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.

This shows, that subjective and objective measures of cognitive function represent two distinct approaches to assessing cognition. Subjective assessments rely on self-reported experiences and perceptions (Stewart, 2012), while objective assessments use standardized tests and tasks to evaluate cognitive performance in various functional areas. Several studies have illustrated these discrepancies between subjective and objective measures further. In fact, most studies have reported higher rates of cognitive impairment through subjective cognitive complaints than through objective test results (Schild, 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, underscoring the discrepancies between patients' self-reports and objective neuropsychological test results. Bland et al. (2024) observed that there was no significant relation between objective and subjective measures of cognitive function, implying that self-reports of "brain fog" may not be reflected by objectively measured cognitive dysfunction.

Subjective cognitive deficits in everyday situations are predicted by elevated anxiety and fatigue levels more than by objective cognitive performance (Zamarian et al., 2024). This lack of alignment highlights the complexity of cognitive impairment and raises questions about which additional factors may influence individuals' perceptions of cognitive difficulties. Recent research has addressed these questions by examining how psychological symptoms influence subjective cognitive and objective cognitive impairment.
Zamarian et al. (2024) discovered that subjective cognitive deficits in everyday situations can be better explained by elevated anxiety and fatigue levels than by objective cognitive performance. In addition to anxiety (Almeria, Cejudo, Sotoca, Deus & Krupinski, 2020; Brück et al., 2019; Costas-Carrera et al., 2022; Hill et al., 2016; Zamarian et al., 2024) and fatigue (Bland et al., 2024; Delgado-Alonso et al., 2023; Zamarian et al., 2024), sleep disturbances (Zamarian et al., 2024) and depressive symptoms (Almeria et al., 2020; Brück et al., 2019; Costas-Carrera et al., 2022; Hill et al., 2016; Zamarian et al., 2024) have been found to be associated with subjective but not objective cognitive impairment (Henneghan, Lewis, Gill & Kesler, 2022). Objective cognitive function, on the other hand, was found to be related to perceived stress (Bland et al., 2024).

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.

Cognition

Cognition is defined as "the mental action or process of acquiring knowledge and understanding through thought, experience, and the sense" (Cambridge Cognition, 2015).

Cognition is essential for everyday functioning and refers to a range of mental processes such as the acquisition, storage, manipulation, and retrieval of information (Cambridge Cognition, 2015).

Cognitive impairment. Mild cognitive impairment will be explained in this section.

EEG findings in MCI. Reduced delta power during resting state EEG has been identified in patients with MCI (Liddell et al., 2007). Furthermore, in the study, individuals with MCI demonstrated a significant positive correlation between delta power and immediate memory recall. Liddell et al. (2007) proposed that these findings suggest that delta power may be linked to memory decline in MCI, indicating that it could serve as a sensitive indicator of prodromal or early cognitive decline. 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). A decrease in beta power has been found in individuals with mild AD (Hogan, Swanwick, Kaiser, Rowan & Lawlor, 2003).

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.

EEG findings in Fatigue.

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. Delta frequency (0.5-3 Hz) is typically absent during the waking state of healthy adults and is associated with deep sleep (Schandry, 2016). 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. Beta frequency (14-30 Hz) is typically present when individuals are awake and mentally or physically active, or under psychological stress (Schandry et al., 2016). 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 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.

Methods

Study Design and Participants

This study is part of a larger research project (EPOC), which investigates neurophysiological parameters identified from neuropsychological paradigms using high-resolution stationary EEG to reflect cognitive impairment and fatigue.

Participants for the EPOC study were recruited from the population-based cohort study COVIDOM, which investigates PCS (Bahmer et al., 2022). As EPOC is still ongoing at the time of writing this thesis, the analysis is being conducted based on a preliminary subset of 79 participants, of which 49 participants have PCS and 30 do not.

Procedure. In brief, the experiment consisted of neuropsychological tests (TMT, Odd-ball task, n-back task, PVT, and RTE), assessing cognitive domains such as working memory, attention, preprocessing speed, cognitive flexibility, executive functions, and multisensory integration, EEG recordings, and questionnaires assessing fatigue, sleep quality, depression, and anxiety. All data were collected at the University Medical Center Schleswig-Holstein (UKSH), Campus Kiel. In all, the experiment took up to three hours.

Since this thesis focuses on behavioral data obtained from the TMT, n-back, and PVT, as well as EEG resting state data, and data from the questionnaires, the RTE, and the oddball task will not be further explained. In addition, the MoCA score was measured in the previous COVIDOM study.

Cognitive Tasks

Montreal Cognitive Assessment (MoCA). The Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) is a widely used, validated screening tool originally designed to detect mild cognitive impairment (MCI) (Freitas, Simões, Alves, Vicente & Santana, 2012; Freitas, Simões, Marôco, Alves & Santana, 2012; Hoops et al., 2009). It assesses several cognitive domains, including visuospatial skills/ability, executive function, naming, memory (short-term and delayed recall), working memory, attention and concentration, language, abstraction, and orientation (Freitas, Simões, Alves & Santana, 2013; Hobson, 2015; Kang et al., 2018; Nasreddine et al., 2005). The MoCA has a total possible score of 30 points, with a score of ≥ 26 considered normal (Nasreddine et al., 2005)

TMT Part A and B. Originally, developed as part of the Army Individual Test Battery (AITB) in 1944, the Trail Marking Test (TMT) was later integrated into the Halstead-Reitan Battery (Reitan & Wolfson, 1985; Tombaugh, 2004). It is now one of the most popular and widely used neuropsychological assessments, included in most test batteries (Tombaugh, 2004). Its widespread use is supported by strong evidence of its validity (Arbuthnott & Frank, 2000; Sánchez-Cubillo et al., 2009). The TMT assesses cognitive processing speed and executive functioning (Lezak, 1995; Mitrushina, Boone, Razani & D'Elia, 2005; Sánchez-Cubillo et al., 2009; Straus, Sherman & Spreen, 2006; Tombaugh, 2004), as well as visual search/scanning, and mental flexibility (Sánchez-Cubillo et al., 2009; Tombaugh, 2004).

The TMT consists of two parts: Part A (TMT-A), a number-connection task, and Part B (TMT-B), a number-letter alternation task. Both parts were administered in this study according to the guidelines provided by Straus et al., 2006.

N-back task. The n-back task (Kirchner, 1958) has become a widely used tool in neuroscience for assessing working memory (Jaeggi, Buschkuehl, Perrig & Meier, 2010; Pelegrina et al., 2015). N-back tasks are continuous-recognition measures, that present sequences of stimuli (Kane, Conway, Miura & Colflesh, 2007). In these tasks, participants must determine whether a given stimulus matches one that was presented "n" trials before. In this study, participants completed two blocks of the n-back task. A 1-back task and a 2-back task. Reaction time, hits, misses, and false alarms were recorded for analysis.

PVT. The Psychomotor Vigilance Task (PVT) is a widely used reaction time test originally developed in 1985 to measure sustained attention (Drummond et al., 2005). Specifically, used to evaluate sustained attention and cognitive functions, particularly in contexts involving fatigue and sleep deprivation (Jakobsen, Sorensen, Rask, Jensen & Kondrup, 2011; Molina, Sanabria, Jung & Correa, 2019). This study employed a 5-minute version of the PVT, which has been established as a valid alternative to the traditional 10-minute PVT-192 (Lamond et al., 2008).

Questionnaires

PSQI. The Pittsburgh Sleep Quality Index (PSQI), developed by Buysse, Reynolds, Monk, Berman, and Kupfer in 1988 is a self-rated questionnaire that assesses sleep quality and disturbance over the past month. The PSQI is the most commonly used sleep health assessment tool in both clinical and research settings. Its reliability and validity have been consistently demonstrated in multiple studies (e.g. Carpenter & Andrykowski, 1998; Manzar et al., 2018; Mollayeva et al., 2016). Scores >5 indicate poor sleep quality (Buysse et al., 1989)

HADS. The self-assessment Hospital Anxiety and Depression Scale (HADS) was originally developed by Zigmond & Snaith in 1983 to identify the presence of anxiety and depression states among patients in nonpsychiatric hospital clinics. HADS is an extensively used, reliable, and valid instrument to measure anxiety and depression, not only in psychiatric, and clinical patients (Herrmann, 1997) but in general populations (Bjelland, Dahl, Haug & Neckelmann, 2002; Herrero et al., 2003; Spinhoven et al., 1997). Scores ≥8 indicate elevated anxiety and depression (Bjelland et al., 2002; Herrero et al., 2003; Zigmond & Snaith, 1983).

FACIT-F. The 13-item Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale (FACIT-F; Version 4) was used to assess self-reported fatigue and its impact on daily activities and functions (Cella, Lai, Chang, Peterman & Slavin, 2002; Yellen et al., 1997) during the last 7 days. While it was originally developed for cancer-related fatigue (Cella et al., 2002; Yellen et al., 1997), it has been shown, that the FACIT-F is a reliable and valid measure of fatigue across various health conditions (Cella et al., 2002), making it a widely used tool for both clinical practice and research (Cella et al., 2022; Butt et al., 2013; Montan, Löwe, Cella, Mehnert & Hinz, 2018; Tinsley, Macklin, Korzenik & Sands, 2011). Scores ≤30 indicate significant fatigue (Piper & Cella, 2010).

Cluster Analysis

Cluster analysis is an explorative statistical method used to organize objects, data points, or observations into homogeneous groups, known as clusters, based on similarities (Ketchen & Shook, 1996). The goal is to achieve high homogeneity within groups (intragroup homogeneity) and high heterogeneity between groups (intergroup heterogeneity) (Bacher, Pöge & Wenzig, 2010; Backhaus, Erichson, Gensler, Weiber & Weiber, 2011). In this study, the behavioral cognitive data from the PVT, TMT, MoCA, and n-back task will be utilized as cluster variables, aiming to identify two clusters that differ in their cognitive performance levels suggesting, that one group may perform better or worse than the other.

Data Preprocessing. All participant data will be imported into R, where preprocessing and analysis of the data will be conducted. The MoCA variable will be converted to a binary variable: scores ≤25 indicate cognitive impairment, while scores >25 indicate no impairment. Rows with missing values will be removed. Winzorising will be used to replace outliers by capping extreme values beyond 1.5 times the interquartile range (IQR). To account for the influence of age on cognitive performance, participants will be divided into age groups, and z-scores will be calculated within each group to adjust the data.

Cluster Analysis. A hierarchical cluster analysis will be performed on the preprocessed test data to identify clusters among participants. PVT reaction time, TMT a, TMT b, TMT b-a, MoCA, and n-back scores will be included. Euclidean distance will be used as a distance matrix, and Wars's method is selected for clustering, as it is widely used in practice and known for its effectiveness in identifying distinct clusters (Backhaus et al., 2011). It is considered a reliable algorithm, provided that the variables are on a metric scale, are uncorrelated, and do not contain outliers (Wentura & Pospeschill, 2015). As stated earlier, cluster analysis is an explorative method used to identify patterns in data. However, in this study, the approach is only semi-exploratory, as the number of clusters to be generated will be predetermined based on prior knowledge. A two-cluster solution will be explored, as that aligns with the self-reported groups (with PCS, and without PCS), thereby allowing for good comparisons between the cluster solution and the self-reported groups. One could also consider this as a confirmatory cluster analysis (Bacher et al., 2010). The stability of the clusters will be tested by comparing different proximity measures and algorithms using the adjusted Rand index (Hubert & Arabie, 1985).

Statistical analysis. The two clusters will be compared in several aspects. First, the two clusters will be compared in their cognitive performance levels to validate whether significant differences exist between clusters. Clusters will then be compared across demographic variables and results in questionnaires. Of particular interest is examining how those two clusters differ from or align with the self-reported perception of cognitive performance level. To investigate differences between objective and subjective cognitive performance levels, comparisons will occur not only between two clusters but also within the clusters between the subjective groups with PCS and without PCS. Additionally, to maximize the insights from the cluster analysis, the with PCS groups in cluster 1 will be compared to the with PCS group in cluster 2, and similarly for the without PCS groups. A t-test will be used for these comparisons.

Alongside the comparisons of demographic, cognitive data, and questionnaire results, the clusters will also be examined for their EEG resting state patterns.

EEG Recording and Analysis

For each group (withPCS and withoutPCS), 5 minutes of resting state with eyes open and 5 minutes of resting state with eyes closed is recorded using high-density EEG. EEG signals are recorded using a 128-channel EEG cap (128Ch Standard Brain Cap for actiCHamp Plus, Easycap GmbH, Wörthsee, Germany) with electrodes positioned in an equidistant layout, connected to an actiCHamp Plus amplifier (Brain Products GmbH, Gilching, Germany). The sampling rate is 1000 Hz with an amplitude resolution of 0.1 µV. Electrolyte gel is applied to improve conductivity between skin and electrodes, ensuring impedances remain below 20 kΩ. EOG activity is monitored using two EOG electrodes placed below each eye, with impedances also maintained below 20 kΩ. In addition, a ground electrode is positioned on the forehead, and a reference electrode is positioned on the tip of the nose. Impedances for both the reference and ground electrode are kept below 5 kΩ.

Preprocessing. Data preprocessing will be performed using the FieldTrip toolbox (Fieldtrip-20240504; Oostenveld, Fries, Maris & Schoffelen, 2011) and the EEGLab toolbox (v2024.0; Delorme & Makeig, 2004) in Matlab (v24.1.0.2578822 (R2024a) Mathworks Inc., 2024, MathWorks® https://de.mathworks.com).

Filtering and Resampling. A finite impulse response (FIR) windowed-sinc (firws) filter will be used for both high-pass and low-pass filtering. High-pass filtering will be applied with a cut-off frequency of 0.1 Hz to remove DC offset and low-frequency noise (slow drifts) for accurate analysis. Following the high-pass filtering, the data will be downsampled from 1000 Hz to 250 Hz. This resampling step will be conducted to reduce computational load while maintaining sufficient temporal resolution for subsequent analyses (Chiarion et al., 2023). After resampling, low-pass filtering will be performed with a cut-off frequency of 45 Hz to eliminate high-frequency noise and mitigate potential 50 Hz line noise (Delorme, 2023).

Artifact removal. First, large artifacts will be removed using the EEGLAB pop_clean_rawdata function. After that, Independent Component Analysis (ICA) will be performed, to detect and reject further artifacts, such as eye or muscle movement (Makeig et al., 1995). The data will be checked again to reject more possible bad channels or epochs. After that, all previously excluded channels will be interpolated (Miljevic, Bailey, Vila-Rodriguez, Herring & Fitzgerald, 2022).

Epoch length. The data will be cut into 5 s long epochs for delta and beta power analysis, since for resting state delta power, longer segments are preferred.

Power Analysis. Donoghue et al. (2020) noted that changes in absolute power may indicate a true change, but they could also reflect alterations in the aperiodic exponent, broad-band offset, or a shift in frequency center. Therefore, the focus will be on analyzing relative power while also examining the exponent. The power analysis will be conducted in R.

Statistical Analysis. When calculating the power in the delta band (frontal region of interest) and the beta band (sensorimotor areas as the region of interest), a single value will derived for each band. These values will then be compared between clusters/groups using a t-test. Similarly to the statistical analysis conducted after the cluster analysis, all possible comparisons will be made regarding EEG power in delta and beta bands.

References

Adler, G., Bramesfeld, A., & Jajcevic, A. (1999). Mild Cognitive Impairment in Old-Age Depression Is Associated with Increased EEG Slow-Wave Power. *Neuropsychobiology*, *40*(4), 218–222. https://doi.org/10.1159/000026623

Almeria, M., Cejudo, J. C., Sotoca, J., Deus, J., & Krupinski, J. (2020). Cognitive profile following COVID-19 infection: Clinical predictors leading to neuropsychological impairment. *Brain, Behavior, & Immunity-Health*, *9*, 100163. https://doi.org/10.1016/j.bbih.2020.100163

Andrei Appelt, P., Taciana Sisconetto, A., Baldo Sucupira, K. S. M., Neto, E. D. M., Chagas, T. D. J., Bazan, R., Moura Cabral, A., Andrade, A. D. O., De Souza, L. A. P. S., & José Luvizutto, G. (2022). Changes in Electrical Brain Activity and Cognitive Functions Following Mild to Moderate COVID-19: A one-Year Prospective Study After Acute Infection. *Clinical EEG and Neuroscience*, *53*(6), 543–557. https://doi.org/10.1177/15500594221103834

Antony, A. R., & Haneef, Z. (2020). Systematic review of EEG findings in 617 patients diagnosed with COVID-19. *Seizure*, *83*, 234–241. https://doi.org/10.1016/j.seizure.2020.10.014

Arbuthnott, K., & Frank, J. (2000). Trail Making Test, Part B as a Measure of Executive Control: Validation Using a Set-Switching Paradigm. *Journal of Clinical and Experimental Neuropsychology*, *22*(4), 518–528. https://doi.org/10.1076/1380-3395(200008)22:4;1-0;FT518

Bahmer, T., Borzikowsky, C., Lieb, W., Horn, A., Krist, L., Fricke, J., Scheibenbogen, C., Rabe, K. F., Maetzler, W., Maetzler, C., & others. (2022). Severity, predictors and clinical correlates of Post-COVID syndrome (PCS) in Germany: A prospective, multi-centre, population-based cohort study. *EClinicalMedicine*, *51*. https://doi.org/10.1016/j.eclinm.2022.101549

Bjelland, I., Dahl, A. A., Haug, T. T., & Neckelmann, D. (2002). The validity of the Hospital Anxiety and Depression Scale: An updated literature review. *Journal of Psychosomatic Research*, *52*(2), 69–77. https://doi.org/10.1016/S0022-3999(01)00296-3

Bland, A., Barraclough, M., Trender, W., Mehta, M., Hellyer, P., Hampshire, A., Penner, I.-K., Elliott, R., & Harenwall, S. (2024). Profiles of objective and subjective cognitive function in Post-

COVID Syndrome, COVID-19 recovered, and COVID-19 naïve individuals. *Scientific Reports*, *14*(1), 13368. https://doi.org/10.1038/s41598-024-62050-x

Brück, E., Larsson, J. W., Lasselin, J., Bottai, M., Hirvikoski, T., Sundman, E., Eberhardson, M., Sackey, P., & Olofsson, P. S. (2019). Lack of clinically relevant correlation between subjective and objective cognitive function in ICU survivors: A prospective 12-month follow-up study. *Critical Care*, *23*, 1–11. https://doi.org/10.1186/s13054-019-2527-1

Butt, Z., Lai, J., Rao, D., Heinemann, A. W., Bill, A., & Cella, D. (2013). Measurement of fatigue in cancer, stroke, and HIV using the Functional Assessment of Chronic Illness Therapy—Fatigue (FACIT-F) scale. *Journal of Psychosomatic Research, 74*(1), 64–68. https://doi.org/10.1016/j.jpsychores.2012.10.011

Buysse, D. J., Reynolds III, C. F., Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. *Psychiatry Research*, *28*(2), 193–213. https://doi.org/10.1016/0165-1781(89)90047-4

Carpenter, J. S., & Andrykowski, M. A. (1998). Psychometric evaluation of the Pittsburgh sleep quality index. *Journal of Psychosomatic Research*, *45*(1), 5–13. https://doi.org/10.1016/S0022-3999(97)00298-5

Ceban, F., Ling, S., Lui, L. M., Lee, Y., Gill, H., Teopiz, K. M., Rodrigues, N. B., Subramaniapillai, M., Di Vincenzo, J. D., Cao, B., & others. (2022). Fatigue and cognitive impairment in Post-COVID-19 Syndrome: A systematic review and meta-analysis. *Brain, Behavior, and Immunity*, *101*, 93–135. https://doi.org/10.1016/j.bbi.2021.12.020

Cecchetti, G., Agosta, F., Canu, E., Basaia, S., Barbieri, A., Cardamone, R., Bernasconi, M. P., Castelnovo, V., Cividini, C., Cursi, M., Vabanesi, M., Impellizzeri, M., Lazzarin, S. M., Fanelli, G. F., Minicucci, F., Giacalone, G., Falini, A., Falautano, M., Rovere-Querini, P., … Filippi, M. (2022). Cognitive, EEG, and MRI features of COVID-19 survivors: A 10-month study. *Journal of Neurology*, *269*(7), 3400–3412. https://doi.org/10.1007/s00415-022-11047-5

Cella, D., Lai, J., Chang, C.-H., Peterman, A., & Slavin, M. (2002). Fatigue in cancer patients compared with fatigue in the general United States population. *Cancer*, *94*(2), 528–538. https://doi.org/10.1002/cncr.10245

Chiarion, G., Sparacino, L., Antonacci, Y., Faes, L., & Mesin, L. (2023). Connectivity Analysis in EEG Data: A Tutorial Review of the State of the Art and Emerging Trends. *Bioengineering*, *10*(3), 372. https://doi.org/10.3390/bioengineering10030372

Costas-Carrera, A., Sánchez-Rodríguez, M. M., Cañizares, S., Ojeda, A., Martín-Villalba, I., Primé-Tous, M., Rodríguez-Rey, M. A., Segú, X., Valdesoiro-Pulido, F., Borras, R., & others. (2022). Neuropsychological functioning in post-ICU patients after severe COVID-19 infection: The role of cognitive reserve. *Brain, Behavior, & Immunity-Health*, *21*, 100425. https://doi.org/10.1016/j.bbih.2022.100425

Delgado-Alonso, C., Díez-Cirarda, M., Pagán, J., Pérez-Izquierdo, C., Oliver-Mas, S., Fernández-Romero, L., Martínez-Petit, Á., Valles-Salgado, M., Gil-Moreno, M. J., Yus, M., & others. (2023). Unraveling brain fog in post-COVID syndrome: Relationship between subjective cognitive complaints and cognitive function, fatigue, and neuropsychiatric symptoms. *European Journal of Neurology*. https://doi.org/10.1111/ene.16084

Delorme, A. (2023). EEG is better left alone. *Scientific Reports*, *13*(1), 2372. https://doi.org/10.1038/s41598-023-27528-0

Delorme, A., & Makeig, S. (2004). EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of Neuroscience Methods*, *134*(1), 9–21. https://doi.org/10.1016/j.jneumeth.2003.10.009

Donoghue, T., Haller, M., Peterson, E. J., Varma, P., Sebastian, P., Gao, R., Noto, T., Lara, A. H., Wallis, J. D., Knight, R. T., Shestyuk, A., & Voytek, B. (2020). Parameterizing neural power spectra into periodic and aperiodic components. *Nature Neuroscience*, *23*(12), 1655–1665. https://doi.org/10.1038/s41593-020-00744-x

Drummond, S. P. A., Bischoff-Grethe, A., Dinges, D. F., Ayalon, L., Mednick, S. C., & Meloy, M. J. (2005). The Neural Basis of the Psychomotor Vigilance Task. *Sleep*. https://doi.org/10.1093/sleep/28.9.1059

Freitas, S., Simões, M. R., Alves, L., & Santana, I. (2013). Montreal cognitive assessment: Validation study for mild cognitive impairment and Alzheimer disease. *Alzheimer Disease & Associated Disorders*, *27*(1), 37–43. https://doi.org/10.1097/WAD.0b013e3182420bfe

Freitas, S., Simões, M. R., Alves, L., Vicente, M., & Santana, I. (2012). Montreal Cognitive Assessment (MoCA): Validation Study for Vascular Dementia. *Journal of the International Neuropsychological Society*, *18*(6), 1031–1040. https://doi.org/10.1017/S135561771200077X

Freitas, S., Simões, M. R., Marôco, J., Alves, L., & Santana, I. (2012). Construct Validity of the Montreal Cognitive Assessment (MoCA). *Journal of the International Neuropsychological Society*, *18*(2), 242–250. https://doi.org/10.1017/S1355617711001573

Furlanis, G., Buoite Stella, A., Biaduzzini, F., Bellavita, G., Frezza, N. A., Olivo, S., Menichelli, A., Lunardelli, A., Ajčević, M., & Manganotti, P. (2023). Cognitive deficit in post-acute COVID-19: An opportunity for EEG evaluation? *Neurological Sciences*, *44*(5), 1491–1498. https://doi.org/10.1007/s10072-023-06615-0

Henneghan, A. M., Lewis, K. A., Gill, E., & Kesler, S. R. (2022). Cognitive impairment in non-critical, mild-to-moderate COVID-19 survivors. *Frontiers in Psychology*, *13*, 770459. https://doi.org/10.3389/fpsyg.2022.770459

Herrero, M. J., Blanch, J., Peri, J. M., De Pablo, J., Pintor, L., & Bulbena, A. (2003). A validation study of the hospital anxiety and depression scale (HADS) in a Spanish population. *General Hospital Psychiatry*, *25*(4), 277–283. https://doi.org/10.1016/S0163-8343(03)00043-4

Herrmann, C. (1997). International experiences with the Hospital Anxiety and Depression Scale-a review of validation data and clinical results. *Journal of Psychosomatic Research*, *42*(1), 17–41. https://doi.org/10.1016/S0022-3999(96)00216-4

Hill, N. L., Mogle, J., Wion, R., Munoz, E., DePasquale, N., Yevchak, A. M., & Parisi, J. M. (2016). Subjective cognitive impairment and affective symptoms: A systematic review. *The Gerontology*, *56*(6), e109–e127. https://doi.org/10.1093/geront/gnw091

Hobson, J. (2015). The montreal cognitive assessment (MoCA). *Occupational Medicine*, *65*(9), 764–765. https://doi.org/10.1093/occmed/kqv078

Hogan, M. J., Swanwick, G. R. J., Kaiser, J., Rowan, M., & Lawlor, B. (2003). Memory-related EEG power and coherence reductions in mild Alzheimer's disease. *International Journal of Psychophysiology*, *49*(2), 147–163. https://doi.org/10.1016/S0167-8760(03)00118-1

Hoops, S., Nazem, S., Siderowf, A. D., Duda, J. E., Xie, S. X., Stern, M. B., & Weintraub, D. (2009). Validity of the MoCA and MMSE in the detection of MCI and dementia in Parkinson disease. *Neurology*, *73*(21), 1738–1745. https://doi.org/10.1212/WNL.0b013e3181c34b47

Inc, T. M. (2024). *MATLAB version: 24.1.0.2578822 (R2024a)* [Computer software]. The MathWorks Inc. https://www.mathworks.com

Jaeggi, S. M., Buschkuehl, M., Perrig, W. J., & Meier, B. (2010). The concurrent validity of the N-back task as a working memory measure. *Memory*, *18*(4), 394–412.

Jakobsen, L. H., Sorensen, J. M., Rask, I. K., Jensen, B. S., & Kondrup, J. (2011). Validation of reaction time as a measure of cognitive function and quality of life in healthy subjects and patients. *Nutrition*, *27*(5), 561–570. https://doi.org/10.1016/j.nut.2010.08.003

Kane, M. J., Conway, A. R. A., Miura, T. K., & Colflesh, G. J. H. (2007). Working memory, attention control, and the n-back task: A question of construct validity. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, *33*(3), 615–622. https://doi.org/10.1037/0278-7393.33.3.615

Kang, J. M., Cho, Y.-S., Park, S., Lee, B. H., Sohn, B. K., Choi, C. H., Choi, J.-S., Jeong, H. Y., Cho, S.-J., Lee, J.-H., & others. (2018). Montreal cognitive assessment reflects cognitive reserve. *BMC Geriatrics*, *18*, 1–8. https://doi.org/10.1186/s12877-018-0951-8

Kirchner, W. K. (1958). Age differences in short-term retention of rapidly changing information. *Journal of Experimental Psychology*, *55*(4), 352.

Koenig, T., Smailovic, U., & Jelic, V. (2020). Past, present and future EEG in the clinical workup of dementias. *Psychiatry Research: Neuroimaging*, *306*, 111182. https://doi.org/10.1016/j.pscychresns.2020.111182

Kopańska, M., Ochojska, D., Muchacka, R., Dejnowicz-Velitchkov, A., Banaś-Ząbczyk, A., & Szczygielski, J. (2022). Comparison of QEEG Findings before and after Onset of Post-COVID-19 Brain Fog Symptoms. *Sensors*, *22*(17), 6606. https://doi.org/10.3390/s22176606

Kubota, T., Gajera, P. K., & Kuroda, N. (2021). Meta-analysis of EEG findings in patients with COVID-19. *Epilepsy & Behavior*, *115*, 107682. https://doi.org/10.1016/j.yebeh.2020.107682

Kwan, A. T., Lakhani, M., Le, G. H., Singh, G., Teopiz, K. M., Ceban, F., Nijjar, C. S., Meshkat, S., Badulescu, S., Ho, R., & others. (2024). Subjective and objective measures of cognitive function are correlated in persons with Post-COVID-19 Condition: A secondary analysis of a Randomized Controlled Trial. *European Archives of Psychiatry and Clinical Neuroscience*, 1–8. https://doi.org/10.1007/s00406-024-01877-x

Lamond, N., Jay, S. M., Dorrian, J., Ferguson, S. A., Roach, G. D., & Dawson, D. (2008). The sensitivity of a palm-based psychomotor vigilance task to severe sleep loss. *Behavior Research Methods*, *40*(1), 347–352. https://doi.org/10.3758/BRM.40.1.347

Lezak, M. D. (2004). *Neuropsychological assessment*. Oxford University Press, USA.

Liddell, B. J., Paul, R. H., Arns, M., Gordon, N., Kukla, M., Rowe, D., Cooper, N., Moyle, J., & Williams, L. M. (2007). RATES OF DECLINE DISTINGUISH ALZHEIMER'S DISEASE AND MILD COGNITIVE IMPAIRMENT RELATIVE TO NORMAL AGING: INTEGRATING COGNITION AND BRAIN FUNCTION. *Journal of Integrative Neuroscience*, *06*(01), 141–174. https://doi.org/10.1142/S0219635207001374

Makeig, S., Bell, A., Jung, T.-P., & Sejnowski, T. J. (1995). Independent component analysis of electroencephalographic data. *Advances in Neural Information Processing Systems*, *8*.

Manzar, M. D., BaHammam, A. S., Hameed, U. A., Spence, D. W., Pandi-Perumal, S. R., Moscovitch, A., & Streiner, D. L. (2018). Dimensionality of the Pittsburgh Sleep Quality Index: A systematic review. *Health and Quality of Life Outcomes, 16,* 1–22. https://doi.org/10.1186/s12955-018-0915-x

Miljevic, A., Bailey, N. W., Vila-Rodriguez, F., Herring, S. E., & Fitzgerald, P. B. (2022). Electroencephalographic Connectivity: A Fundamental Guide and Checklist for Optimal Study Design and Evaluation. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *7*(6), 546–554. https://doi.org/10.1016/j.bpsc.2021.10.017

Mitrushina, M., Boone, K. B., Razani, J., & D'Elia, L. F. (2005). *Handbook of normative data for neuropsychological assessment*. Oxford University Press.

Molina, E., Sanabria, D., Jung, T.-P., & Correa, Á. (2019). Electroencephalographic and peripheral temperature dynamics during a prolonged psychomotor vigilance task. *Accident Analysis & Prevention*, *126*, 198–208. https://doi.org/10.1016/j.aap.2017.10.014

Mollayeva, T., Thurairajah, P., Burton, K., Mollayeva, S., Shapiro, C. M., & Colantonio, A. (2016). The Pittsburgh sleep quality index as a screening tool for sleep dysfunction in clinical and non-clinical samples: A systematic review and meta-analysis. *Sleep Medicine Reviews*, *25*, 52–73. https://doi.org/10.1016/j.smrv.2015.01.009

Montan, I., Löwe, B., Cella, D., Mehnert, A., & Hinz, A. (2018). General population norms for the functional assessment of chronic illness therapy (FACIT)-fatigue scale. *Value in Health*, *21*(11), 1313–1321. https://doi.org/10.1016/j.jval.2018.03.013

Moretti, D. V., Zanetti, O., Binetti, G., & Frisoni, G. B. (2012). Quantitative EEG Markers in Mild Cognitive Impairment: Degenerative versus Vascular Brain Impairment. *International Journal of Alzheimer's Disease*, *2012*, 1–12. https://doi.org/10.1155/2012/917537

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J. L., & Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society*, *53*(4), 695–699. https://doi.org/10.1111/j.1532-5415.2005.53221.x

Oostenveld, R., Fries, P., Maris, E., & Schoffelen, J.-M. (2011). FieldTrip: Open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. *Computational Intelligence and Neuroscience*, *2011*(1), 156869. https://doi.org/10.1155/2011/156869

Organization, W. H. (2023). *WHO Coronavirus (COVID-19) Dashboard > Cases*. https://data.who.int/dashboards/covid19/cases

Organization, W. H. & others. (2021). *A clinical case definition of post COVID-19 condition by a Delphi consensus, 6 October 2021*. World Health Organization. https://www.who.int/publications/i/item/clinical-case-definition-of-post-covid-19-condition

Ortelli, P., Quercia, A., Cerasa, A., Dezi, S., Ferrazzoli, D., Sebastianelli, L., Saltuari, L., Versace, V., & Quartarone, A. (2023). Lowered Delta Activity in Post-COVID-19 Patients with Fatigue and Cognitive Impairment. *Biomedicines*, *11*(8), 2228. https://doi.org/10.3390/biomedicines11082228

Pasini, E., Bisulli, F., Volpi, L., Minardi, I., Tappatà, M., Muccioli, L., Pensato, U., Riguzzi, P., Tinuper, P., & Michelucci, R. (2020). EEG findings in COVID-19 related encephalopathy. *Clinical Neurophysiology*, *131*(9), 2265–2267. https://doi.org/10.1016/j.clinph.2020.07.003

Pastor, J., Vega-Zelaya, L., & Martín Abad, E. (2020). Specific EEG Encephalopathy Pattern in SARS-CoV-2 Patients. *Journal of Clinical Medicine*, *9*(5), 1545. https://doi.org/10.3390/jcm9051545

Pelegrina, S., Lechuga, M. T., García-Madruga, J. A., Elosúa, M. R., Macizo, P., Carreiras, M., Fuentes, L. J., & Bajo, M. T. (2015). Normative data on the n-back task for children and young adolescents. *Frontiers in Psychology*, *6*. https://doi.org/10.3389/fpsyg.2015.01544

Piper, B. F., & Cella, D. (2010). Cancer-related fatigue: Definitions and clinical subtypes. *Journal of the National Comprehensive Cancer Network*, *8*(8), 958–966. https://doi.org/10.6004/jnccn.2010.0070

Reitan, R. M., & Wolfson, D. (1985). *The Halstead-Reitan neuropsychological test battery: Theory and clinical interpretation* (Vol. 4). Neuropsychology press.

Roberto, K. T., Espiritu, A. I., Fernandez, M. L. L., & Gutierrez, J. C. (2020). Electroencephalographic findings in COVID-19 patients: A systematic review. *Seizure*, *82*, 17–22. https://doi.org/10.1016/j.seizure.2020.09.007

Sánchez-Cubillo, I., Periáñez, J. A., Adrover-Roig, D., Rodríguez-Sánchez, J. M., Ríos-Lago, M., Tirapu, J., & Barceló, F. (2009). Construct validity of the Trail Making Test: Role of task-switching, working memory, inhibition/interference control, and visuomotor abilities. *Journal of the International Neuropsychological Society*, *15*(3), 438–450. https://doi.org/10.1017/S1355617709090626

Schandry, R. (2016). *Biologische Psychologie. 4., überarbeitete Auflage*. Beltz - Psychologie-Verlags-Union.

Schild, A.-K., Goereci, Y., Scharfenberg, D., Klein, K., Lülling, J., Meiberth, D., Schweitzer, F., Stürmer, S., Zeyen, P., Sahin, D., & others. (2023). Multidomain cognitive impairment in non-hospitalized patients with the post-COVID-19 syndrome: Results from a prospective monocentric cohort. *Journal of Neurology*, *270*(3), 1215–1223. https://doi.org/10.1007/s00415-022-11444-w

Schild, A.-K., Scharfenberg, D., Kirchner, L., Klein, K., Regorius, A., Goereci, Y., Meiberth, D., Sannemann, L., Lülling, J., Schweitzer, F., & others. (2023). Subjective and objective cognitive deficits in patients with post-COVID syndrome. *Zeitschrift Für Neuropsychologie*. https://doi.org/10.1024/1016-264X/a000374

Spinhoven, P., Ormel, J., Sloekers, P., Kempen, G., Speckens, A. E., & van Hemert, A. M. (1997). A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. *Psychological Medicine*, *27*(2), 363–370. https://doi.org/10.1017/S0033291796004382

Stewart, R. (2012). Subjective cognitive impairment. *Current Opinion in Psychiatry*, *25*(6), 445–450. https://doi.org/10.1097/YCO.0b013e3283586fd8

Straus, E., Sherman, E., & Spreen, O. (2006). A compendium of neuropsychological tests: Administration, norms, and commentary. *American Journal of Hypnosis*, 267–270.

Tinsley, A., Macklin, E., Korzenik, J., & Sands, B. (2011). Validation of the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) in patients with inflammatory bowel disease. *Alimentary Pharmacology & Therapeutics*, *34*(11–12), 1328–1336. https://doi.org/10.1111/j.1365-2036.2011.04871.x

Tombaugh, T. (2004). Trail Making Test A and B: Normative data stratified by age and education. *Archives of Clinical Neuropsychology*, *19*(2), 203–214. https://doi.org/10.1016/S0887-6177(03)00039-8

Wojcik, G. M., Shriki, O., Kwasniewicz, L., Kawiak, A., Ben-Horin, Y., Furman, S., Wróbel, K., Bartosik, B., & Panas, E. (2023). Investigating brain cortical activity in patients with post-COVID-19 brain fog. *Frontiers in Neuroscience*, *17*, 1019778. https://doi.org/10.3389/fnins.2023.1019778

Yellen, S. B., Cella, D. F., Webster, K., Blendowski, C., & Kaplan, E. (1997). Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. *Journal of Pain and Symptom Management*, *13*(2), 63–74. https://doi.org/10.1016/S0885-3924(96)00274-6

Zamarian, L., Rass, V., Goettfried, E., Mayr, V., Carbone, F., Kindl, P., Delazer, M., Djamshidian, A., Fanciulli, A., Mahlknecht, P., & others. (2024). Objective and subjective cognitive outcomes one year after COVID-19. *Annals of Clinical and Translational Neurology*. https://doi.org/10.1002/acn3.52149

Zigmond, A. S., & Snaith, R. P. (1983). The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica*, *67*(6), 361–370. https://doi.org/10.1111/j.1600-0447.1983.tb09716.x