi.org/10.1093/sleep/15.4.352

Commented [JH104]: @article{brovelli2004beta, ...

Commented [JH105]: https://doi.org/10.1073/pnas.030 ...

Commented [JH106]: @article{liang2020time, ...

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Commented [JH108]: @article{pesonen2007brain, ...

Commented [JH109]: https://doi.org/10.1016/j.brainre ...

Commented [JH110]: @article{poppelaars2018frontal, ...

Commented [JH111]: https://doi.org/10.3758/s13415- ...

Commented [JH112]: @article{tzagarakis2015brain, ...

Commented [JH113]: https://doi.org/10.3389/fnins.20 ...

Commented [JH114]: Is it enough if I only mention Atta ...

Commented [JH115]: Maybe also mention Gamma?

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Commented [JH117]: https://doi.org/10.17712/nsj.202 ...

Commented [JH118]: Yes?

Commented [JH119]: From Perez

Commented [JH120]: In normal aging, there may be a ...

Commented [JH121]: From Perez

Commented [JH122]: @article{d2021eeg, title={EEG ...

Commented [JH123]: https://doi.org/10.1016/j.isci.20 ...

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However, findings in MCI and SCD 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 obserbed primarily in the frontal (D'Atri et al., 2021), left temporo-parietal (Farina et al., 2020), and temporal-occipital regions (Jelic et al., 2020).

Commented [JH125]: Here?

Commented [JH126]: This heterogeneity suggests that MCI represents a transitional stage, with neurophysiological changes that may vary depending on disease progression and the likelihood of conversion to AD

Commented [JH127]: @article{babiloni2006sources, title={Sources of cortical rhythms change as a function of cognitive impairment in pathological aging: a multicenter study}, author={Babiloni, Claudio and Binetti, Giuliano and Cassetta, Emanuele and Dal Forno, Gloria and Del Percio, Claudio and Ferreri, Florinda and Ferri, Raffaele and Frisoni, Giovanni and Hirata, Koichi and Lanuzza, Bartolo and others}, journal={Clinical neurophysiology}, volume={117}, number={2}, pages={252--268}, year={2006}, publisher={Elsevier} }

Commented [JH128]: https://doi.org/10.1016/j.clinph.2005.09.019

Commented [JH129]: @article{babiloni2010cortical, title={Cortical sources of resting EEG rhythms in mild cognitive impairment and subjective memory complaint}, author={Babiloni, Claudio and Visser, Pieter Jelle and Frisoni, Giovanni and De Deyn, Peter Paul and Bresciani, Lorena and Jelic, Vesna and Nagels, Guy and Rodriguez, Guido and Rossini, Paolo M and Vecchio, Fabrizio and others}, journal={Neurobiology of Aging}, volume={31}, number={10}, pages={1787--1798}, year={2010}, publisher={Elsevier} }

Commented [JH130]: https://doi.org/10.1016/j.neurobiolaging.2008.09.020

Commented [JH131]: @article{konig2005decreased, title={Decreased EEG synchronization in Alzheimer's disease and mild cognitive impairment}, author={K{\"o}nig, Thomas and Prichep, Leslie and Dierks, Thomas and Hubl, Daniela and Wahlund, Lars O and John, Erwin R and Jelic, Vesna}, journal={Neurobiology of aging}, volume={26}, number={2}, pages={165--171}, year={2005}, publisher={Elsevier} }

Commented [JH132]: https://doi.org/10.1016/j.neurobiolaging.2004.03.008

Commented [JH133]: @article{ya2015electroencephalogram, title={Is the electroencephalogram power spectrum valuable for diagnosis of the elderly with cognitive impairment?}, author={Ya, Miao and Xun, Wang and Wei, Li and Ting, He and Hong, Yan and Yuan, Zhong}, journal={International Journal of Gerontology}, volume={9}, number={4}, pages={196--200}, year={2015}, publisher={Elsevier} }

Commented [JH134]: https://doi.org/10.1016/j.ijge.2014.07.001

Commented [JH135]: And some

Commented [JH136]: @article{kwak2006quantitative, title={Quantitative EEG findings in different stages of Alzheimer's disease}, author={Kwak, Yong Tae}, journal={Journal of clinical neurophysiology}, volume={23}, number={5}, pages={457--462}, year={2006}, publisher={LWW} }

Commented [JH137]: https://doi.org/10.1097/01.wnp.0000223453.47663.63

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 rehions (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.

Need headline here and transaction

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

Commented [JH138]: @article{babiloni2006sources, title={Sources of cortical rhythms change as a function of cognitive impairment in pathological aging: a multicenter study}, author={Babiloni, Claudio and Binetti, Giuliano and Cassetta, Emanuele and Dal Forno, Gloria and Del Percio, Claudio and Ferreri, Florinda and Ferri, Raffaele and Frisoni, Giovanni and Hirata, Koichi and Lanuzza, Bartolo and others}, journal={Clinical neurophysiology}, volume={117}, number={2}, pages={252--268}, year={2006}, publisher={Elsevier} }

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Commented [JH143]: https://doi.org/10.1016/j.neurobiolaging.2004.03.008

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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.

Transaction, why do I now mention Fatigue!?

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.

And why this now?

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. 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-slowing 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. 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-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.

Hypotheses

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. Individuals with objectively assessed lower cognitive performance will report higher levels of self-reported cognitive limitations compared to the group that performed better. Individuals, that have self-reported cognitive impairment, but were not recognized as low performers in objective cognitive assessment may have higher fatigue, anxiety, and depression scores than all other individuals. Concerning the delta frequency, a decreased delta power, in patients with objective cognitive lower performance compared to the better performers is expected, suggesting, that abnormal delta power is correlated to cognitive impairment. However, abnormal delta power may also be related to fatigue, suggesting that

Commented [Janka Hau147]: 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

Commented [JH148]: Setzen wir voraus, keine Hypothese

Commented [JH149]: Auf methodischer Ebene haben wir es geschafft zwei Gruppen - Auswerung, ob meine Methode funktioniert.

Commented [JH150]: Nehme ich voweg, 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 ...

Commented [JH151]: Chi2 test hier. Um das zu überprüfen

Commented [JH152]: Step 1: Wir überprüfen Hypothesen. Nenne Hypothesen die ich habe. Gucken uns aber danach auch die Unterschiede zwischen allen anderen Gruppen an, um ein allgemeines Bild zu kriegen. Und explorativ

Commented [JH153]: Darf mir alles explorativ darstellen. Wie kann ich das interessante auf den Punkt bringen. Alles, wozu ich eine Hypothese habe ist schon auf den Punkt gebracht. Dazu dann auch grafische darstellung.
Wenn explorativ, nicht unbedingt alles interessant. Daher ...

Commented [JH154]: Hypothesen müssen abgeleitet sein aus Theoreieteil. Warum vermuten wir das und was würde das bedeuten?

Commented [JH155]: Vorausannahme/Grund für Hypothese: Sie schätzen sich als kognitiv schlechter ein, weil sie andere Symptome haben, die sich auch auf Aufmerksamkeit…. Auswirken können (keine gute Begründung) -> Irgendwann natürlich auch in Diskussion. D...

Commented [JH156]: Mit Fatigue kann ich auch immer viel arbeiten. Nur Fatigue z.B. aber keine kognitive Einschränkung. Wenn sie sich so fühlen, sind sie es vielleicht auch aber die Studie nihct gereicht um fatigue auszulösen. Da ja Fatigue über 7 Tage abgefragt wurde (Quellen)

decreased delta power could be observed in patients with subjective cognitive impairment who do not exhibit lower objective cognitive performance. This would imply that their perceived cognitive limitations might be a symptom of fatigue rather than actual cognitive deficits. Concerning the beta frequency, an increase, in patients with objective lower performance compared to the better performers is expected, suggesting, that abnormal beta power is correlated to cognitive impairment. However, abnormal beta power may be (as delta power) also related to fatigue, suggesting that increased beta power could be observed in patients with subjective cognitive impairment who do not exhibit lower objective cognitive performance.

Schild et al., 2022: https://doi.org/10.1007/s00415-022-11444-w

In addition, it is uncertain at present, which cognitive domains are preferentially affected in the cognitive post-COVID-19 syndrome (theoretical background).

The post-COVID-19 syndrome is a multifaceted condition, which may affect cognition [4, 19] (first sentence of discussion (in general start of discussion quite good – use as guidline, love it!!!)).

Cognitive impairment in across all cognitive domains in line with other studies reporting deficits in learning and memoory, language, or executive functions.

Testet NCD!!!!

Neurocognitive impairment can be confirmed in around 60% of individuals with self-reported deficits as part of post-COVID-19 syndrome following a mild acute COVID-19 disease course (Schild et al., 2022). Notably, screening tests cannot reliably detect this dysfunction. Standard psychiatric assessments showed no association with cognitive profiles.

Bohlken, Weber, Heller, Michalowsky & Kostev, 2022:

Investigated whether COVID-19 diagnosis is associated with MCD.

Found: MCI was significantly more common in those diagnosed with COVID-19 than those diagnosed with other respiratory infections. However, incidence rate was low and only slightly higher. The incidence rate

ratio decreased strongly with increasing age. The

association between COVID-19 and MCD was only

significant among patients ≤50 and aged 51–60 years. Finally, COVID-19 was significantly associated with MCD in women but not men.

Commented [JH157]: @article{schild2023multidomain, title={Multidomain cognitive impairment in non-hospitalized patients with the post-COVID-19 syndrome: results from a prospective monocentric cohort}, author={Schild, Ann-Katrin and Goereci, Yasemin and Scharfenberg, Daniel and Klein, Kim and L{\"u}lling, Joachim and Meiberth, Dix and Schweitzer, Finja and St{\"u}rmer, Sophie and Zeyen, Philip and Sahin, Derya and others}, journal={Journal of neurology}, volume={270}, number={3}, pages={1215--1223}, year={2023}, publisher={Springer} }

This study conducted in Germany found that primary care patients diagnosed with COVID-19 were at a significantly increased risk of MCD compared to their counterparts who were diagnosed with other acute upper respiratory infections.