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MASTERARBEIT

**Exploring Delta and Beta Frequency Power and  
Connectivity in Post COVID Syndrome Using EEG**

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**Abstract**

Post COVID Syndrome (PCS) affects a significant number of individuals following SARS-CoV-2 infection, often including cognitive difficulties and fatigue. By capturing oscillatory brain activity across different frequency bands, EEG provides insights into neural dynamics underlying cognitive processes and fatigue. Previous EEG studies have reported varying levels of delta power in PCS patients, but the role of delta power in relation to these symptoms remains unclear. Additionally, a relationship between higher beta connectivity and fatigue has been hypothesized. This high-density EEG study aimed to investigate the relationship between delta and beta power/connectivity and subjective cognitive difficulties and fatigue in patients with PCS. A total of 46 participants were included and divided into two age-matched groups of equal size, based on whether they reported subjective cognitive difficulties following infection or not. All participants underwent a 5-minute resting state EEG recording. Relative delta and beta power, the aperiodic offset and exponent, functional connectivity as well as the graph measures Clustering Coefficient, Characteristic Path Length and Small World Index were analyzed. Results indicated no significant differences in delta or beta power or delta connectivity between groups. However, beta functional connectivity was found to be significantly higher in the PCS group, supporting previous research on the link between beta connectivity and fatigue. These findings contribute to the understanding of fatigue in PCS, but still warrant further investigation in the source space.

**Keywords:** Post COVID Syndrome, EEG, Delta Power, Beta Connectivity, Fatigue

**German Abstract**

Das Post-COVID-Syndrom (PCS) betrifft eine bedeutende Anzahl von Personen nach einer SARS-CoV-2-Infektion und involviert oft kognitive Beeinträchtigungen und Fatigue. Durch die Erfassung oszillatorischer Gehirnaktivität in verschiedenen Frequenzbändern liefert das EEG Einblicke in neuronale Dynamiken, die kognitiven Prozessen und Fatigue zugrunde liegen. Frühere EEG-Studien haben unterschiedliche Niveaus der Deltawellenaktivität bei PCS-Patienten berichtet, aber die Rolle der Deltawellen im Zusammenhang mit diesen Symptomen bleibt unklar. Zusätzlich wurde eine Hypothese über den Zusammenhang zwischen höherer Beta-Konnektivität und Fatigue aufgestellt. Diese EEG-Studie mit 128 Elektroden hatte zum Ziel, den Zusammenhang zwischen Delta- und Beta-Power/Konnektivität sowie subjektiven kognitiven Beeinträchtigungen und Fatigue bei Patienten mit PCS zu untersuchen. Insgesamt wurden 46 Teilnehmende eingeschlossen und in zwei altersangepasste Gruppen gleicher Größe aufgeteilt, basierend darauf, ob sie subjektive kognitive Schwierigkeiten nach der Infektion angaben oder nicht. Alle Teilnehmenden unterzogen sich einer 5-minütigen EEG-Aufzeichnung im Ruhezustand. Relative Delta- und Beta-Power, der aperiodische Offset und Exponent, funktionelle Konnektivität sowie verschiedene Netzwerkeigenschaften wurden analysiert: der Cluster-Koeffizient, die charakteristische Pfadlänge und der Small-World-Index. Die Ergebnisse zeigten keine signifikanten Unterschiede in der Delta- oder Beta-Power oder der Delta-Konnektivität zwischen den Gruppen. Allerdings wurde eine signifikant höhere Beta-Konnektivität in der PCS-Gruppe festgestellt, was frühere Forschungsergebnisse über den Zusammenhang zwischen Beta-Konnektivität und Fatigue unterstützt. Diese Erkenntnisse tragen zum Verständnis von Fatigue bei PCS bei, erfordern jedoch weitere Untersuchungen bezüglich der Lokalisation.

**Keywords:** Long COVID, EEG, Delta Power, Beta Konnektivität, Fatigue

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## **Exploring Delta and Beta Frequency Power and Connectivity in Post COVID Syndrome Using EEG**

### **Theoretical Background**

Starting with its initial identification in 2019, the severe acute respiratory syndrome coronavirus 2 (Sars-CoV-2) became an urgent public health matter (Tang et al., 2020). The disease following it was termed COVID-19 by the World Health Organization (WHO) and may entail symptoms such as fever, cough, fatigue, shortness of breath or taste disorders (Jiang et al., 2020; Tang et al., 2020). There are neuropsychiatric or neurologic symptoms among these, e.g. brain fog or inability to concentrate, which is in line with the susceptibility of neuronal cells to Sars-CoV-2 (Baig, 2020; Chu et al., 2020).

Subsequently, different studies were conducted to investigate possible changes in the brain, including Electroencephalography (EEG) studies. In a meta-analysis of EEG studies in patients with COVID-19, around 96% showed abnormal background activity and 92% a generalized slowing (Kubota et al., 2021). The infection seems to coincide with some abnormalities in the EEG pattern (Antony & Haneef, 2020; Cecchetti et al., 2020; Kopańska et al., 2021). Sometimes the EEG patterns seemed to visually be comparable to epilepsy (W. Chen et al., 2020; Galanopoulou et al., 2020) or to encephalopathy (W. Chen et al., 2020; Koutroumanidis et al., 2021; Pasini et al., 2020; Pastor et al., 2020).

### **Post COVID Syndrome**

Soon after the outbreak of the disease, several people were experiencing ongoing symptoms after being diagnosed with COVID-19, which was termed long(-haul) or post COVID (Callard & Perego, 2021; Rubin, 2020; Yong, 2021a). In this study the term post COVID Syndrome (PCS) will be used. The prevalence range spans 9% to 82%, with generally higher prevalence among previously hospitalized patients (C. Chen et al., 2022). However, hospitalization or strong infection does not seem a necessary requirement for developing PCS (Rubin, 2020). At first, many different descriptions of the disease appeared (Yong, 2021a). The National Institute for Health and Care Excellence came up with a guideline in 2021, as outlined by Venkatesan (2021). If

symptoms persisted for more than 12 weeks, they would define it as PCS. The WHO also defined the condition in 2021. According to them, the symptoms would need to appear at least three months after acute infection and would need to last at least two months. As common symptoms they list among others fatigue, shortness of breath and cognitive dysfunction (Soriano et al., 2022). Fittingly, a systematic review and meta-analysis by Ceban et al. (2022) identified fatigue and cognitive impairment as the main symptoms in PCS-pts, with 32% experiencing fatigue and 22% reporting cognitive impairment 12 weeks after infection. The fatigue of post COVID Syndrome patients (PCS-pts) can, for example, include that daily activities are exhausting and that working for more than a couple of minutes is nearly impossible (Marshall, 2020). Cognitive impairment can be measured with tests like the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) or the Mini-Mental State Examination (MMSE; Tombaugh & McIntyre, 1992). In some studies, the PCS-pts scored worse in the MoCA (Clemente et al., 2023; Ortelli et al., 2023; Rahimi et al., 2024) or MMSE (Cecchetti et al., 2022), in one other study they did not (Appelt et al., 2022). Importantly, although their scores may be lower than those of healthy controls, they often remain above the clinical cutoff for cognitive impairment (Lynch et al., 2022). While some argue the MoCA may not be ideal for assessing PCS (Lynch et al., 2022), it is considered more sensitive regarding subclinical changes than the MMSE (Aiello et al., 2022). As previously outlined, COVID-19 and PCS are different per definition (Venkatesan, 2021; World Health Organization, 2021). Most importantly, COVID-19 is an acute illness state, while PCS is not (Venkatesan, 2021). For instance, none of the PCS-pts reported experiencing a fever, a symptom typically associated with acute illness (Carfi et al., 2020).

While acute symptoms tend to be more visible and might seem more immediately relevant, the experienced persistent symptoms in PCS, particularly fatigue, reduce the quality of life profoundly (Ceban et al., 2022; Malik et al., 2022). Additionally, the indirect societal costs, due to for example absenteeism, are substantial (Ida et al., 2024). Emerging hypotheses suggest that PCS with neurological symptoms might be related to biological changes, such as the degeneration of glial cells in the brain (Baig, 2020). There are also findings that involve the main symptoms of

cognitive difficulties and fatigue: for example, increased cortical thickness was found to be associated with worse MoCA scores (Besteher et al., 2024) and structural brain changes were found to be associated with fatigue severity in PCS-pts (Heine et al., 2023).

### **Why Investigate PCS With EEG?**

There are still many uncertainties to what extent and how exactly the infection might change the brain's activity. EEG studies play a role in identifying abnormal brain signals and linking them to changes in behavior and perception. The EEG is a non-invasive method to study neuronal activity with high temporal resolution. Some of its parameters are widely studied, for example power, which is the squared amplitude (Schandry, 2016). Further, the frequency bands may reflect different mental processes. In general, there are the alpha, beta, theta, delta and gamma frequency bands, but this paper will focus on delta and beta. The delta frequency (0.5-4 Hz) is characteristic for sleep and usually absent during the waking state (Amzica & Steriade, 1998; Colrain, 2011). In contrast, the beta frequency (14-30 Hz) is usually present when a person is awake and mentally or physically active (Barone & Rossiter, 2021; Tanaka et al., 2012). For research in general and individuals with PCS in particular, understanding whether their subjective cognitive difficulties and/or fatigue are linked to biological or neurological alterations would be valuable. However, identifying these links is not trivial. Finding group differences in one or multiple frequencies can be an indicator for differences in the functioning of the brain. In some cases, EEG has been utilized to discover biomarkers that facilitate diagnosis, monitoring, and treatment of specific disorders. For example, the location and frequency of resting state oscillations could distinguish patients with Parkinson's dementia from those with Alzheimer's Disease (Babiloni et al., 2011). This approach could similarly support biomarker discovery in PCS.

It would be interesting to evaluate, whether the EEG patterns of PCS align with EEG patterns of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), a disease with similar symptoms to PCS (Wong & Weitzer, 2021). One study tried this already, comparing Fybromyalgia, ME/CFS, and PCS, but concluded that for PCS the evidence is still too scarce (Silva-Passadouro et al., 2024). Therefore, one value of this studies lies in adding to the number of

EEG studies in PCS.

While EEG literature regarding PCS might be scarce, EEG literature in (neurological) diseases is plentiful. Here, it could be insightful to draw on results from EEG studies that investigate the same symptoms in other diseases, for example fatigue, when formulating first hypotheses for the novel PCS.

Another aspect that can be studied in PCS by means of the EEG is synchronization, also called functional connectivity (FC), in the brain. Friston (2011) defines FC as statistical dependencies, such as correlations between distant neurophysiological events. The idea behind it is that synchronization of neuronal populations should facilitate the exchange of information (Cohen, 2019). However, too much synchronization can be problematic and may signal an issue in the brain. To illustrate, in Parkinson's patients, the excessive beta band synchronization in the sensorimotor cortex seems to go in line with the observed rigidity (Brown, 2003; Halje et al., 2019; Lamoš et al., 2023). In the same vein as EEG power, EEG connectivity measures could potentially serve as biomarkers (Barzegaran et al., 2016; Hassan et al., 2017; Marino & Mantini, 2024).

The Small-World Index (SWI) is an additional connectivity measure based on FC. A Small-World network is characterized by high local clustering, measured by a clustering coefficient (CC) and additionally by having small characteristic path lengths (CPL), like random networks (Watts & Strogatz, 1998). In such networks, infectious diseases were found to spread faster in a simulation, implying that any network, including brain networks, without Small-World properties would have slower, less efficient signal transmission due to an imbalance between integration, as indicated by the CPL and segregation, as indicated by the CC (Watts & Strogatz, 1998). Calculating the SWI from FC requires thresholding to eliminate spurious connections (Rubinov & Sporns, 2010), but identifying such spurious connections is challenging. One approach to handle it is to process only a certain percentage of connections, such as the top 10% (Langer et al., 2013). This, however, could risk "fishing" for thresholds that show a difference, which is why results from all thresholds should be reported, with cautious interpretation (Miljevic

et al., 2022; Rubinov & Sporns, 2010).

## EEG Findings in PCS

A number of studies finding abnormal EEG patterns in PCS-pts support the notion that a somewhat abnormal EEG signal seems to persist or develop after acute infection (Appelt et al., 2022; Babiloni et al., 2024; Benis et al., 2024; Cecchetti et al., 2022; Clemente et al., 2023; Furlanis et al., 2023; Gaber et al., 2024; Kopańska et al., 2022, 2023; Ortelli et al., 2023; Rubega et al., 2022; Wojcik et al., 2023). A selection of findings relevant for the current study will be discussed in the following sections. Analyzing all frequency bands would go beyond the scope of this master's thesis. The delta frequency seemed especially promising due to previous PCS EEG findings (Cecchetti et al., 2022; Furlanis et al., 2023; Ortelli et al., 2023). Two studies investigating fatigue in other diseases sounded promising enough to investigate the beta frequency in PCS (Vecchio et al., 2017; Wu et al., 2023). Most PCS studies reported here focus on resting state data.

**The Delta Power in PCS.** Multiple studies report findings in the delta frequency (Benis et al., 2024; Cecchetti et al., 2022; Furlanis et al., 2023; Ortelli et al., 2023). Findings in PCS-pts include more bilateral frontal and central-temporal delta power (Cecchetti et al., 2022) and an observed delta slowing-pattern in 69% of patients who presented with abnormal EEG, especially in frontal brain regions (Furlanis et al., 2023). On the other hand less delta power in the bilateral frontal-parietal lobe and in the left temporal lobe have appeared (Ortelli et al., 2023). Kopańska et al. (2022) found mixed results, entailing higher delta wave amplitude at C4 site in an eyes closed condition but lower delta wave amplitude at C3 site in an eyes open condition. Benis et al. (2024) reported a case report of an individual with PCS having elevated whole-scalp delta activity, which in their study was defined between 2 and 6 Hz. Both Kopańska et al. (2023) and Babiloni et al. (2024) did not find differences in delta activity.

**The GABA-Hypothesis.** Ortelli et al. (2023) propose a hypothesis for their finding of less delta power in PCS-pts that identifies a dysfunctional GABAergic system as a main contributor. Sars-CoV-2 enters the body via angiotensin-converting enzyme 2 (ACE2) receptors (Letko et al., 2020), which usually upregulate GABA. The virus takes over, which disturbs the

GABAergic system (Sfera et al., 2022). In line with this, Versace et al. (2021) conducted a Transcranial Magnetic Stimulation study and found the short-interval intracortical inhibition, which reflects GABA<sub>A</sub>-mediated inhibition, to be reduced after COVID-19 infection. There is no established direct link between delta power and GABAergic inhibition. However, the hypothesis connects higher delta power during cognitive tasks - thought to be related to the inhibition of distractors (Harmony, 2013) - with findings that increased GABA concentration in frontal brain areas is associated with improved distractor suppression as well (Sumner et al., 2010). Additionally, the more GABA is measured in frontal brain areas, the better people tend to perform at a cognitive test (Porges et al., 2017). In conclusion, Ortelli et al. (2023) argue that neuroinflammation could lead to less GABA in the PCS-pts' brain, which according to them, is a mutual characteristic of fatigue and executive deficits.

***The Brainstem-Hypothesis.*** On the other hand, Cecchetti et al. (2022) explain their finding of more delta power with a hypothesis suggested by Yong in 2021b. Yong (2021b) proposes a brainstem involvement in PCS, primarily based on autopsy studies that have identified Sars-Cov-2 RNA and proteins within the brainstem (Matschke et al., 2020; Solomon et al., 2020). Additionally, given the brainstem's role in functions such as breathing, sleep, and alertness, disruptions here could explain several PCS symptoms (Yong, 2021b).

One critical brainstem function is its regulation of the reticular activation system. During the waking state, this system should be active, leading to less delta activity (Lindsley et al., 1949). In PCS-pts, however, disturbances in this system may lead to excessive delta wave activity, possibly contributing to cognitive impairment and fatigue due to insufficient arousal (Cecchetti et al., 2022; Yong, 2021b). Fittingly, Verger et al. (2022) could show hypometabolism in the brainstem of PCS-pts that is visible in Positron Emission Tomography scans. Additionally, Martin et al. (2023) recently found indicators of hypoarousal in the brain of PCS-pts. They observed decreased processing speed in PCS-pts which was explained by a reduced central nervous activation and a higher level of mental fatigue. On top of that, a damage of the locus coeruleus in the brainstem and the following hypoarousal has been proposed as a mechanism underlying

fatigue in Multiple Sclerosis (MS; Niepel et al., 2013). Lastly, ME/CFS has been compared to PCS due to the overlap of symptoms (Wong & Weitzer, 2021). Here, brainstem dysfunction is also connected to the symptoms that occur (Barnden et al., 2011) and individuals with ME/CFS showed higher delta power (Sherlin et al., 2007; M. A. Zinn et al., 2018). In sum, these findings suggest that brainstem dysfunction may better explain increased delta power in PCS than the alternative GABA-hypothesis.

**The Delta Connectivity in PCS.** Viral infection and inflammation can cause problems in axonal transport and synaptic transmission (Yachou et al., 2020). This might lead to reduced FC. Additionally, delta FC in other diseases, that share symptoms such as fatigue and cognitive difficulties, was decreased. For example, in cognitively impaired MS patients (Van Schependom et al., 2014), patients with Alzheimer's Disease (Yan et al., 2021) and patients with ME/CFS (M. L. Zinn et al., 2016).

Surprisingly, in the PCS, Cecchetti et al. (2022) found higher FC in the delta band. Higher FC resulted in comparatively better cognitive performances, and they hypothesized that this might be due to compensatory mechanisms. Since the evidence still seems inconclusive, it would be interesting to correlate FC with the performance in different cognitive tests and fatigue score. Especially since Cecchetti et al. (2022) did not carry out every test with their control group and only provided plots for correlation of delta power with Trail Making Test (TMT) and Frontal Assessment Battery (FAB), but not for the FC.

Intriguingly, the brainstem hypothesis could also be applicable in the context of delta connectivity. There are two neuromodulators, the cholinergic and the noradrenergic system, that are hypothesized to have a direct impact on integration and segregation in the brain (Shine, 2019). The cholinergic basal nucleus is not part of the brainstem, but the noradrenergic locus coeruleus is. Shine (2019) argues that an imbalance of the two systems could potentially cause the usual balance of segregation and integration inside the brain to change. This might be a consequence of COVID-19. Previous research, reported in a conference paper, suggests that there is a loss of Small-World organization in the brains of PCS-pts (Mishra et al., 2023).

**The Beta Power in PCS.** Kopańska et al. (2022, 2023) reported higher beta wave amplitudes in PCS-pts. In the 2022 study, they only investigated central channels, in 2023 the authors additionally included frontal, and parietal sites. In both studies, the higher beta (beta2) activity seemed to differ more between the groups than the lower beta (beta1). However, they do not specify the exact frequency range that they used to define 'beta2'. Benis et al. (2024) found differential effects for low (13-19 Hz) vs. high beta (19-36 Hz) as well. In their case report the patient with PCS and apathy had elevated high beta power but decreased low beta power compared to controls. Two other studies did not find differences in beta power of PCS-pts (Cecchetti et al., 2022; Ortelli et al., 2023) and one study found decreased beta power reported as part of a higher theta/beta ratio (Gaber et al., 2024).

Having pronounced beta activity could, according to Engel and Fries (2010), be associated with a lasting status quo and a degeneration of flexible behavioral and cognitive control. While the authors mention that the causal role of beta in the sensorimotor system is not yet fully understood, some studies with experimental beta oscillation induction tried to shed light on this matter. Beta band stimulation led to slower voluntary movement (Pogosyan et al., 2009) and bradykinesia (C. C. Chen et al., 2007; Fogelson et al., 2005). Increasing the brain's dopamine concentration via Levodopa reduced beta band activity (Brown et al., 2001). This is why dopamine depletion might be a reason for an abnormally high amount of beta oscillations (Brown et al., 2001). In a newer review by Barone and Rossiter (2021), they concluded through various studies that GABAergic inhibition seems to be linked to the amplitude of beta oscillations. If higher GABA should be the cause for more beta, then this would not align well with the fact that Sars-CoV-2 is thought to reduce GABA (Sfera et al., 2022). If beta power in PCS is not higher because of rather low GABA, this could be a reason why two studies did not find differences in beta power of PCS-pts. However, since the number of studies on beta power in PCS-pts is low, the matter requires further investigation.

**The Beta Connectivity in PCS.** Currently, there is no established causal theoretical framework for abnormal beta connectivity in PCS. However, two studies have observed changes in

beta connectivity in relation to fatigue levels. Wu et al. (2023) found that higher fatigue in stroke survivors was associated with a more random network organization, meaning higher Small-Worldness, in the beta frequency in the somatosensory networks, while lower Small-Worldness was observed in the motor network. Similarly, Vecchio et al. (2017) conducted a correlative analysis, which linked increased fatigue symptoms of MS patients to Small-Worldness specifically in the sensory network of the left dominant hemisphere in the lower beta range (13-20 Hz).

Increased Small-Worldness, akin to higher beta power, suggests a tendency to maintain the status quo, which in this context translates to a state of rest (Wu et al., 2023). This inclination towards rest may result in greater effort required to initiate action, potentially leading to increased fatigue (Wu et al., 2023). Consistent with this notion, Buyukturkoglu et al. (2017) observed increased beta FC at rest in individuals with MS-related fatigue. Notably, beta FC in the temporo-parietal region correlated with the severity of fatigue symptoms. Taken together, it would be valuable to correlate beta FC and SWI of PCS-pts with a fatigue score.

The TMT is a cognitive test that assesses processing speed and visual attention (Reitan, 1958). The TMT B assesses cognitive flexibility or the ability to switch between tasks. The aforementioned increase in effort might be the cause behind the PCS-pts being slower in the TMT A than the control group in some studies (Appelt et al., 2022; Cecchetti et al., 2022; Morawa et al., 2023; Rahimi et al., 2024). Note that Morawa et al. (2023) investigated a large sample of PCS-pts and only found the TMT A to differ from healthy norm values in an age group from 18 to 34, but not in older ones. There were no differences in TMT B-A (Appelt et al., 2022; Cecchetti et al., 2022) indicating that the cognitive shifting still seems to work.

### Aim of the Study

With Cecchetti et al. (2022) finding higher delta power and Ortelli et al. (2023) finding lower delta power in PCS-pts' resting state data, there is a need for further investigations of this aspect. An inconclusive situation presents itself regarding the beta power (Benis et al., 2024; Gaber et al., 2024; Kopańska et al., 2022, 2023). Finding abnormal connectivity in PCS-pts at rest could

contribute to our understanding of the underlying mechanisms of symptoms like cognitive impairment and fatigue. Finding abnormal connectivity in the beta band, as found in MS patients and stroke patients with fatigue (Vecchio et al., 2017; Wu et al., 2023), in PCS-pts with fatigue could further highlight the beta band as a disease overarching EEG pattern connected to fatigue.

To sum it up, this study seeks to analyze the resting state power, FC and SWI in the delta and beta band of PCS-pts and compare it to a control group of people who had COVID-19 but do not experience persistent cognitive difficulties afterwards. This study aims to explore potential relationships between neuropsychological variables and EEG parameters in PCS-pts. The resting state was chosen on the one hand because the majority of studies on PCS so far reported resting state data and on the other hand to avoid task-specific variability in for example motivation or fatigue during the experiment. Furthermore, the study can be a starting point for the exploration of suitable biomarkers of the PCS. Given the simplicity of resting state implementation, it would serve as an accessible and practical method for biomarker discovery.

## Hypotheses

First, concerning the delta frequency, an increased mean delta power in the PCS-pts compared to the control group is expected. The analysis will be conducted over a frontal region of interest (ROI). Furthermore, it is assumed that the SWI will be decreased while the FC might be increased or decreased. These abnormalities are expected to be found in the frontal ROI as well. Exploratory investigations are, whether an abnormal delta power and connectivity is correlated to fatigue and/or cognitive impairment, operationalized with a fatigue questionnaire, the TMT, and MoCA.

Secondly, concerning the beta frequency, the connectivity, that is Small-Worldness as well as FC, is predicted to be higher in PCS-pts compared to the control group. Such abnormalities are expected to be prevalent in a sensorimotor (central) ROI. Exploratory investigations are, whether the beta power is different in PCS-pts compared to the control group. Furthermore, it will be investigated if an abnormal beta power and connectivity is correlated to fatigue and/or cognitive impairment, operationalized with a fatigue questionnaire, the TMT, and MoCA.

Recognizing that the categorization of participants into PCS-pts and control groups based

on perceived cognitive difficulties post-infection may be subjective, the study will also include exploratory analyses of correlations between power/connectivity and more objective behavioral tests administered across the whole sample.

## Methods

This section provides an overview of the study design, including details on the behavioral measures, questionnaires, EEG recording characteristics, and participant descriptions. Additionally, it outlines the preprocessing pipeline, along with the power and connectivity analyses (both FC and SWI) for the delta and beta frequency band. The section concludes with a detailed explanation of the statistical analysis methods.

## Participants

Between November 2020 and September 2021, people with a polymerase chain reaction confirmed incident of SARS-CoV-2 infection were recruited via the local public health authorities for a population-based cohort study in Kiel, Berlin and Würzburg, called COVIDOM (Bahmer et al., 2022). It was made sure that the period between infection and an inclusion into the study was greater than 6 months and that there was no reinfection during this time.

Participants from the COVIDOM study were recruited to take part in this EEG study at the University Hospital Schleswig-Holstein (UKSH) in Kiel, called EEG Post COVID (EPOC). Participants did not receive any remuneration, but transportation and parking costs were covered by the UKSH. The EPOC study was approved by the ethics committee of Kiel University's medical faculty (D 446/23). Written consent was obtained from all subjects in accordance with the Helsinki Declaration.

At the time of analysis, 79 participants had been recruited for the EPOC study. The exclusion criteria were equal to the COVIDOM study and can for example be found in Bahmer et al. (2022). The participants in the EEG study were asked whether they experience subjective cognitive deficits after their first infection. If they answered yes, they were categorized into the with PCS group, if they answered no, they were categorized into the without PCS group. A total of 49 participants said that they did experience subjective cognitive difficulties after infection ( $M_{age} = 50.3$ ,  $SD_{age} = 12.6$ , 32 F) and 30 said that they did not ( $M_{age} = 44.6$ ,  $SD_{age} = 15.5$ , 16 F). Five out of 79 participants were excluded from analysis due to file naming issues or missing data. Since age influences the relevant EEG parameters (Auer et al., 2024; Cesnaite et al., 2023;

Rossiter et al., 2014), an age-matching algorithm was used to create two groups of 23 participants each, ensuring no significant age difference between those with and without PCS,  $z = 0.36$ ,  $p = .717$ ,  $r = .05$ . Table 1 shows the demographic data of the two groups.

**Table 1**

*Socio-demographics of Study Subjects (Grouped in With and Without Post COVID Syndrome (PCS))*

Socio-demographic variable	group		<i>p</i>
	with PCS	without PCS	
n	23	23	-
Sex [M/F]	7/16	10/13	-
Age [years]	$47.4 \pm 14.3$	$45.3 \pm 16.7$	.717
Age range [years]	22-78	22-77	-
Education [years]	$15.1 \pm 3.2$	$15.3 \pm 3.2$	.851
Hospitalization [yes/no] <sup>a</sup>	0	2	-

*Note.* Two-sided Wilcox Tests were conducted to test differences in age and education.

<sup>a</sup> Amount of people hospitalized during the acute infection with Sars-CoV-2. A value of 0 corresponds to 'No' and a value of 1 to 'Yes'.

## Study Design

During the EPOC study, the participants completed multiple behavioral tests as well as questionnaires. One session lasted approximately 2.5 hours. The behavioral tests included the TMT (Reitan, 1958), the Psychomotor Vigilance Test (Dinges & Powell, 1985), an Oddball task, an experiment for the Redundant Target Effect (Mercier et al., 2015) and an n-back task. The questionnaires completed were the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F; Yellen et al., 1997) the Hospital Anxiety and Depression Scale – German Version (HADS-D; Petermann, 2011) and the Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989). The MoCA was not conducted at the time of the EPOC study but taken from the COVIDOM study. A resting EEG was then recorded, five minutes with eyes open and five minutes with eyes closed. Lights in the room were turned off during resting state and the participants looked at a

fixation cross on a monitor in front of them. The analysis focused on the eyes open condition only. All code described in the following sections can be found in a public GitHub repository ([https://github.com/LGodbersen/MA\\_EEG\\_Post\\_Covid](https://github.com/LGodbersen/MA_EEG_Post_Covid)).

### **Behavioral Tests and Questionnaires**

For this study, data of the TMT, the MoCA, the FACIT-F and the HADS-D were chosen. They will be correlated with the EEG measures of interest.

The TMT consists of a version A and a version B (Reitan, 1958). In version A, numbers from 1 to 25 shall be connected in ascending order. In version B, there are the numbers 1 to 13 and the letters A to L, and they shall be connected in ascending order, alternating between numbers and letters. The paper and pencil version was used. For further analysis the TMT B-A was established. Here, you subtract the time of version A from version B to deduct the time needed for connecting, thus only reflecting the time needed for shifting between letters and numbers.

The MoCA is a screening tool for cognitive functioning (Nasreddine et al., 2005). Nasreddine et al. (2005) designed 16 items with 11 categories to assess the following domains: Visuo-spatial/Executive, Naming, Memory, Attention, Language, Abstraction, Orientation. The maximum score is 30, with a cut-off for mild cognitive impairment at 26 (Nasreddine et al., 2005). The German version was used (<https://mocacognition.com>).

The FACIT-F, a 13-item questionnaire, was employed to evaluate self-reported fatigue (Yellen et al., 1997). It uses a five-point Likert scale, with total scores ranging from 0 (indicating severe fatigue) to 52 (indicating no fatigue). According to general population data, scores of 30 or below suggest clinically significant fatigue (Piper & Celli, 2010). The German version was used (Montan et al., 2018).

The HADS-D is a 7-item depression subscale of the HADS (Petermann, 2011). The other part is a 7-item anxiety subscale (HADS-A). Both subscales are assessed using a four-point Likert scale, resulting in subscale scores that range from 0 to 21 (Zigmond & Snaith, 1983). Zigmond and Snaith (1983) recommend a cut-off score of 8 for both subscales: Scores greater than or exactly 8 indicate caseness. The German version was used (Petermann, 2011).

## **EEG Recording**

EEG signals were recorded using the actiCHamp Plus Amplifier (Brain Products GmbH, Gilching, Germany) in combination with a 128-channel EEG cap with electrodes in an equidistant layout (128Ch Standard Brain Cap for actiCHamp Plus, Easycap GmbH, Wörthsee, Germany). The sampling rate was 1000 Hz with an amplitude resolution of 0.1  $\mu$ V. Electrolyte gel was used to achieve conductivity between skin and electrodes, maintaining the impedances below 20 k $\Omega$ . Two Electrooculogram (EOG) electrodes were placed onto the face, diagonally under each eye, and one reference electrode onto the nose.

## **Preprocessing**

Preprocessing of the EEG data was performed in MATLAB Version R2021a (The Mathworks, USA) using the FieldTrip (version 20231127; Oostenveld et al., 2011) and EEGLAB (version 2023.1; Delorme & Makeig, 2004) Toolboxes. The data were organized in the BIDS-Format prior to analysis (Gorgolewski et al., 2016; Pernet et al., 2019). Then, they were read into MATLAB using the FieldTrip Toolbox. A trial defining function was created so that only the signal during the eyes open resting state condition was chosen for further processing. This resulted in approximately 300 s per participant.

Subsequently, high-pass filtering was administered. A high-pass hamming windowed sinc FIR filter was used at 0.1 Hz (Delorme, 2023). The data was down sampled from 1000 Hz to 250 Hz. A low-pass hamming windowed sinc FIR filter at 45 Hz was applied in order to filter out line noise around 50 Hz. Common average reference (CAR) was used to remove the influence of the reference (Ludwig et al., 2009). The data was converted into the EEGLAB data structure at this point.

## ***Artifact Removal***

The data was cleaned using EEGLABs 'pop\_clean\_rawdata' function with the following criteria: The Flatline Criterion was set to 5, meaning that channels showing a flat line for at least 5 seconds would be removed. A flat line could indicate bad electrode connection. The Channel Criterion was set to 0.85, excluding all channels having high variance values for at least 85% of the

recorded time. This was supposed to detect and eliminate noisy channels. The Burst Criterion was set to 100, meaning that artifact-bursts that had a higher than 100  $SD$  amplitude compared to neighboring segments were removed. Bursts of such high amplitude are thought not to reflect brain signals. The Window Criterion was set to 0.4, meaning that a data window where over 40% of all channels have been marked as noisy/bad, would be excluded. This helped detecting periods in time that contained a lot of artifacts simultaneously. CAR was applied one more time.

Afterwards, Independent Component Analysis (ICA) was used to detect and reject artifacts, such as eye or muscle movements (Makeig et al., 1995). The 'runica' decomposition algorithm, implemented in EEGLAB, was used to run an ICA with the InfoMax method, as can be read on the EEGLAB website ([https://eeglab.org/tutorials/06\\_RejectArtifacts/RunICA.html#which-ica-algorithm](https://eeglab.org/tutorials/06_RejectArtifacts/RunICA.html#which-ica-algorithm)). Automatic artifact rejection should be preferred over the manual one since research requires standardization (Miljevic et al., 2022). That is why ICLabel was used, which is a tool that automatically detects and removes non-brain components (Pion-Tonachini et al., 2019). Components exceeding an 80% probability of being muscle activity and a 50% probability of being eye movements were rejected. The EOG channels were removed after the ICA. After the previous steps, on average, 108.4 good channels were left in both groups ( $SD_{withPCS} = 13.0$ ,  $Range_{withPCS} = 77-122$ ,  $SD_{withoutPCS} = 9.5$ ,  $Range_{withoutPCS} = 92-123$ ). This corresponded to approximately 86% good channels in both groups.

After the ICA, the data were checked again to reject more possible bad channels or epochs. For each participant, all data points were taken and the mean of both mean and standard deviation were calculated. Thresholds were defined as average mean plus or minus three times the mean standard deviation. Afterwards, channels were rejected if their values exceeded these thresholds. This resulted in, on average, 105.9 good channels in the with PCS group ( $SD = 13.4$ ,  $Range = 75-120$ ) and on average 106.3 good channels in the without PCS group ( $SD = 9.4$ ,  $Range = 90-121$ ). This corresponded to approximately 84% good channels in both groups. Subsequently, it is important to interpolate every previously excluded channel, where EEGLAB's

'pop\_interp' function with a default of spherical interpolation was used. It was made sure that the interpolated channels were inserted into the original channel order. Correspondingly, it means that on average 16% of the channels in each group were interpolated.

### ***Epoch Length and Number***

In their advisory paper for connectivity studies, Miljevic et al. (2022) point out that there is a lack of studies investigating what the ideal epoch length for the different frequencies would be. The minimum epoch length to observe patterns of stability in different connectivity measures seems to be 4 s (Fraschini et al., 2016). Miljevic et al. (2022) thus recommend using more than 6 s. The authors also highlight the importance of epoch number chosen as investigated by Bastos and Schoffelen in 2016: They showed coherence was higher in a smaller number of trials (5, 10, 50) compared to a higher number of trials (100, 500). Cutting the 300 s into 6 s epochs would have resulted in only 50 trials. Thus, it was cut into 4-second-long epochs in order to have close to 75 trials while still meeting the minimum requirement for the connectivity analysis. The preprocessing and age matching resulted in on average 48.5 good epochs ( $SD = 19.2$ , Range 4-75) in the with PCS group and on average 51.2 good epochs ( $SD = 17.6$ , Range 7-75) in the without PCS group. A two-sided *t*-Test did not indicate differences in epoch number between the groups,  $t(58.07) = 0.60$ ,  $p = .55$ ,  $d = 0.14$ .

### ***Volume Conduction***

In the EEG, field spread can confound a number of connectivity measures (Schoffelen & Gross, 2009). In a simulation, the authors modeled the problem of this so-called volume conduction. Even though underlying sources were temporally uncorrelated, many sensors measured a high correlation. To avoid this problem a spatial filter can be used, for example, the Laplacian/current source density. By separating the activity under the electrode from the surrounding ones, this method is able to minimize effects of volume conduction on for example coherence (Srinivasan et al., 2007). Mike X Cohen wrote a function for this that uses the theory from Perrin et al. (1989) and published it on GitHub: [https://github.com/mikexcohen/AnalyzingNeuralTimeSeries/blob/a34f888c30a98b8f19fc82699c19a59b2a3a1578/laplacian\\_perrinX.m#L4](https://github.com/mikexcohen/AnalyzingNeuralTimeSeries/blob/a34f888c30a98b8f19fc82699c19a59b2a3a1578/laplacian_perrinX.m#L4). It is best to apply

additional prevention of volume conduction, for example by choosing the imaginary part of coherence as a measure of FC (Miljevic et al., 2022), which will be explained in the section of the connectivity analysis.

### Power Analysis

Donoghue et al. (2020) summarize that evaluating a change in (periodic) absolute power could potentially be related to a true change but might also reflect changes in aperiodic exponent, in broadband offset or a frequency center shift. Therefore, the aim was to analyze the relative power and have a look at the aperiodic exponent and offset as well. The exponent represents the slope of the aperiodic power spectrum when frequency and power are plotted on a logarithmic scale (Donoghue et al., 2020). In contrast, the offset corresponds to the y-intercept of the spectrum, reflecting a uniform shift of the entire power spectrum across all frequencies. The method of Donoghue et al. (2020) was initially referred to as foof (fitting oscillations and one-over-F) but was renamed to specparam (Spectral Parameterization). It is implemented in the Brainstorm Toolbox (Tadel et al., 2011) in MATLAB and this code is available in FieldTrip. The subsequent power analysis was computed with FieldTrip in MATLAB as well. The frequency analysis was carried out between 0.3 and 30 Hz with steps of 0.2 Hz. The foof output was specified in FieldTrip with a fixed aperiodic mode. In order to achieve relative delta and beta power, the aperiodic components were subtracted from the original power spectra. Delta power was defined between 0.6 and 4 Hz. Beta power was defined between 14 and 30 Hz. The values of each frequency inside a frequency band were added up and the result was relative power per channel.

For resting state delta power longer epochs are preferred, since delta contains slower frequencies and the longer the epoch, the higher the resolution. This is why in the preprocessing for delta and beta power, the data was cut into 5 s epochs. The maximum would be 60 good epochs here. The preprocessing and age matching resulted in on average 40.7 good epochs ( $SD = 11.9$ , Range 15-60) in the with PCS group and on average 43.2 good epochs ( $SD = 11.1$ , Range 21-60) in the without PCS group. A two-sided  $t$ -Test did not indicate differences in epoch number between the groups,  $t(43.38) = -0.73$ ,  $p = .470$ ,  $d = -0.22$ .

Having power per channel, this was transferred to R Studio (v2023.12.1.402; RStudio Team 2020) for analyses with R Statistical Software (v4.3.2; R Core Team 2021). A first outlier removal took the mean relative power  $\pm 3 SD$  per participant and excluded every channel that was above or below that threshold. This was done separately for delta and beta power, for aperiodic exponent and offset. Starting with 2898 channels per group, this outlier removal retained 98% of channels in both groups for the delta power, 98% in both groups for the beta power, 99% in both groups for the aperiodic exponent and 99% (with PCS) and 100% (without PCS) for the aperiodic offset. Afterwards, the channels from the ROIs were selected, 23 per person for the frontal ROI and 37 for the central ROI. But there were still outliers in the data. André (2022) vouched for hypothesis blind outlier removal (meaning across groups), while Karch (2023) argues that this method is also problematic. He points out that erroneous values should be corrected or removed and statistical methods that are not that sensitive to extreme values such as a sign rank test should be used. Across group outlier removal was chosen for delta and beta power, resulting in 97% (with PCS) and 96% (without PCS) retained channels for delta power and 96% in both groups for beta power. It was checked and seen that there was no difference in significance between the within and across group outlier removals.

There is no such thing as negative EEG power. With the fooof/specparam method, however, negative power values can result. Therefore, in order to obtain the final relative power results, negative power values were set to 0. Taking these data out can for example result in less variance. To be precise, 39.7% and 38.0% of channels had negative values in the with and without PCS group respectively. For beta, it was just a small proportion with 2.0% and 2.5% in the with and without PCS group respectively. The fooof/specparam algorithm comes with a measure to depict the correspondence of the original spectrum with the fit, called  $R^2$  (Donoghue et al., 2020). This value per channel was extracted and added to the power table.

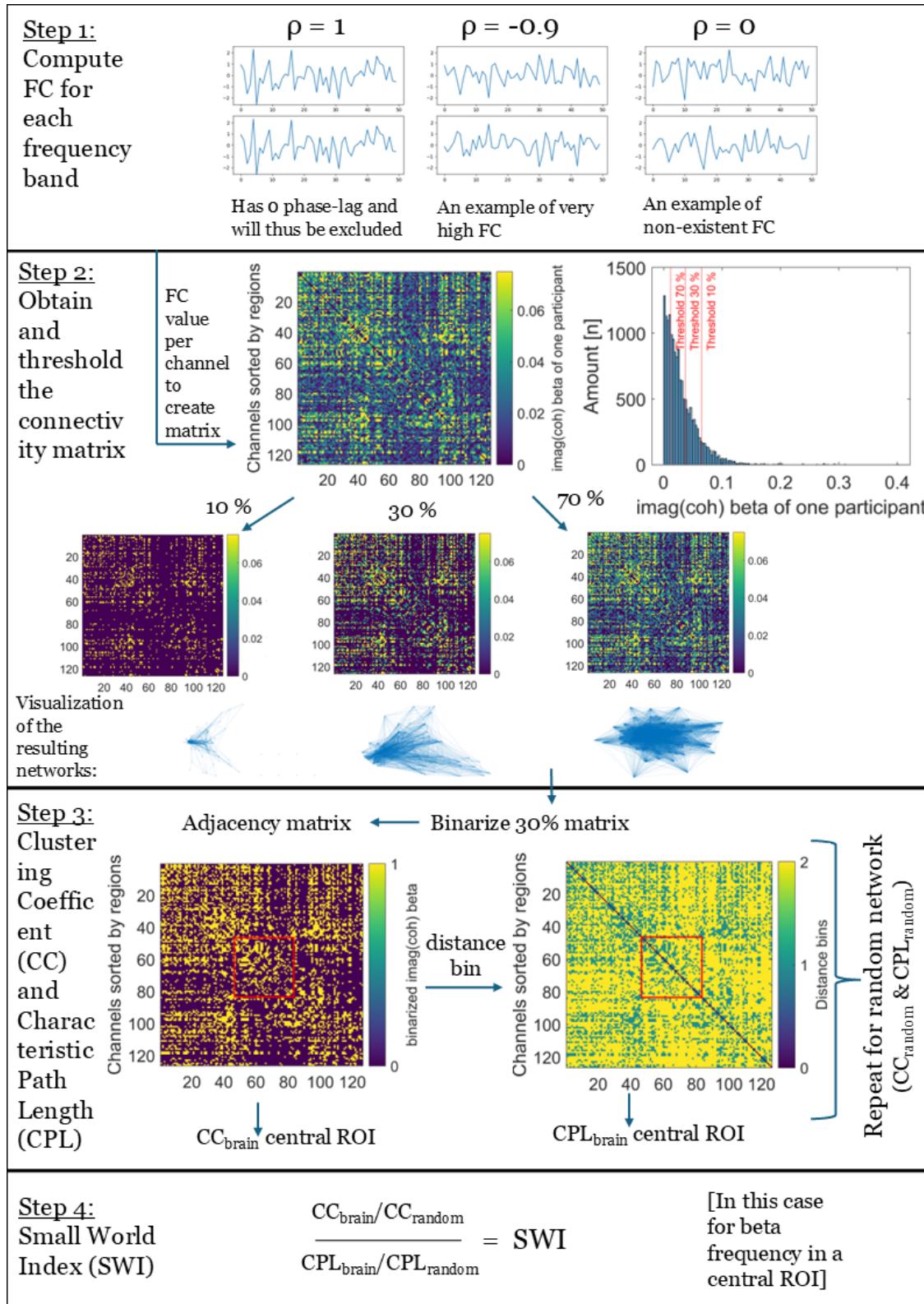
## Connectivity Analysis

Preprocessed data were loaded and converted back into FieldTrip data structure. The two ROIs for delta and beta were defined prior to analysis and the corresponding channels stored into objects.

The frontal delta ROI consisted of 23 channels, the central beta ROI of 37 channels. The first step was to do a Frequency Analysis between 0.3 and 30 Hz in 0.2 Hz steps using the 'mtmfft' method with a 'dpss' taper and a 'nextpow2' padding. As the output, 'fourier' was specified. Next, a Connectivity Analysis based on these frequency outputs was carried out. This study computed the coherence, which is based on frequency, not on the exact timing. It detects how well the phases of two signals align. Importantly, the imaginary part of coherence was chosen here due to its more conservative nature that minimizes volume conduction (Nolte et al., 2004). As explained before and as written by Nolte et al. (2004), there are underlying sources in the brain that can lead to an artificial connection between two electrodes that otherwise would not be synchronous. This connection is instantaneous because it comes from the same source. The imaginary part of coherence therefore excludes connections with zero phase lag. This comes at the expense of potentially losing some real signal, but it is a valid method to prevent volume conduction. The imaginary part of coherence can have positive or negative values, but the absolute number of it was taken. To proceed with the calculations, the connectivity matrix of delta was averaged over the frequency dimension between 0.6 and 4 Hz, for beta between 14 and 30 Hz. For the mean coherence, the coherence was averaged over the respective ROI. Both steps together resulted in two values per person, the average beta FC in a central ROI and the average delta FC in a frontal ROI.

After calculating the FC, graph measures were extracted, that is, the Clustering Coefficient (CC), Characteristic Path Length (CPL) and finally SWI. The concept for the SWI is that there is the CC as an indicator of the local connectedness, sometimes also referred to as segregation, and then the CPL as an indicator of the integration of said clusters. There are several steps necessary to obtain these graph measures. Figure 1 gives an overview of the steps. Code from the DISCOVER-EEG Pipeline was used and modified to our needs (Gil Ávila et al., 2023). They mainly used functions from the Brain Connectivity Toolbox (BCT, version 2019\_03\_03) by Rubinov and Sporns (2010).

1. All steps were done separately for delta and beta frequency. The FC is the base for all graph measures, so the FC was taken that was computed as previously described. It is organized

**Figure 1***Schematic Explanation of the SWI Calculation*

*Note.* As an example, beta frequency in a central ROI for one participant was chosen. Thanks to Janus Rønn Lind Kobbersmed for the simulated time series Python code.

in a 126x126 connectivity matrix. Figure 1 uses the beta frequency as an example. Remember, that values of 1 were excluded per definition since there was no phase lag, which also included the diagonal, which would be each channel's correlation with itself.

2. We took for example the connectivity matrix of the beta frequency and sorted all the values in a descending order. Then we took a proportion of these values to create an adjacency matrix. This step was necessary because the functions from the BCT require a binarized matrix as an input (Rubinov & Sporns, 2010). The idea behind it is that you remove unimportant noise from the data and only keep meaningful connections. How big a connection must be in order to be meaningful and if there are non-meaningful connections at all, is unclear (Sporns & Betzel, 2016). The threshold is being chosen quite arbitrary, for example 0.2 in the DISCOVER-EEG Pipeline (Gil Ávila et al., 2023). Adamovich et al. (2022) have pointed out that before choosing a threshold, a distribution of multiple thresholds should be evaluated. Langer et al. (2013) as well as Jäncke and Langer (2011) and Cainelli et al. (2020) chose a threshold after looking at multiple thresholds. They ended up taking the one where the SWI is closest to the optimal value, which would be 1. The problem with this approach of Langer et al. (2013) is, however, that it is unclear how exactly the 'optimal' threshold was found and how it then was applied to the individual subject. This is why in concordance with the advice in Miljevic et al. (2022) multiple thresholds were tested and all of them will be reported. In total, 9 different thresholds were chosen here (0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9). If you, for example, take the 0.1 threshold this means that inside each participant the connectivity matrix is sorted in a descending order and then only the top 10% of FC values are kept, see Figure 1 under Step 2 on the top right. This is implemented in the 'threshold\_proportional' function in the BCT, where you just have to specify the threshold, you want to have applied (Rubinov & Sporns, 2010). Having only the top 10% results in a quite scarce matrix. As an example, in Figure 1 we proceeded with 30%.

3. On this matrix containing only the top 30%, we would apply the 'weight\_conversion' function. This set all values above 0 to 1 (and all the other spaces to 0). The result was the so-called adjacency matrix. It indicates whether pairs of nodes are adjacent or not. This adjacency

matrix was used to calculate the CC with the 'clustering\_coef\_bu' function from the BCT. It means that you have a binarized and undirected matrix as an input. The function resulted in one value for each channel. Here, the average over the ROI results in the 'global' CC. The adjacency matrix was also needed for the CPL, because the 'distance\_bin' function was applied to it in order to get a distance matrix out of it. Here, the respective ROI was defined to get the distance matrix for the ROI only. This output could be put into the 'charpath' function, which returned the CPL. Further, a random network had to be established that had the same attributes as the empirical network but was randomly wired. Such a network could be created using the 'makerandCII' function from the BCT. Based on this random network, another CC and CPL were obtained.

4. Last step was the calculation of the SWI. For this both the 'global' CC and the CPL are needed. The SWI is a result of the normalized 'global' CC and CPL. In this context, normalized means that the empirical 'global' CC and CPL were divided by the ones that resulted from the random network in Step 3. The formula was proposed by Humphries and Gurney in 2008 and looked like this:

$$CC_{norm} = \frac{CC_{brain}}{CC_{random}} \quad \text{and} \quad CPL_{norm} = \frac{CPL_{brain}}{CPL_{random}} \quad \text{resulting in} \quad SWI = \frac{CC_{norm}}{CPL_{norm}}$$

All steps one to four were done for all 9 thresholds. Afterwards everything was saved in a table and exported into R Studio for further analysis. To look for outliers the mean  $\pm$  standard deviation of the coherence was calculated. One person was excluded from further analysis due to a value that exceeded the threshold.

Miljevic et al. (2022) proposed a checklist for assessing the quality of a FC study that consists of eight different aspects: re-reference technique, epoch length, number of sample epochs, artifact rejection technique, control for volume conduction, control for multiple comparisons, the way thresholds in graph measures are selected and lastly, sample size estimation and consideration. Methods that are not advised for use get 0 points, methods which you can use will get 0.5 points and ones that are in favor get 1 point. The overall score is able to tell about the

quality of the connectivity study. The methods of our study would get the following scoring: CAR referencing (0.5), an epoch length of 4 s (0.5), some epoch numbers are below 50 (0), all types of artifacts addressed (1), double control for volume conduction with Laplacian and imaginary part of coherence (1), control for multiple comparisons due to our ROI selection (1), arbitrary thresholding (0.5) and no sample size considerations (0). This results in a total of 4.5 points, which is 0.5 points below the cut-off for a high-quality EEG connectivity study and therefore categorized as of moderate quality (Miljevic et al., 2022).

### **Statistical Analysis**

Differences between the groups for the hypotheses concerning both power and connectivity should be investigated with a *t*-Test. Before carrying out any *t*-Tests, it was checked whether the theoretical assumptions were met, namely normality and equal variances. Shapiro-Wilks and Levene-Tests respectively were used for this. If at least one of these assumptions were not met, a nonparametric Wilcox Test was conducted. Exploratory cluster-based permutation tests over all channels of the EEG data for both delta and beta frequency were carried out in MATLAB with 1000 iterations and the Montecarlo method (Maris & Oostenveld, 2007). This step was supposed to test, if the prior selected ROIs made sense. The cognitive tests and questionnaires (FACIT-F, HADS-D, TMT A and TMT B-A, MoCA) were inspected concerning the assumptions as well. Again, if at least one of them were not met, a nonparametric Wilcox Test was conducted. For correlations, Spearman's rank correlation was calculated, if normality assumption of the data was not met. Regarding SWI, group differences were tested across multiple thresholds. Langer et al. (2013) point out that the thresholds are not independent from one another which is why they advise to use permutation tests and in general to always report effect sizes as well. A custom-made permutation function in R with 1000 iterations was used. This custom-made function used *t*-Tests and a *p* value was calculated with the following formula:

$$p_{\text{permutation}} = \frac{\text{sum}(t_{\text{permutation results}} > t_{\text{observed}})}{n_{\text{iterations}}}$$

The same formula and permutation test was used to investigate whether aperiodic offset and exponent differed between the two groups. In this case, a permutation test for each channel was conducted. Since the requirements for *t*-Tests were not met, instead of the *t*-statistic, the test statistic *W* from the nonparametric Wilcox Test was used instead.

## Results

### Clinical Data

The behavioral data were inspected concerning normal distribution and equal variances. Since in most cases, except for the MoCA, both assumptions were not met, a nonparametric Wilcoxon Test was conducted. Table A1 in Appendix A displays the results of all tested prerequisites. The with PCS group showed lower average FACIT-F score, indicating higher experienced fatigue in this group. The with PCS group showed higher average HADS-D scores compared to the without PCS group. Note, that the average in the with PCS group still is inside the normal range, not indicating clinical depression. In the TMT A, the with PCS group was significantly slower than the without PCS group. The TMT B-A did not exhibit a significant difference between the two groups. Table 2 shows the group averages of the questionnaires and cognitive tests.

**Table 2**

*Cognitive Features Grouped in With and Without Post COVID Syndrome (PCS). Displayed Are Mean and Standard Deviations, the Test Statistic, p-Value and Effect Size*

Test/Questionnaire	$M \pm SD$				
	with PCS	without PCS	statistic	p-value	effect size
FACIT-F [0-50] <sup>a</sup>	$32.1 \pm 12.1$	$42.4 \pm 9.5$	-3.0	<b>.003</b>	.45
HADS-D [0-21] <sup>b</sup>	$6.0 \pm 4.0$	$3.7 \pm 4.8$	2.2	<b>.028</b>	.33
TMT A [0-200]	$26.9 \pm 8.1$	$22.5 \pm 7.5$	2.1	<b>.038</b>	.31
TMT B-A	$31.4 \pm 23.6$	$24.5 \pm 14.8$	1.1	.277	.16
MoCA	$27.3 \pm 2.0$	$27.7 \pm 1.5$	0.8	.419	-0.24

*Note.* FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue, HADS-D = Hospital Anxiety and Depression Scale – Depression in the German Version, TMT = Trail Making Test, MoCA = Montreal Cognitive Assessment. Nonparametric Wilcoxon Tests were conducted for all comparisons, except the MoCA, and the test statistic  $z$  as well as the  $p$ -value and the effect size of the Wilcoxon Tests  $r$  are displayed. Since MoCA met all requirements, a  $t$ -Test was used and the test statistic  $t$  as well as the  $p$ -value and the effect size Cohen's  $d$  are displayed. One person in the with PCS group did not have a FACIT-F score.

<sup>a</sup> values under 30 are considered as ‘high fatigue’ (Piper & Cella, 2010).

<sup>b</sup> classification is ‘normal’ (0-7), ‘borderline abnormal’ (8-10), ‘abnormal’ (11-21) (Petermann, 2011).

## Power

Normality assumption was not met for delta and beta power. Equal variances were seen in both cases. Table A1 in Appendix A displays the results of all tested prerequisites. Delta power was calculated within the frontal ROI, where the with PCS group retained 91.7% of the initial 529 frontal channels per group, and the without PCS group retained 88.4%. Beta power was calculated in the central ROI, with the with PCS group retaining 97.2% of the initial 851 central channels per group, and the without PCS group retaining 96.4%.

### ***Delta (Frontal ROI)***

The with PCS group exhibited a lower average relative delta power in the frontal ROI ( $M = 1.02$ ,  $SD = 0.99$ ) compared to the without PCS group ( $M = 1.13$ ,  $SD = 0.93$ ). A one-sided Wilcox Test did not indicate a significant difference between the groups,  $z = -0.56$ ,  $p = .288$ ,  $r = .08$ . All power results are displayed in Figure 2.

Permutation tests were administered to check the relevance of selected ROI. While no significant clusters were detected, frontal right channels seem to have higher values in the with PCS group as can be seen in the cluster-test results in Figure 2.

### ***Beta (Central ROI)***

The with PCS group exhibited higher average relative beta power in the central ROI ( $M = 1.95$ ,  $SD = 2.04$ ) compared to the without PCS group ( $M = 1.56$ ,  $SD = 1.64$ ). A two-sided Wilcox Test did not indicate a significant difference between the groups,  $z = 0.76$ ,  $p = .449$ ,  $r = .11$ .

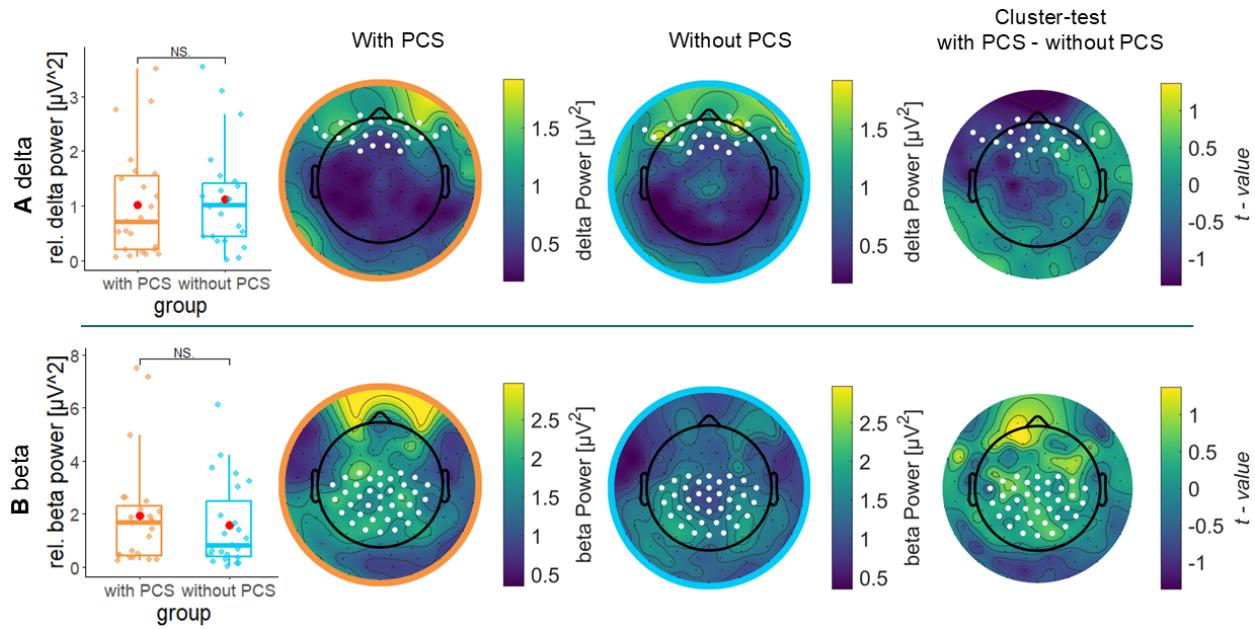
Permutation tests were administered to check the relevance of selected ROI. While no significant clusters were detected, frontal and central channels in the with PCS group seem to have higher values and occipital channels lower values as can be seen in the cluster-test results in Figure 2.

### ***Correlations With Clinical Data***

The frontal delta power correlated significantly with the HADS-D,  $\rho(44) = .31$ ,  $p = .042$ , as can be seen in Table 3. There were negative correlations of delta with the MoCA,  $\rho(44) = -.33$ ,  $p = .028$ , aperiodic exponent,  $\rho(44) = -.51$ ,  $p = <.001$ , and offset,  $\rho(44) = -.39$ ,  $p = .007$ . A trend towards a

**Figure 2**

*Results of Power Analysis in the Delta and Beta Frequency for the With and Without PCS Group*



*Note.* **A** displays power values for delta (0.6-4 Hz) and **B** for beta (14-30 Hz) frequency bands. Red data points in the boxplots display means. White dots in the topoplots indicate the respective ROIs. A cluster-test is a way to handle the multiple comparisons problem in the EEG and indicates spatially near clusters found in the data (Maris & Oostenveld, 2007). In this case, no cluster reached significance. The *t*-value can still show, where the with PCS group had lower (higher *t*-value) or higher values (lower *t*-value) than the without PCS group.

negative correlation with FACIT-F score was visible descriptively and was close to significance in a Spearman Rank correlation,  $\rho(43) = -.29, p = .051$ . Beta power was significantly correlated with the TMT A,  $\rho(44) = .35, p = .017$ , and negatively correlated with the aperiodic exponent,  $\rho(44) = -.39, p = .008$ . The HADS-D correlated negatively with the aperiodic exponent,  $\rho(44) = -.34, p = .024$ , but not with the offset,  $\rho(44) = -.26, p = .087$ . The TMT A correlated negatively with the aperiodic exponent,  $\rho(44) = -.38, p = .010$ . The aperiodic exponent and offset were highly correlated,  $\rho(44) = .57, p = <.001$ .

**Table 3***Correlations of Delta and Beta Power With Clinical Parameters*

Variable	1	2	3	4	5	6	7	8	9
1. $\delta$	1								
2. $\beta$	.05	1							
3. FACIT-F	-.29	.10	1						
4. HADS-D	.31*	-.00	-.74***	1					
5. TMT A	.25	.35*	-.04	.18	1				
6. TMT B-A	.24	.05	-.03	.09	.30*	1			
7. MoCA	-.33*	-.21	.10	-.05	-.31*	-.34*	1		
8. AE	-.51***	-.39**	.10	-.34*	-.38**	-.10	.17	1	
9. AO	-.39*	-.06	.07	-.26	.02	.09	.10	.57***	1

Note. \* $p < .05$ , \*\* $p < .01$ , \*\*\* $p < .001$ .  $\delta$  = delta power,  $\beta$  = beta power, FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue, HADS-D = Hospital Anxiety and Depression Scale – Depression in the German Version, TMT = Trail Making Test, MoCA = Montreal Cognitive Assessment, AE = aperiodic exponent, AO = aperiodic offset.

## Connectivity

Normality assumption was not met for delta coherence, while equal variances were. For beta coherence, all assumptions for parametric testing were fulfilled, see Table A1.

### *Delta (Frontal ROI)*

The average delta FC looks not identical in the connectivity matrix per group, see Figure 3. In both the central and parietal region, the with PCS seems to exhibit lower FC values than the without PCS group. Both groups seem to show enhanced FC values in both temporal regions. In the occipital region, it looks like the with PCS group might have higher FC values.

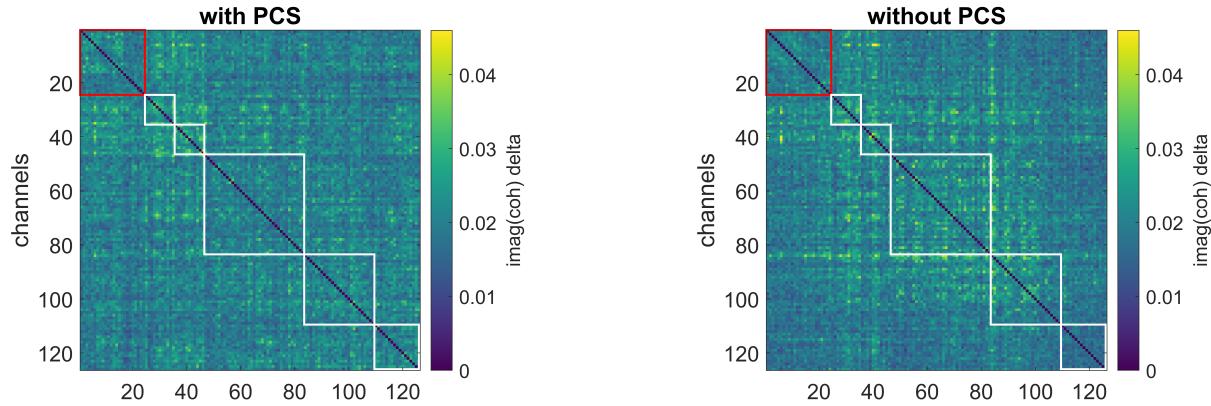
Statistically, the with PCS group exhibited a nearly identical average delta coherence (imaginary part) in the frontal ROI ( $M = 0.0207$ ,  $SD = 0.0054$ ) compared to the without PCS group ( $M = 0.0205$ ,  $SD = 0.0052$ ). A Wilcox Test did not indicate a significant difference between the groups,  $z = -0.27$ ,  $p = .785$ ,  $r = .04$ .

Descriptively, the without PCS had a higher mean SWI at every threshold except 70% and 80%. Permutation tests did not indicate differences in SWI at any threshold, see Table A2 in the

Appendix.

### Figure 3

*Average Delta FC per Group*



*Note.* Boxes are ROIs, the red box is the frontal ROI that was used for group differences. Sequence of boxes from the top left corner to bottom right is frontal, temporal left, temporal right, central, parietal, occipital.

#### Beta (Central ROI)

The average beta FC in the with PCS group seems to at least descriptively be enhanced in a frontal region, which was not the ROI for the beta connectivity hypothesis, see Figure 4. In both temporal regions, the with PCS seems to exhibit less FC than the without PCS group. Both groups seem to show similar FC in central and parietal regions, with central being the ROI. In the occipital region, the without PCS group might have higher FC.

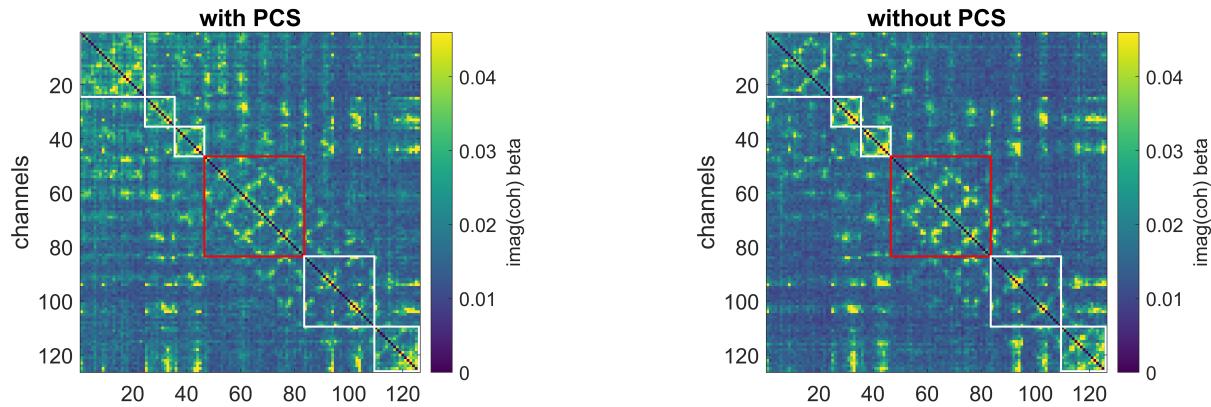
Statistically, the with PCS group exhibited a higher average beta coherence (imaginary part) in the central ROI ( $M = 0.0181$ ,  $SD = 0.0056$ ) compared to the without PCS group ( $M = 0.0156$ ,  $SD = 0.0034$ ). A one sided Welch two sample  $t$ -Test indicated a significant difference between the groups,  $t(36.37) = -1.80$ ,  $p = .041$ ,  $d = -0.53$ .

Descriptively, the with PCS group had a higher mean central beta SWI at every threshold except 80% and 90%. Permutation tests did not indicate differences in SWI at any threshold, see Table A2 in the Appendix. However, at 30% the  $p$ -value was only slightly above 5% ( $p = .053$ )

which is why it will be considered for correlations with behavioral data in the next section. Since the SWI is calculated from the CPL and CC it is of interest to have a look at the individual values at 30% threshold as well. The with PCS group has higher CPL ( $M_{withPCS} = 1.73$ ,  $SD_{withPCS} = 0.14$ ,  $M_{withoutPCS} = 1.72$ ,  $SD_{withoutPCS} = 0.07$ ). The CC seems to be higher in this group as well ( $M_{withPCS} = 0.39$ ,  $SD_{withPCS} = 0.04$ ,  $M_{withoutPCS} = 0.37$ ,  $SD_{withoutPCS} = 0.03$ ).

**Figure 4**

*Average Beta FC per Group*



*Note.* Boxes are ROIs, the red box is the central ROI that was used for group differences. Sequence of boxes from the top left corner to bottom right is frontal, temporal left, temporal right, central, parietal, occipital.

***Correlations With Clinical Data***

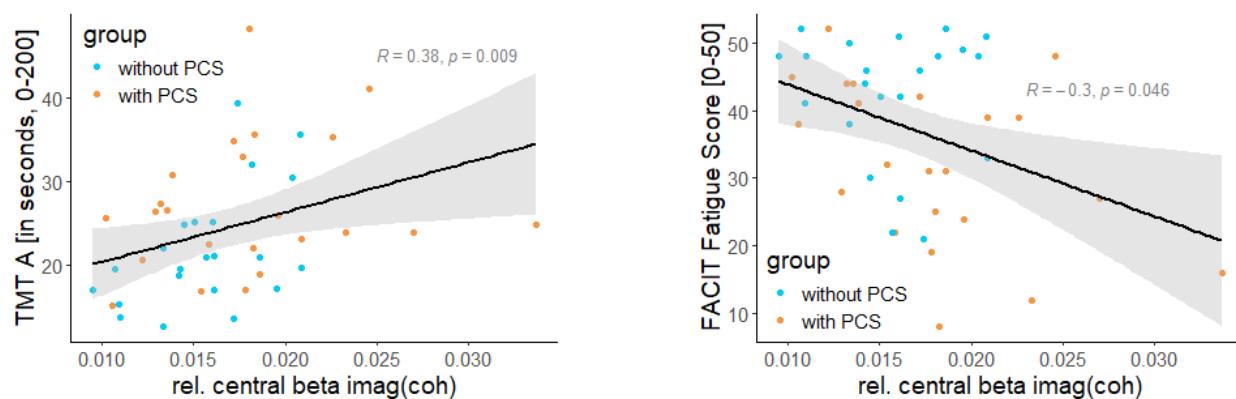
For the delta FC there were no significant correlation with any tests or questionnaires. See Table 4 for all correlation values. The beta FC, however, correlated with beta SWI at 30% threshold,  $\rho(43) = .71, p = <.001$ . It was additionally positively correlated with the TMT A,  $\rho(42) = .38, p = .010$ , and negatively correlated with the FACIT-F,  $\rho(42) = -.30, p = .046$ , see Figure 5. Beta SWI at 30% was also negatively correlated with FACIT-F Score,  $\rho(42) = -.32, p = .032$ . Correlation values of all nine SWI thresholds with FACIT-F, HADS-D, TMT A and TMT B-A can be found in Appendix A, Table A2.

**Table 4***Correlations of Connectivity Measures With Clinical Tests and Questionnaires*

Variables of interest	$\delta$ imag(coh)	$\beta$ imag(coh)	$\beta$ SWI (30%)
$\delta$ imag(coh)	1		
$\beta$ imag(coh)	-.05	1	
$\beta$ SWI (30%) <sup>a</sup>	-.26	.71***	1
<b>FACIT-F</b>	.03	<b>-.30*</b>	<b>-.32*</b>
<b>HADS-D</b>	.22	.28	.25
<b>TMT A</b>	.26	<b>.38**</b>	.27
<b>TMT B-A</b>	.26	-.07	-.22
<b>MoCA</b>	.00	-.18	-.23

Note. \* $p < .05$ , \*\* $p < .01$ , \*\*\* $p < .001$ . FC = functional connectivity, imag(coh) = imaginary part of coherence, SWI = Small World Index, FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue, HADS-D = Hospital Anxiety and Depression Scale – Depression in the German Version, TMT = Trail Making Test, MoCA = Montreal Cognitive Assessment.

<sup>a</sup> 30% means that the threshold for establishing this SWI was at 30%

**Figure 5***Correlations of Mean Central Beta FC with the TMT A and FACIT-F Questionnaire*

Note. TMT = Trail Making Test, FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue.

### Sex Differences

Descriptively, especially in the beta band, there seem to be sex differences, see Figure B2 in Appendix B. Especially for the connectivity but also in the beta power, the values of the female group appear to be elevated compared to the male group. This seems to happen in both groups but

might be even more pronounced in the with PCS group. For the delta power, there are two interesting aspects. First, the delta power for males in the with PCS group seems descriptively lower than for females in the with PCS group, but it secondly seems lower than for males and females in the without PCS group.

### **Aperiodic Components**

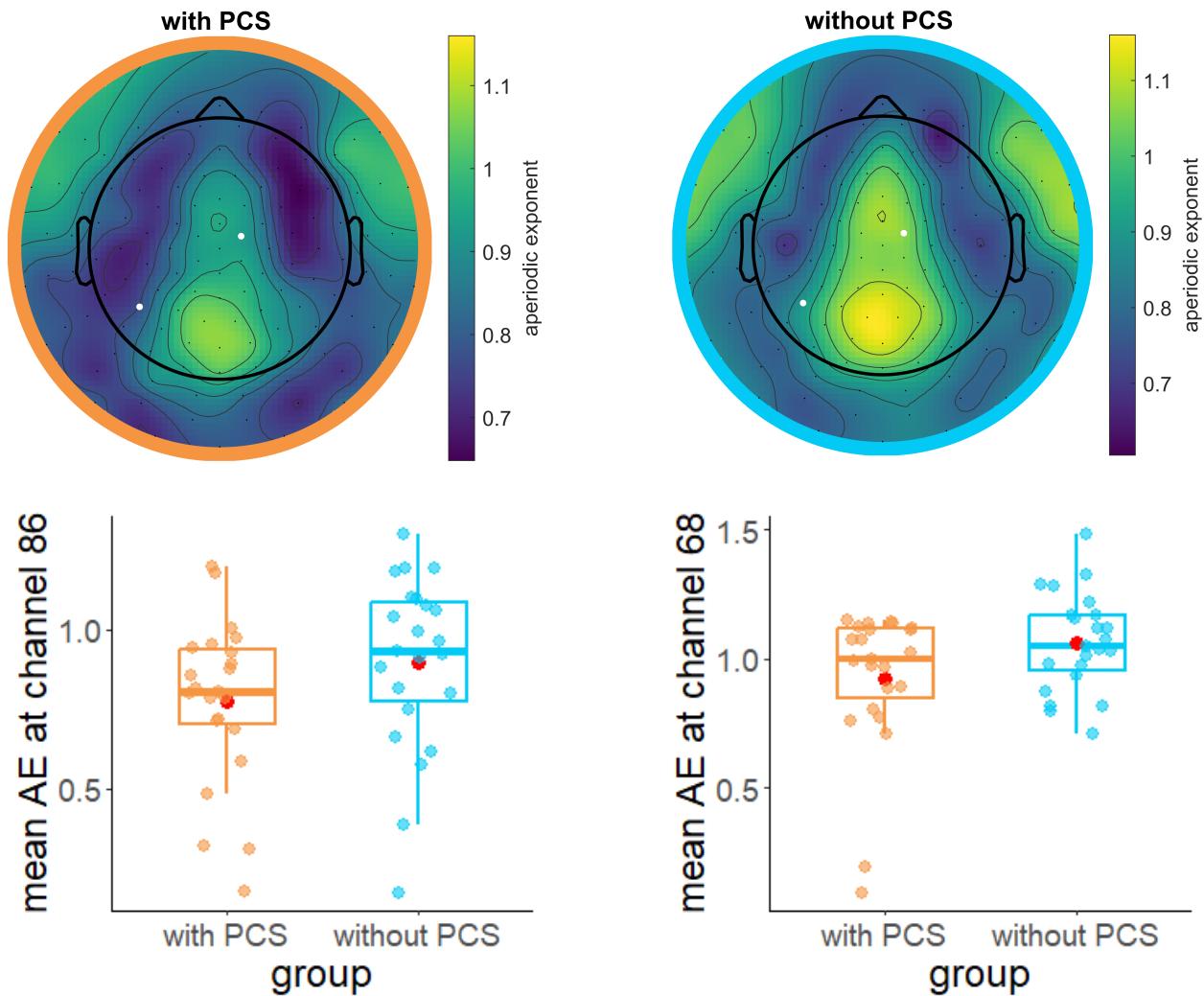
For the aperiodic offset and exponent, the assumptions were also investigated. Normality assumption was not met for the aperiodic exponent. Equal variances were seen in the exponent but not the offset,  $F(1,44) = 4.25, p = .045$ . Table A1 in Appendix A displays the results of all tested prerequisites.

Over the whole brain, a Wilcox Test did not indicate a difference in aperiodic exponent between the with PCS ( $M = 0.85, SD = 0.19$ ) and without PCS group ( $M = 0.90, SD = 0.22$ ),  $z = -0.52, p = .606, r = .08$ . Neither did the aperiodic offset differ between with PCS ( $M = -0.28, SD = 0.36$ ) and without PCS group ( $M = -0.25, SD = 0.19$ ),  $z = 0.05, p = .956, r = .01$ .

Looking at the topoplots in Figure 6, the midline seems to have higher values in general, as seen before in other studies plotting the aperiodic components, for example Cesnaite et al. (2023). In the topography of the aperiodic exponent, the values along the midline descriptively seem higher in the without PCS group. Permutation tests per channel indicated only two channels, however, where the groups differed significantly ( $p < .05$ ), see Figure 6. The topography of the aperiodic offset looked similar per group descriptively and permutation tests did not indicate any significantly different channels, see Figure B1 in the Appendix B.

**Figure 6**

*Topoplot of the Aperiodic Exponent (AE)*



*Note.* The boxplots display the average AE per group. White dots in the topoplots indicate a difference between the groups in the channels 68 (right dot) and 86 (left dot), with a  $p < .05$  in a permutation test. Red data points in the boxplots display means. The aperiodic exponent is unitless.

## Discussion

This study investigated differences in selected EEG measures between a group of people that reported subjective cognitive difficulties after Sars-CoV-2 infection and a group of people who did not experience difficulties thereafter. Five minutes of eyes open resting state data with a 128 electrode EEG cap were recorded and delta and beta power and connectivity were analyzed. In short, no significant differences in delta power and connectivity or beta power were found. Only beta FC was higher in the with PCS group. The beta FC was significantly correlated with time taken for the TMT A as well as fatigue score.

### Delta Power Hypothesis

Our result of no difference in delta power at frontal ROI neither supports the GABA-hypothesis for lower delta power in PCS-pts as proposed by Ortelli et al. (2023) nor the brainstem-hypothesis for higher delta power in PCS-pts as suggested in Cecchetti et al. (2022) and Yong (2021b). Kopańska et al. (2022) did not find any significant differences in delta power either. Their control was qEEG values of the same participants prior to infection and not an independent control group. This pre-post design could potentially provide a more robust framework for understanding the disease's impact, since a baseline is assessed, and subsequent changes could be attributable to the disease. This might point towards no change in delta power being plausible, if participants are grouped by subjective cognitive symptoms.

It is, however, not trivial, that we found a significant positive correlation of delta power with the HADS-D as well as a negative correlation with the MoCA and a close to significant negative correlation with the FACIT-F across all participants. These findings would indicate that having pronounced frontal delta power coincides with more depressive tendencies, more fatigue and less cognitive functioning. This stands in direct contrast to Ortelli et al. (2023), who found the score of their perceived cognitive difficulties scale to be negatively correlated with delta power, meaning less cognitive difficulties at higher delta power. It is also in contrast with Cecchetti et al. (2022), who found the FAB to be positively correlated with delta power (left and right central-temporal). Here, a higher FAB score indicates better cognitive functioning. Our

correlation of MoCA with delta power is also surprising, given that Furlanis et al. (2023) did not find a correlation between MoCA scores and the presence or absence of EEG abnormalities in a group of 20 patients with self-reported cognitive deficits after infection.

Both with the power results and the correlations, the following aspect can be discussed. Silva-Passadouro et al. (2024) point out that the heterogeneous results in PCS may arise due to the many different symptoms that PCS-pts may have. They argue that there may be different phenotypes of the disease with different symptoms being most prominent. The participants in the PCS EEG studies could therefore have had different phenotypes that resulted in different power values. For example, Cecchetti et al. (2022) focus on cognitive aspects, Ortelli et al. (2023) on cognitive aspects and fatigue, while Kopańska et al. (2022, 2023) focus on brain fog and concentration disorders respectively. Our participants showed symptoms of fatigue, but not so much in the cognitive domain, since TMT B-A and MoCA score did not differ between the groups. Additionally, there might be differences due to the methods used to obtain power values. Cecchetti et al. (2022) normalized the power instead of taking relative power. Ortelli et al. (2023) do not describe a method of normalization or fooof/specparam or anything similar.

Another aspect that could play a role is whether participants were hospitalized during their acute illness (Silva-Passadouro et al., 2024). Silva-Passadouro et al. (2024) think, this could be relevant because different levels of severity in acute COVID-19 infection, along with potential effects on the central nervous system caused by intensive care treatment, might contribute to the difference in EEG pattern. While Cecchetti et al. (2022) only included participants who were hospitalized and Ortelli et al. (2023) did the opposite by including only non-hospitalized participants, Kopańska et al. (2022) did not explicitly specify this. Among the initial 79 participants of our study, only six had a history of hospitalization, and just two of those were included, both in the non-PCS group. This is surprising given that PCS prevalence is typically higher in hospitalized cases (C. Chen et al., 2022). However, Rubin (2020) report that PCS can still occur after mild acute COVID-19, and Morawa et al. (2023) conclude that also after a rather mild disease period, cognitive difficulties can show, with only 13% of their sample having been

hospitalized.

In our study, permutation tests did not indicate any other significant clusters but descriptively, the with PCS group had lower values at central ROI. Ortelli et al. (2023) find lower delta power for example in the left pre- and postcentral gyrus as well as the right superior parietal lobule, which might fit to the tendency that can be seen in our topographies. Since no significant clusters were found, it cannot be investigated whether they would fit possible projections from the brainstem.

### **Delta Connectivity Hypothesis**

There was no difference in delta FC or SWI between the two groups in our frontal ROI. This contrasts with Cecchetti et al. (2022) who found higher FC in their PCS group. Additionally, the authors state that those patients who had higher FC scored better in the executive tests that they did. In our study, however, delta FC did not correlate with the MoCA score. The TMT B-A for example had a positive, not significant, relationship with delta FC. This would indicate that higher delta FC and slower switching in the TMT B-A coincide, which would not fit the compensation hypothesis either.

The fact that no difference in SWI was found does not deliver evidence for the loosely proposed hypothesis that brainstem dysfunction in PCS could disturb the neuromodulators there, which are thought to be involved in a balance of functional integration and segregation (Shine, 2019). Looking at the correlations of the different SWI thresholds with for example TMT B-A, there is no inverted u-shaped relation visible, as would be expected according to Shine (2019). One could also argue that if a control group, who never had COVID-19 would have been there, this inverted u-shape might have been present, but this is just speculation.

In ME/CFS, delta SWI was lower than in a control group and negatively associated with neurocognition (M. A. Zinn et al., 2017). Importantly, the paper does not clarify how thresholding was handled. In our data, using a 10% delta SWI threshold, a trend towards lower delta SWI in the with PCS group is visible as well as a positive correlation with Fatigue score, meaning higher SWI goes in line with lower fatigue. However, this trend is less clear when considering other

thresholds. Additionally, since it is the only study investigating SWI in ME/CFS so far, there is no established reference point or widely accepted standard for comparison.

### Beta Power Hypothesis

There was no clear direction in which the with PCS group was supposed to deviate from the without PCS group in terms of beta power. Our data support this further, since there was no significant difference between the two groups in our central ROI.

Descriptively, frontal and occipital regions appeared to differ between the groups, but the permutation test did not show significance. Higher frontal beta power in the with PCS group could seem like an artifact or like it may be driven by one individual. In relative beta values across individual channels, the maximum value was  $10.91 \mu V^2$ . Using an arbitrary threshold of  $7.50 \mu V^2$  (the top 1.2% values) all 69 channels belonged to PCS participants, with 17 (25%) being frontal channels, across six individuals. The fact that high values were observed in different brain regions and participants suggests, that PCS individuals may exhibit more extreme relative beta power values. While elevated frontal beta has been linked to stress in task-related settings (Ehrhardt et al., 2022), its role in resting state is less understood. A study identified frontal and occipital resting state power as potential objective measures of vigilance (Mayeli et al., 2020). Activity in both sites was positively correlated with tonic alertness, as measured by pupil size changes. This would be interesting to explore, in line with the hypoarousal theory mentioned before. However, our findings - showing opposite directions for frontal and occipital beta power - do not fit this pattern, making the argument inconclusive.

Interestingly, beta power was positively correlated with TMT A. It could reflect the movement component inherent in the task, since beta has been repeatedly shown to be involved in movement (Barone & Rossiter, 2021). Higher beta power was seemingly related to slower speed, since the groups differed in TMT A but not TMT B-A. Beta usually comes in bursts and is strongest when movement stops (Kilavik et al., 2013). This is why the hypothesis of higher beta power leading to increased rest would still be plausible. Since no group differences were found, this beta activity is likely not related to prior COVID-19 infection but could instead reflect other

individual differences.

Kilavik et al. (2013) report that the beta band may be categorized into low (< 20 Hz) and high (> 20 Hz) beta. Multiple studies referenced before investigate the PCS with low vs. high beta (Kopańska et al., 2022, 2023; Vecchio et al., 2017). Beta power was thus exploratory divided into low (beta1; 14-20 Hz) and high (beta2; 21-30 Hz). For beta1, a two-sided Wilcox Test did not indicate a significant difference between the groups,  $z = 0.45, p = .652, r = .07$ . For beta2, a two-sided Wilcox Test did not indicate a significant difference between the groups either,  $z = 1.68, p = .093, r = .25$ . While beta1 did not correlate with the TMT A,  $\rho(44) = .24, p = .105$ , or TMT B-A,  $\rho(44) = .06, p = .675$ , the beta2 did correlate with the TMT A,  $\rho(44) = .44, p = .002$ , but not TMT B-A,  $\rho(44) = -.09, p = .573$ . Neither beta1 nor beta2 correlated with the FACIT-F,  $\rho_{beta1}(44) = .23, p = .131, \rho_{beta2}(44) = -.15, p = .330$ .

### Beta Connectivity Hypothesis

The hypothesis was that the with PCS group would have higher beta FC values in our central ROI. This pattern was indeed reflected in our data. Beyond the group difference, beta FC was positively correlated with the TMT A and negatively with the Fatigue Score, looking at both groups combined. These correlations would fit the proposed hypothesis that higher FC would go in line with a maintenance of the status quo, that is rest (Wu et al., 2023).

According to Barone and Rossiter (2021), the sensorimotor cortex and the basal ganglia are the two principal origins of beta activity. High beta FC is, for example, often mentioned in connection with Parkinson's Disease and its rigidity symptoms, supporting the role of specific beta activity patterns in motor control and stability (Bergman et al., 1998; Lamoš et al., 2023). The limited origins of beta activity might help explain the connectivity matrix pattern, which shows high connectivity in certain areas but lack of connections in others. Higher beta connectivity in PCS could go in line with abnormal structural connectivity that was found with diffusion imaging in the basal ganglia and thalamus of PCS-pts (Heine et al., 2023). Fittingly, those atypical diffusion markers were correlated with fatigue severity. A functional Magnetic Resonance Imaging (fMRI) connectivity study in PCS-pts found the connectivity in the

paracentral lobule and the cingulate, especially posterior, to be correlated with the TMT A (Bungenberg et al., 2024). This would fit our found FC correlation with the TMT A. Bungenberg et al. (2024) explain, that the posterior cingulate is a part of the default mode network and that a hyperconnectivity there could possibly explain executive deficits.

But how could COVID-19 cause basal ganglia damage? Fishman et al. (1985) detected that a mouse coronavirus preferentially infected the basal ganglia. In humans that had COVID-19, a review mostly found reduced gray matter volume in the basal ganglia in structural MRI scans and only few studies reporting an increase (Mohammadi & Ghaderi, 2024). They say that it would align with existing evidence of gray matter atrophy observed in various neuroinflammatory and neuroinfectious conditions. One possible idea is that damage might be due to hypoxic or vascular injury to the basal ganglia because of the infection (Merello et al., 2021). As established before, the virus might enter through ACE2 receptors (Letko et al., 2020). High ACE2 receptor expression in dopaminergic neurons may allow SARS-CoV-2 to invade the substantia nigra and basal ganglia, worsening neurological symptoms (Cavallieri et al., 2022; Sinha et al., 2021). Interestingly, those dopaminergic neurons are the key cells affected in Parkinson's disease. There is even a small number of people even reporting COVID-19-related parkinsonism (Cavallieri et al., 2022), which should not be overemphasized due to the limited evidence. Heine et al. (2023) also found accumulating evidence for structural changes in the basal ganglia, correlating with fatigue severity. Drawing on previous studies that associate dopamine with fatigue (Dobryakova et al., 2013), Heine et al. (2023) suggest that PCS fatigue may result from a disruption in corticostriatal pathways, along with an imbalance in dopamine within the basal ganglia.

Descriptively, beta FC appeared elevated in the with PCS group in the frontal region. While frontal changes are not unexpected - given emerging evidence that SARS-CoV-2 may preferentially target the frontal lobes through retrograde axonal transport from the olfactory epithelium (Antony & Haneef, 2020; Guedj et al., 2021; Karimi-Galougahi et al., 2020; Meinhardt et al., 2021) - this finding contrasts the common hypothesis that fatigue in neurological conditions might stem from suppression of the excitatory system, rather than over-activity of the

inhibitory system (Kuppuswamy et al., 2015; Tanaka & Watanabe, 2012). Previous studies, such as Wu et al. (2023) have differentiated between somatomotor and motor networks, observing hyper-connectivity in sensory networks and hypo-connectivity in motor networks, reflecting reduced excitability in the primary motor cortex. Similarly, findings from Ortelli et al. (2022) showing higher resting motor thresholds and lower motor-evoked potential amplitudes in PCS-pts, despite normal spinal and peripheral motor conduction, suggest motor cortex hypo-excitability and central fatigue. These patients reported greater physical exertion compared to healthy controls, even when exerting the same force, indicating a central dysfunction in motor regulation. Russo et al. (2017) also found that fatigue in neurological disorders, such as MS is associated with disruptions in brain networks involved in motor preparation, particularly frontal-thalamic pathways. While this was shown in MS, it suggests that disruptions in similar circuits may contribute to PCS fatigue. But surprisingly, there descriptively is no hypoconnectivity in frontal areas in our PCS-pts and they still experienced significantly more fatigue than the other group.

There was a trend across thresholds for higher central beta SWI in the with PCS group. One threshold (30%) nearly reached significance and was positively correlated with speed of the TMT A, which would also fit the proposed hypothesis for an increased tendency to rest (Engel & Fries, 2010; Wu et al., 2023) as well as the results of Vecchio et al. (2017) and Wu et al. (2023). Still, the thresholding represents an issue. Taking for example a threshold of 10% does not guarantee that the network is still connected. This can be problematic, since according to Zanin (2015), the SWI is not defined for disconnected networks. He proposes that the CPL would diverge to infinity in these cases. Practically this means, that the CPL will be influenced by missing connections (Bialonski et al., 2010). Further, disconnected networks might have a different number of nodes at differing sites, which impairs comparability between subjects (Zanin, 2015). Thresholding in general could potentially make the result less realistic, as Granovetter (1973) pointed out that weak ties can be crucial for a system and this probably also applies to the brain (Bassett & Bullmore, 2017). This is a problem of validity: If different results are obtained at different thresholds, how can we be sure that we are measuring the right thing? It is especially

concerning when eliminating small connections, as it is unclear whether they are truly irrelevant (Sporns & Betzel, 2016). Calculating the SWI in the EEG has been criticized further (Papo et al., 2016), which will be discussed in the limitations section.

### **Experienced Cognitive Impairment and Fatigue**

Regarding the cognitive impairment, in our study the MoCA scores did not deviate between the groups, same as in Appelt et al. (2022), but in contrast to multiple other studies (Clemente et al., 2023; Ortelli et al., 2023; Rahimi et al., 2024). The TMT B-A did not deviate, which seems to be a common phenomenon (Appelt et al., 2022; Cecchetti et al., 2022). As mentioned before, even though the with PCS group did report subjective cognitive difficulties, this did not show in the measures looked at in this studies. Since EPOC provides multiple other measures, like PVT, n-back, etc. there is room for more exploration there.

Fatigue appears to play a critical role in the PCS. Compared to a pre-pandemic cohort, patients who had COVID-19 experience significantly higher levels of clinically relevant fatigue (Hartung et al., 2022). Not only is fatigue one of the most prominent symptoms (C. Chen et al., 2022), but it also severely compromises the quality of life (Malik et al., 2022). In our sample, the difference in Fatigue Score was evident. Note, that the mean FACIT-F Score was slightly above the cut-off for 'high fatigue' (Cella et al., 2011), meaning not every PCS-pts met this criterion. The FACIT-F is a self-report measure focused on the previous seven days, assessing trait fatigue rather than state fatigue.

It is important to note that other studies investigating EEG measures in PCS populations employed different fatigue measures, limiting direct comparison. Cecchetti et al. (2022) who observed higher delta power, did not include a fatigue measure. Ortelli et al. (2023) used the Fatigue Severity Scale (FSS), a unidimensional tool that investigates how fatigue affects daily functioning across various areas, such as family, work, social life, and physical activity (Krupp et al., 1989). However, the FSS does not differentiate between mental and physical fatigue (Krupp et al., 1989). This raises an important question: what facets of PCS-related fatigue are we measuring, and are we using the most appropriate tools? The FACIT-F, for instance, merges both

the experience and the impact of fatigue into a single scale (Cella et al., 2011), which makes it not clearly divided into physical and mental fatigue either.

One aspect not mentioned so far is the mood of PCS-pts. Our two groups differed in HADS-D score, indicating mood differences. However, the mean of PCS-pts was still in a normal range. Similarly, Ortelli et al. (2021) reported significantly higher Beck Depression Inventory scores in PCS-pts, but not evidence of major depression. In general, fatigue has been closely related to affective disorders with mood disturbances (Demyttenaere et al., 2005). This fits the high correlation we found between the HADS-D and FACIT-F score.

The groups differ in their distribution of clinical values. In the FACIT-F, the HADS-D and the TMT A the data of the with PCS group did not hurt the statistical prerequisite of normality distribution while data of the without PCS group did. It looks like some kind of ceiling effect since the without PCS group says that they do not experience subjective cognitive difficulties and accordingly score better on certain cognitive tests and the questionnaires. The variance in answers does surprisingly not differ significantly between the groups. It seems that there is also variety in the group of people who say that they do not experience cognitive difficulties.

### **Aperiodic Components**

Recent research has introduced the idea of a hypoarousal model for PCS (Martin et al., 2023), which presents an intriguing framework for understanding the condition. While our findings of no delta power difference did not fully align with the hypothesis, exploring the aperiodic components may offer new insights. Aperiodic components have been proposed as indices of excitation and inhibition balance (Gao et al., 2017; Waschke et al., 2021). For instance, the aperiodic offset has been positively correlated with neuronal population spiking (Manning et al., 2009), and the exponent may reflect the ratio of excitatory and inhibitory activity as demonstrated on rat local field potentials (Gao et al., 2017).

Further support comes from research in non-human primates, where a steeper aperiodic exponent following propofol induction might reflect the increase in inhibition induced by it (Gao et al., 2017). Similarly, Jacob et al. (2021) found that steeper aperiodic exponents may indicate

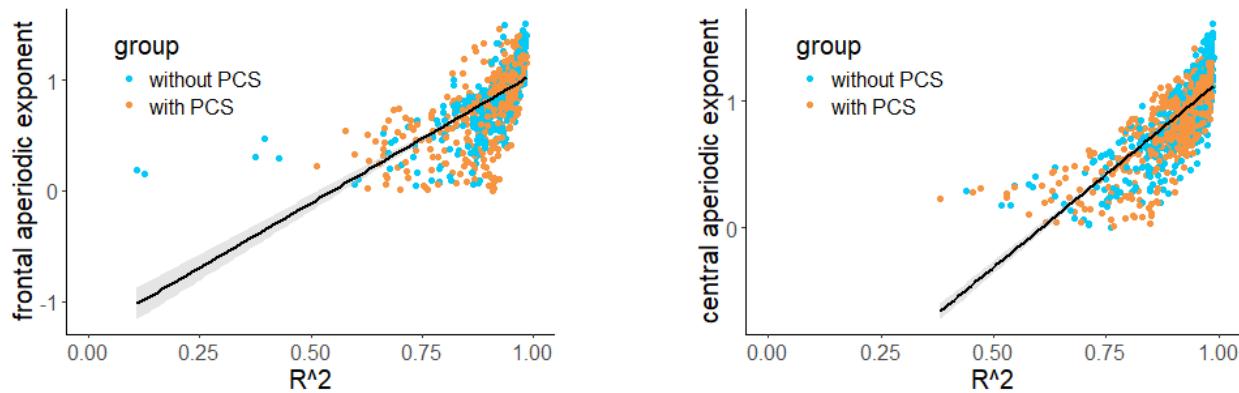
increased arousal and/or attention to external stimuli, while a flatter exponent could conversely suggest hypoarousal. For example, age-related flattening of the aperiodic exponent has been observed (Donoghue et al., 2020). Interestingly, we found a negative correlation between delta power and aperiodic exponent, where higher delta power was associated with a flatter slope, consistent with this hypothesis.

It is important to note, however, that delta power and aperiodic components are often intertwined methodologically, as the lower end of the spectrum is critical in calculating the slope (Gerster et al., 2022). In our sample, the mean exponent for PCS-pts was descriptively flatter than that of the without PCS group, with two channels showing a significant difference. Nonetheless, this is preliminary and further investigation is needed, especially since no differences were found in the aperiodic offset.

Additionally, in an exploratory analysis, a strong positive correlation of the aperiodic exponent and  $R^2$  was found in both the frontal,  $\rho(44) = .78, p = <.001$ , and central ROI,  $\rho(44) = .80, p = <.001$ , see Figure 7.  $R^2$  was distributed extremely skew, see Table A1, which is why nonparametric testing was used and Bonferroni correction was applied, since the two ROIs were tested separately. Since  $R^2$  is seen as a measure for goodness of model fit, it would be interesting if the two groups differ significantly in this parameter. The mean  $R^2$  values are lower in the with PCS groups in the frontal ROI ( $M_{withPCS} = .90, SD_{withPCS} = .08, M_{withoutPCS} = .92, SD_{withoutPCS} = .09$ ),  $z = -0.27, p = <.001, r = .14$ . The central ROI shows a similar pattern ( $M_{withPCS} = .92, SD_{withPCS} = .08, M_{withoutPCS} = .93, SD_{withoutPCS} = .07$ ),  $z = 8.00, p = <.001, r = .20$ . Taken together, the flatter aperiodic exponent in the with PCS group could somehow be related to the fit. How exactly this relates to arousal is, however, unclear.

## Limitations

First and foremost, our chosen control group was infected with Sars-CoV-2 at one point. It might have been more ideal to compare with individuals who have not had COVID-19. This becomes increasingly more difficult with the time. The bigger issue at hand might be that we do not have the pre-infection neuropsychological (or neurophysiological) data of the participants. Take for

**Figure 7***Correlations of Aperiodic Exponent With  $R^2$* 

*Note.* Correlation of frontal aperiodic exponent with  $R^2$  (left) and of central aperiodic exponent with  $R^2$  (right). The aperiodic exponent is unitless.

example the fact that our two groups do not differ in terms of TMT B-A. You could now argue that this does not make sense, since one group says that they have subjective cognitive difficulties while the others say they do not and still do not perform significantly worse. The problem is that the question is rather subjective, and a person might have gotten a lower score than they would have had prior to infection but this very score might have been higher than another person's to begin with. We simply do not know the starting point and cannot make assumptions on changes but only those group comparisons.

We did not explicitly list, which Sars-CoV-2 variant everyone had. There have been numerous variants, called Alpha, Beta, Delta, Gamma and Omicron (Meinhardt et al., 2024). Chronic symptom burden seems to be for example lower after Omicron than after Delta (Antonelli et al., 2022; Magnusson et al., 2022). Omicron, however, became dominant first in December 2021 (Meinhardt et al., 2024), which is after our recruitment period. It is possible that different variants have differential effects on brain parameters, it might also be neglectable.

Another aspect is that comorbidities are not listed in this study. Higher delta power for example can be a quite unspecific measure for different illnesses (Babiloni et al., 2017, 2020). It

would be necessary to check the comorbidities to exclude any systematic relations there.

It could be viewed negatively, that we chose ROI selection instead of a cluster-based permutation test. Additionally, here we did not divide the statistical tests into right vs. left hemisphere, although for example Kopańska et al. (2022) found differences per hemisphere. However, at least for the power analysis, exploratory permutation tests did not refute our ROI selection. In accordance, neither method detected significant differences between the two groups.

It could be criticized that our male to female ratio is different per group. In the without PCS group, it is way more balanced. At least it is realistic that the with PCS group has more females since this seems to be a trend in PCS (C. Chen et al., 2022). Vecchio et al. (2017) had more females in general with fatigue and the female to male ratio was higher in the high fatigue group. Wu et al. (2023) also had a higher female ratio in their high fatigue group, and they did see sex differences in beta SWI per group. They concluded, however, that sex would not be the sole driver of those differences, since sensorimotor networks (as found in an fMRI study) are supposedly less influenced by sex compared to other brain regions (Li et al., 2022). Not only for connectivity but also for the power sex could potentially be relevant. Ortelli et al. (2023) had rather balanced sexes and found lower delta power, while Cecchetti et al. (2022) had a balanced control group but only 36% males in their patient group. Could this have led to higher delta power values? At least in our studies, the males in the with PCS group had lower delta values than the females. This advocates for the need of studies that investigate fatigue differences in the sexes in the EEG, not only fMRI (Stumme et al., 2020). Until then, it might be better to sex-match the groups to rule out any systematic differences.

Another crucial aspect is that we did not do a source analysis for our EEG results. This would mean that the EEG signal is transformed to determine the underlying sources, which is sometimes called 'the inverse problem' (Grech et al., 2008). We stayed on sensor level with no attempt to estimate sources, because that would have been out of scope for this study. Ortelli et al. (2023) found significant ROIs with this method. Additionally, Babiloni et al. (2024) who found lower alpha power in their PCS group at source level report conducting a control analysis at the

sensor level that did not yield any significant results. They think that maybe the electric fields have become unclear over the surface.

Further, we did not do any sample size calculations, although Miljevic et al. (2022) suggest doing apriori sample size calculations as good research practice. Unfortunately, neither Cecchetti et al. (2022) nor Ortelli et al. (2023) report all the values needed for effect size calculations. The sample sizes were thus rather defined by the group size of the without PCS group, since they got age-matched counterparts from the other group.

A problem was some 'bad' fits of the fooof/specparam method, especially at the beginning of the power spectrum. A large proportion of relative delta power values at the channels that were left after the individual outlier removal were negative. This large amount at delta might be the case because for example Gerster et al. (2022) point out that delta oscillation rarely presents as a distinct peak in the double logarithmic representation. The fooof/specparam website recommends to use the 'min\_peak\_height' setting, if you know or expect not to have any peaks, so maybe this should have been used (VoytekLab, 2018/2023). But then again, we did expect delta peaks. This setting would require checking the scaling of your power spectra. Like this you can define an absolute threshold to define peaks. Another aspect for bad fits could be, that the resting state eyes open condition was identified to have fewer good fits compared to eyes closed (McKeown et al., 2024). Descriptively, there were also some "hard" spectra in our data, which could also lead to negative values because getting the right fit is harder (Gerster et al., 2022). We also tried, if setting the aperiodic mode to 'knee' would result in less negative values (VoytekLab, 2018/2023), but this was not the case.

After addressing the issue with the thresholding procedure to obtain the SWI, the question can be raised, whether SWI should be measured with the EEG at all (Papo et al., 2016). By calculating a CC and CPL you try to infer structural properties. In the EEG, the nodes are the electrodes and not real brain regions, and the paths are the relation of these nodes, meaning purely statistical. At least since we did not do source localization. SWI in the fMRI might make more sense, because actual structural properties might be included. However recently, claims have been

made that functional brain networks as shown in the fMRI reflect mostly spatial and temporal autocorrelation (Shinn et al., 2023). On top of this, we still do not actually know, if Small-Worldness really is the optimal property for information processing in the brain (Karsai et al., 2011; Papo et al., 2016). Besides, there are further methodological issues. EEG in general seems to lead to overestimated high CC values, due to the lattice-like sensor organization (Bialonski et al., 2010). And this gets worse with ROI selection. The Discover EEG pipeline that was looked at for the connectivity code only computed an overall SWI (Gil Ávila et al., 2023). This is why the ROI selection had to be added at some point. Here, it was not quite clear, when this was the most appropriate. In our code, we first calculated the adjacency matrix and distance matrix over all the channels and extracted the ROIs afterwards. The key problem here is that it makes a difference compared to calculating the adjacency matrix/distance matrix inside ROIs only. When the network is small, the CPL cannot possibly vary a lot and this is why the SWI depends more on the CC in this case (Bassett & Bullmore, 2017; Papo et al., 2016; Zanin, 2015). van Wijk et al. (2010) also found that changes in network size affected the graph measures, despite the network topology remaining unchanged.

### ***Multiverse of Analysis Pipeline***

In EEG research, there is the problem that when you preprocess and analyze the data, there are many paths that you can take (Clayson, 2024). Then, a multiverse opens with numerous possible resulting datasets (Clayson, 2024). This must be kept in mind, when looking at the results of every EEG study, including this study. In this section, awareness shall be raised for this fact by naming steps that were decided against during the preprocessing and analysis process.

There are for example three analysis steps that were suggested as superior for connectivity analyses but that were not feasible in this study. First, the reference electrode standardization technique (REST) is said to be a better reference method for the FC (Yao, 2001), while our study opted for CAR. Yao (2001) explains REST as a method to approximate the standardization of scalp EEG recordings by referencing them to a point at infinity, supposedly the most neutral reference. Secondly, our study did not do a wavelet enhanced ICA (Castellanos & Makarov,

2006). Castellanos and Makarov (2006) state that normal ICA may overestimate coherence, while their wavelet enhanced ICA artifact suppression maintains both the spectral (amplitude) and coherence (phase) properties of the underlying neural signals. Third, Smith et al. (2015) propose a solution for the problem with thresholding to obtain the SWI that was explained earlier. They call it a Cluster-Span-Threshold and their approach uses the CC. It is based on the idea that a balance between 'clustering' and 'spanning' triples creates an effective network topology, with the product of these complementing properties reaching a unique value only when perfectly balanced. Instead of arbitrarily fixing connection density, they threshold networks by setting CC to this balanced value. There was unfortunately no open-science code detectable to implement this. Additionally, a paper has been published that promises a more robust assessment of FC in the M/EEG, which might be preferable to the methods that we have used (Westner et al., 2024).

The length of epochs seems to make a difference as well. For the connectivity analyses we chose 4 s and for power 5 s. If, however, we would have had more, for example 6 s, for the connectivity analyses as recommended in Miljevic et al. (2022), the results might have differed. Same goes for the power analyses. Additionally, the number of epochs for some participants were notably low. Here you could ask if our preprocessing algorithm might have been too strict. If you wanted to keep for example 50 epochs for each individual in the connectivity analysis, then there would not have been many participants left to compare.

Lastly, another FC measure could have been chosen, for example the phase locking value (PLV), phase lag index or pairwise phase consistency (PPC) (Bastos & Schoffelen, 2016). Ideally, Bastos and Schoffelen (2016) would recommend calculating multiple FC measures to compare those. For example, the PPC is said to not be influenced by the trial number as much as coherence and that the PLV would reflect phase synchronicity better than coherence (Bastos & Schoffelen, 2016). Trying out multiple FC measures could therefore lead to different results, this would, however, been out of scope for this study.

## Future Research

Further research should explore different subgroups of PCS. In both our study and Cecchetti et al. (2022), participant groups were defined using subjective reports of cognitive difficulties post-infection. Employing a more standardized measure, such as the PCS score proposed by Bahmer et al. (2022), which is based on 12 long-term symptom complexes, could improve consistency. Alternatively, as in Ortelli et al. (2023) studies could only accept people with a formal diagnosis of PCS. This approach was not always feasible in earlier stages of research due to the challenge of obtaining diagnoses.

It might also make sense to classify participants into fatigue-only and cognitive-symptoms-only subgroups. Accurate subgrouping is crucial, because different PCS subgroups could require tailored treatments. This focus of subgroup differentiation is also relevant to the study of fatigue (Billones et al., 2021). Although the FACIT-F subsumes both experience and impact of fatigue, no comparisons of these individual aspects have been made between the groups in the current study. Future studies should consider using more detailed fatigue measures, such as the Modified Fatigue Impact Scale (Fisk et al., 1994), which provides distinct values for physical, cognitive and psychosocial impact. Moreover, physiological measures, such as an Isometric Muscle Strength Test (Kent-Braun & Miller, 2000) and how they relate to observed EEG parameters could add valuable insights into the fatigue experienced by PCS-pts.

As outlined before, this paper focused on delta and beta power. A transdiagnostic review of EEG parameters in fatigue concluded that higher theta and lower alpha power were largely found in fatigue (Heitmann et al., 2023). It could therefore potentially be interesting to look at those two parameters in our group of PCS. Particularly because Babiloni et al. (2024) recently found differences in posterior alpha in PCS. This was found in the eyes closed condition, which marks another point, namely that we have not yet analyzed the eyes closed condition, so this could be promising.

The previously outlined critique concerning the SWI leads to the necessity of using other types of graph measures instead such as modularity, hierarchical structure or spatial embedding

(Papo et al., 2016). Modularity is interesting, since Sporns and Betzel (2016) conclude that brain networks are probably structured into communities that generally align with established functional subdivisions. Understanding which nodes are part of each module can provide valuable insights into how the network operates (Sporns & Betzel, 2016). It is compelling to explore how these networks are altered by disruptions in brain function due to clinical disorders (Fornito et al., 2015).

Finally, it could also be interesting to have a look at cross frequency hubs like Guillon et al. (2017) did with Alzheimer's Disease. They discovered an altered multi-frequency brain network, with reduced information transfer across frequency bands, including a loss of inter-modular gamma band interactions linked to impaired memory. Investigating whether fatigue could be related to any multi-frequency network disruptions could be valuable.

### **Conclusion**

The two groups, which differed in their self-reported cognitive difficulties post-infection, showed less variation in brain measures than initially expected. However, the groups did differ significantly in terms of reported fatigue and notably, beta FC was significantly higher in PCS. Like in other diseases before, this higher beta connectivity was correlated with reported fatigue. This finding underscores the importance of further investigating beta FC as a marker of PCS-related brain changes and fatigue. Additionally, delta power correlated with higher fatigue scores and lower cognitive performance across participants, suggesting it should not be overlooked in future research. The SWI, on the other hand, does not appear to be a reliable measure of connectivity in EEG studies.

## References

- Adamovich, T., Zakharov, I., Tabueva, A., & Malykh, S. (2022). The thresholding problem and variability in the EEG graph network parameters. *Scientific Reports*, 12(1), Article e18659. <https://doi.org/10.1038/s41598-022-22079-2>
- Aiello, E. N., Fiabane, E., Manera, M. R., Radici, A., Grossi, F., Ottonello, M., Pain, D., & Pistarini, C. (2022). Screening for cognitive sequelae of SARS-CoV-2 infection: A comparison between the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA). *Neurological Sciences*, 43(1), 81–84. <https://doi.org/10.1007/s10072-021-05630-3>
- Amzica, F., & Steriade, M. (1998). Electrophysiological correlates of sleep delta waves. *Electroencephalography and Clinical Neurophysiology*, 107(2), 69–83. [https://doi.org/10.1016/S0013-4694\(98\)00051-0](https://doi.org/10.1016/S0013-4694(98)00051-0)
- André, Q. (2022). Outlier exclusion procedures must be blind to the researcher's hypothesis. *Journal of Experimental Psychology: General*, 151(1), 213–223. <https://doi.org/10.1037/xge0001069>
- Antonelli, M., Pujol, J. C., Spector, T. D., Ourselin, S., & Steves, C. J. (2022). Risk of long COVID associated with delta versus omicron variants of SARS-CoV-2. *Lancet*, 399(10343), 2263–2264. [https://doi.org/10.1016/S0140-6736\(22\)00941-2](https://doi.org/10.1016/S0140-6736(22)00941-2)
- 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>
- Appelt, P. A., Sisconetto, A. T., Baldo Sucupira, K. S. M., de Moura Neto, E., Chagas, T. d. J., Bazan, R., Moura Cabral, A., Andrade, A. d. O., de Souza, L. A. P. S., & Luvizutto, G. J. (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>

- Auer, T., Goldthorpe, R., Peach, R., Hebron, H., & Violante, I. R. (2024). Functionally annotated electrophysiological neuromarkers of healthy ageing and memory function. *Human Brain Mapping*, 45(6), e26687. <https://doi.org/10.1002/hbm.26687>
- Babiloni, C., De Pandis, M. F., Vecchio, F., Buffo, P., Sorpresi, F., Frisoni, G. B., & Rossini, P. M. (2011). Cortical sources of resting state electroencephalographic rhythms in Parkinson's disease related dementia and Alzheimer's disease. *Clinical Neurophysiology*, 122(12), 2355–2364. <https://doi.org/10.1016/j.clinph.2011.03.029>
- Babiloni, C., Del Percio, C., Lizio, R., Noce, G., Cordone, S., Lopez, S., Soricelli, A., Ferri, R., Pascarelli, M. T., Nobili, F., Arnaldi, D., Aarsland, D., Orzi, F., Buttinelli, C., Giubilei, F., Onofrj, M., Stocchi, F., Stirpe, P., Fuhr, P., . . . Bonanni, L. (2017). Abnormalities of cortical neural synchronization mechanisms in patients with dementia due to Alzheimer's and Lewy body diseases: An EEG study. *Neurobiology of Aging*, 55, 143–158. <https://doi.org/10.1016/j.neurobiolaging.2017.03.030>
- Babiloni, C., Gentilini Cacciola, E., Tucci, F., Vassalini, P., Chilovi, A., Jakhar, D., Musat, A. M., Salvatore, M., Soricelli, A., Stocchi, F., Vacca, L., Ferri, R., Catania, V., Mastroianni, C., D'Ettorre, G., & Noce, G. (2024). Resting-state EEG rhythms are abnormal in post COVID-19 patients with brain fog without cognitive and affective disorders. *Clinical Neurophysiology*, 161, 159–172. <https://doi.org/10.1016/j.clinph.2024.02.034>
- Babiloni, C., Pascarelli, M. T., Lizio, R., Noce, G., Lopez, S., Rizzo, M., Ferri, R., Soricelli, A., Nobili, F., Arnaldi, D., Famà, F., Orzi, F., Buttinelli, C., Giubilei, F., Salvetti, M., Cipollini, V., Bonanni, L., Franciotti, R., Onofrj, M., . . . Del Percio, C. (2020). Abnormal cortical neural synchronization mechanisms in quiet wakefulness are related to motor deficits, cognitive symptoms, and visual hallucinations in Parkinson's disease patients: An electroencephalographic study. *Neurobiology of Aging*, 91, 88–111. <https://doi.org/10.1016/j.neurobiolaging.2020.02.029>
- Bahmer, T., Borzikowsky, C., Lieb, W., Horn, A., Krist, L., Fricke, J., Scheibenbogen, C., Rabe, K. F., Maetzler, W., Maetzler, C., Laudien, M., Frank, D., Ballhausen, S.,

- Hermes, A., Miljukov, O., Haeusler, K. G., Mokhtari, N. E. E., Witzenrath, M., Vehreschild, J. J., . . . Schreiber, S. (2022). Severity, predictors and clinical correlates of Post-COVID syndrome (PCS) in Germany: A prospective, multi-centre, population-based cohort study. *eClinicalMedicine*, 51, Article e101549.  
<https://doi.org/10.1016/j.eclinm.2022.101549>
- Baig, A. M. (2020). Deleterious outcomes in long-hauler COVID-19: The effects of SARS-CoV-2 on the CNS in Chronic COVID Syndrome. *ACS chemical neuroscience*, 11(24), 4017–4020. <https://doi.org/10.1021/acschemneuro.0c00725>
- Barnden, L. R., Crouch, B., Kwiatek, R., Burnet, R., Mernone, A., Chryssidis, S., Scroop, G., & Del Fante, P. (2011). A brain MRI study of chronic fatigue syndrome: Evidence of brainstem dysfunction and altered homeostasis. *NMR in Biomedicine*, 24(10), 1302–1312.  
<https://doi.org/10.1002/nbm.1692>
- Barone, J., & Rossiter, H. E. (2021). Understanding the role of sensorimotor beta oscillations. *Frontiers in Systems Neuroscience*, 15, Article e655886.  
<https://doi.org/10.3389/fnsys.2021.655886>
- Barzegaran, E., van Damme, B., Meuli, R., & Knyazeva, M. G. (2016). Perception-related EEG is more sensitive to Alzheimer's disease effects than resting EEG. *Neurobiology of Aging*, 43, 129–139. <https://doi.org/10.1016/j.neurobiolaging.2016.03.032>
- Bassett, D. S., & Bullmore, E. T. (2017). Small-World brain networks revisited. *The Neuroscientist*, 23(5), 499–516. <https://doi.org/10.1177/1073858416667720>
- Bastos, A. M., & Schoffelen, J.-M. (2016). A tutorial review of functional connectivity analysis methods and their interpretational pitfalls. *Frontiers in Systems Neuroscience*, 9, Article e175. <https://doi.org/10.3389/fnsys.2015.00175>
- Benis, D., Voruz, P., Chiuve, S. C., Garibotto, V., Assal, F., Krack, P., Péron, J., & Fleury, V. (2024). Electroencephalographic abnormalities in a patient suffering from long-term neuropsychological complications following SARS-CoV-2 infection. *Case Reports in Neurology*, 16(1), 6–17. <https://doi.org/10.1159/000535241>

- Bergman, H., Feingold, A., Nini, A., Raz, A., Slovin, H., Abeles, M., & Vaadia, E. (1998). Physiological aspects of information processing in the basal ganglia of normal and parkinsonian primates. *Trends in Neurosciences*, 21(1), 32–38.  
[https://doi.org/10.1016/s0166-2236\(97\)01151-x](https://doi.org/10.1016/s0166-2236(97)01151-x)
- Besteher, B., Rocktäschel, T., Garza, A. P., Machnik, M., Ballez, J., Helbing, D.-L., Finke, K., Reuken, P., Güllmar, D., Gaser, C., Walter, M., Opel, N., & Dunay, I. R. (2024). Cortical thickness alterations and systemic inflammation define long-COVID patients with cognitive impairment. *Brain, Behavior, and Immunity*, 116, 175–184.  
<https://doi.org/10.1016/j.bbi.2023.11.028>
- Bialonski, S., Horstmann, M.-T., & Lehnertz, K. (2010). From brain to earth and climate systems: Small-world interaction networks or not? *Chaos*, 20(1), Article e013134.  
<https://doi.org/10.1063/1.3360561>
- Billones, R., Liwang, J. K., Butler, K., Graves, L., & Saligan, L. N. (2021). Dissecting the fatigue experience: A scoping review of fatigue definitions, dimensions, and measures in non-oncologic medical conditions. *Brain, Behavior, & Immunity - Health*, 15, Article e100266. <https://doi.org/10.1016/j.bbih.2021.100266>
- Brown, P., Oliviero, A., Mazzone, P., Insola, A., Tonali, P., & Di Lazzaro, V. (2001). Dopamine dependency of oscillations between subthalamic nucleus and pallidum in Parkinson's disease. *The Journal of Neuroscience*, 21(3), 1033–1038.  
<https://doi.org/10.1523/JNEUROSCI.21-03-01033.2001>
- Brown, P. (2003). Oscillatory nature of human basal ganglia activity: Relationship to the pathophysiology of Parkinson's disease. *Movement Disorders*, 18(4), 357–363.  
<https://doi.org/10.1002/mds.10358>
- Bungenberg, J., Hohenfeld, C., Costa, A. S., Heine, J., Schwichtenberg, K., Hartung, T., Franke, C., Binkofski, F., Schulz, J. B., Finke, C., & Reetz, K. (2024). Characteristic functional connectome related to Post-COVID-19 syndrome. *Scientific Reports*, 14, Article e4997. <https://doi.org/10.1038/s41598-024-54554-3>

- Buyssse, D. J., Reynolds, 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](https://doi.org/10.1016/0165-1781(89)90047-4)
- Buyukturkoglu, K., Porcaro, C., Cottone, C., Cancelli, A., Inglese, M., & Tecchio, F. (2017). Simple index of functional connectivity at rest in Multiple Sclerosis fatigue. *Clinical Neurophysiology*, 128(5), 807–813. <https://doi.org/10.1016/j.clinph.2017.02.010>
- Cainelli, E., Di Bono, M. G., Bisacchini, P. S., & Suppiej, A. (2020). Electroencephalographic functional connectivity in extreme prematurity: A pilot study based on graph theory. *Pediatric Research*, 87, 753–759. <https://doi.org/10.1038/s41390-019-0621-3>
- Callard, F., & Perego, E. (2021). How and why patients made Long Covid. *Social Science & Medicine*, 268, Article e113426. <https://doi.org/10.1016/j.socscimed.2020.113426>
- Carfi, A., Bernabei, R., & Landi, F. (2020). Persistent symptoms in patients after acute COVID-19. *JAMA*, 324(6), 603–605. <https://doi.org/10.1001/jama.2020.12603>
- Castellanos, N. P., & Makarov, V. A. (2006). Recovering EEG brain signals: Artifact suppression with wavelet enhanced independent component analysis. *Journal of Neuroscience Methods*, 158(2), 300–312. <https://doi.org/10.1016/j.jneumeth.2006.05.033>
- Cavallieri, F., Fioravanti, V., Bove, F., Del Prete, E., Meoni, S., Grisanti, S., Zedde, M., Pascarella, R., Moro, E., & Valzania, F. (2022). COVID-19 and parkinsonism: A critical appraisal. *Biomolecules*, 12(7), 970. <https://doi.org/10.3390/biom12070970>
- Ceban, F., Ling, S., Lui, L. M. W., Lee, Y., Gill, H., Teopiz, K. M., Rodrigues, N. B., Subramaniapillai, M., Di Vincenzo, J. D., Cao, B., Lin, K., Mansur, R. B., Ho, R. C., Rosenblat, J. D., Miskowiak, K. W., Vinberg, M., Maletic, V., & McIntyre, R. S. (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>
- Cecchetti, G., Vabanesi, M., Chieffo, R., Fanelli, G., Minicucci, F., Agosta, F., Tresoldi, M., Zangrillo, A., & Filippi, M. (2020). Cerebral involvement in COVID-19 is associated with metabolic and coagulation derangements: An EEG study. *Journal of Neurology*, 267(11), 3130–3134. <https://doi.org/10.1007/s00415-020-09958-2>
- Cella, D., Lai, J.-S., & Stone, A. (2011). Self-reported fatigue: One dimension or more? Lessons from the Functional Assessment of Chronic Illness Therapy—Fatigue (FACIT-F) questionnaire. *Supportive Care in Cancer*, 19(9), 1441–1450.  
<https://doi.org/10.1007/s00520-010-0971-1>
- Cesnaite, E., Steinfath, P., Jamshidi Idaji, M., Stephani, T., Kumral, D., Haufe, S., Sander, C., Hensch, T., Hegerl, U., Riedel-Heller, S., Röhr, S., Schroeter, M. L., Witte, A. V., Villringer, A., & Nikulin, V. V. (2023). Alterations in rhythmic and non-rhythmic resting-state EEG activity and their link to cognition in older age. *NeuroImage*, 268, Article e119810. <https://doi.org/10.1016/j.neuroimage.2022.119810>
- Chen, C., Haupert, S. R., Zimmermann, L., Shi, X., Fritzsche, L. G., & Mukherjee, B. (2022). Global prevalence of post-coronavirus disease 2019 (COVID-19) condition or long COVID: A meta-analysis and systematic review. *The Journal of Infectious Diseases*, 226(9), 1593–1607. <https://doi.org/10.1093/infdis/jiac136>
- Chen, C. C., Litvak, V., Gilbertson, T., Kühn, A., Lu, C. S., Lee, S. T., Tsai, C. H., Tisch, S., Limousin, P., Hariz, M., & Brown, P. (2007). Excessive synchronization of basal ganglia neurons at 20 Hz slows movement in Parkinson's disease. *Experimental Neurology*, 205(1), 214–221. <https://doi.org/10.1016/j.expneurol.2007.01.027>

- Chen, W., Toprani, S., Werbaneth, K., & Falco-Walter, J. (2020). Status epilepticus and other EEG findings in patients with COVID-19: A case series. *Seizure*, 81, 198–200.  
<https://doi.org/10.1016/j.seizure.2020.08.022>
- Chu, H., Chan, J. F.-W., Yuen, T. T.-T., Shuai, H., Yuan, S., Wang, Y., Hu, B., Yip, C. C.-Y., Tsang, J. O.-L., Huang, X., Chai, Y., Yang, D., Hou, Y., Chik, K. K.-H., Zhang, X., Fung, A. Y.-F., Tsoi, H.-W., Cai, J.-P., Chan, W.-M., . . . Yuen, K.-Y. (2020). Comparative tropism, replication kinetics, and cell damage profiling of SARS-CoV-2 and SARS-CoV with implications for clinical manifestations, transmissibility, and laboratory studies of COVID-19: An observational study. *The Lancet Microbe*, 1(1), e14–e23.  
[https://doi.org/10.1016/S2666-5247\(20\)30004-5](https://doi.org/10.1016/S2666-5247(20)30004-5)
- Clayson, P. E. (2024). Beyond single paradigms, pipelines, and outcomes: Embracing multiverse analyses in psychophysiology. *International Journal of Psychophysiology*, 197, Article e112311. <https://doi.org/10.1016/j.ijpsycho.2024.112311>
- Clemente, L., La Rocca, M., Quaranta, N., Iannuzzi, L., Vecchio, E., Brunetti, A., Gentile, E., Dibattista, M., Lobasso, S., Bevilacqua, V., Stramaglia, S., & de Tommaso, M. (2023). Prefrontal dysfunction in post-COVID-19 hyposmia: An EEG/fNIRS study. *Frontiers in Human Neuroscience*, 17, Article e1240831. <https://doi.org/10.3389/fnhum.2023.1240831>
- Cohen, M. X. (2019, December). Intuition about phase synchronization. *YouTube*. Retrieved November 10, 2024, from <https://www.youtube.com/watch?v=MTPE4k8X2tk&list=PLn0OLiymPak1wp4wMQ7tbYrtyFUatMVJs&index=3>
- Colrain, I. M. (2011). Sleep and the brain. *Neuropsychology Review*, 21(1), 1–4.  
<https://doi.org/10.1007/s11065-011-9156-z>
- Delorme, A. (2023). EEG is better left alone. *Scientific Reports*, 13(1), Article e2372.  
<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>

- Demyttenaere, K., De Fruyt, J., & Stahl, S. M. (2005). The many faces of fatigue in major depressive disorder. *International Journal of Neuropsychopharmacology*, 8(1), 93–105. <https://doi.org/10.1017/S1461145704004729>
- Dinges, D. F., & Powell, J. W. (1985). Microcomputer analyses of performance on a portable, simple visual RT task during sustained operations. *Behavior Research Methods, Instruments, & Computers*, 17(6), 652–655. <https://doi.org/10.3758/BF03200977>
- Dobryakova, E., DeLuca, J., Genova, H. M., & Wylie, G. R. (2013). Neural correlates of cognitive fatigue: Cortico-striatal circuitry and effort-reward imbalance. *Journal of the International Neuropsychological Society*, 19(8), 849–853. <https://doi.org/10.1017/S1355617713000684>
- 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>
- Ehrhardt, N. M., Fietz, J., Kopf-Beck, J., Kappelmann, N., & Brem, A.-K. (2022). Separating EEG correlates of stress: Cognitive effort, time pressure, and social-evaluative threat. *The European Journal of Neuroscience*, 55(9-10), 2464–2473. <https://doi.org/10.1111/ejn.15211>
- Engel, A. K., & Fries, P. (2010). Beta-band oscillations—signalling the status quo? *Current Opinion in Neurobiology*, 20(2), 156–165. <https://doi.org/10.1016/j.conb.2010.02.015>
- Fishman, P. S., Gass, J. S., Swoveland, P. T., Lavi, E., Highkin, M. K., & Weiss, S. R. (1985). Infection of the basal ganglia by a murine coronavirus. *Science*, 229(4716), 877–879. <https://doi.org/10.1126/science.2992088>
- Fisk, J. D., Pontefract, A., Ritvo, P. G., Archibald, C. J., & Murray, T. J. (1994). The impact of fatigue on patients with multiple sclerosis. *The Canadian Journal of Neurological Sciences*, 21(1), 9–14. <https://doi.org/10.1017/S0317167100048691>
- Fogelson, N., Kühn, A. A., Silberstein, P., Limousin, P. D., Hariz, M., Trottenberg, T., Kupsch, A., & Brown, P. (2005). Frequency dependent effects of subthalamic nucleus stimulation in

- Parkinson's disease. *Neuroscience Letters*, 382(1-2), 5–9.  
<https://doi.org/10.1016/j.neulet.2005.02.050>
- Fornito, A., Zalesky, A., & Breakspear, M. (2015). The connectomics of brain disorders. *Nature Reviews Neuroscience*, 16(3), 159–172. <https://doi.org/10.1038/nrn3901>
- Fraschini, M., Demuru, M., Crobe, A., Marrosu, F., Stam, C. J., & Hillebrand, A. (2016). The effect of epoch length on estimated EEG functional connectivity and brain network organisation. *Journal of Neural Engineering*, 13(3), Article e036015.  
<https://doi.org/10.1088/1741-2560/13/3/036015>
- Friston, K. J. (2011). Functional and Effective Connectivity: A Review. *Brain Connectivity*, 1(1), 13–36. <https://doi.org/10.1089/brain.2011.0008>
- 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>
- Gaber, M. M., Hosny, H., Hussein, M., Ashmawy, M. A., & Magdy, R. (2024). Cognitive function and quantitative electroencephalogram analysis in subjects recovered from COVID-19 infection. *BMC Neurology*, 24(1), Article e60.  
<https://doi.org/10.1186/s12883-023-03518-7>
- Galanopoulou, A. S., Ferastraoaru, V., Correa, D. J., Cherian, K., Duberstein, S., Gursky, J., Hanumanthu, R., Hung, C., Molinero, I., Khodakivska, O., Legatt, A. D., Patel, P., Rosengard, J., Rubens, E., Sugrue, W., Yozawitz, E., Mehler, M. F., Ballaban-Gil, K., Haut, S. R., . . . Boro, A. (2020). EEG findings in acutely ill patients investigated for SARS-CoV-2/COVID-19: A small case series preliminary report. *Epilepsia Open*, 5(2), 314–324. <https://doi.org/10.1002/epi4.12399>
- Gao, R., Peterson, E. J., & Voytek, B. (2017). Inferring synaptic excitation/inhibition balance from field potentials. *NeuroImage*, 158, 70–78.  
<https://doi.org/10.1016/j.neuroimage.2017.06.078>

- Gerster, M., Waterstraat, G., Litvak, V., Lehnertz, K., Schnitzler, A., Florin, E., Curio, G., & Nikulin, V. (2022). Separating neural oscillations from aperiodic 1/f activity: Challenges and recommendations. *Neuroinformatics*, 20(4), 991–1012.  
<https://doi.org/10.1007/s12021-022-09581-8>
- Gil Ávila, C., Bott, F. S., Tiemann, L., Hohn, V. D., May, E. S., Nickel, M. M., Zebhauser, P. T., Gross, J., & Ploner, M. (2023). DISCOVER-EEG: An open, fully automated EEG pipeline for biomarker discovery in clinical neuroscience. *Scientific Data*, 10(1), Article e613.  
<https://doi.org/10.1038/s41597-023-02525-0>
- Gorgolewski, K. J., Auer, T., Calhoun, V. D., Craddock, R. C., Das, S., Duff, E. P., Flandin, G., Ghosh, S. S., Glatard, T., Halchenko, Y. O., Handwerker, D. A., Hanke, M., Keator, D., Li, X., Michael, Z., Maumet, C., Nichols, B. N., Nichols, T. E., Pellman, J., ...  
Poldrack, R. A. (2016). The brain imaging data structure, a format for organizing and describing outputs of neuroimaging experiments. *Scientific Data*, 3(1), Article e160044.  
<https://doi.org/10.1038/sdata.2016.44>
- Granovetter, M. S. (1973). The strength of weak ties. *American Journal of Sociology*, 78(6), 1360–1380. <https://doi.org/10.1086/225469>
- Grech, R., Cassar, T., Muscat, J., Camilleri, K. P., Fabri, S. G., Zervakis, M., Xanthopoulos, P., Sakkalis, V., & Vanrumste, B. (2008). Review on solving the inverse problem in EEG source analysis. *Journal of NeuroEngineering and Rehabilitation*, 5, Article e25.  
<https://doi.org/10.1186/1743-0003-5-25>
- Guedj, E., Campion, J. Y., Dudouet, P., Kaphan, E., Bregeon, F., Tissot-Dupont, H., Guis, S., Barthelemy, F., Habert, P., Ceccaldi, M., Million, M., Raoult, D., Cammilleri, S., & Eldin, C. (2021). 18F-FDG brain PET hypometabolism in patients with long COVID. *European Journal of Nuclear Medicine and Molecular Imaging*, 48(9), 2823–2833.  
<https://doi.org/10.1007/s00259-021-05215-4>

- Guillon, J., Attal, Y., Colliot, O., La Corte, V., Dubois, B., Schwartz, D., Chavez, M., & De Vico Fallani, F. (2017). Loss of brain inter-frequency hubs in Alzheimer's disease. *Scientific Reports*, 7(1), Article e10879. <https://doi.org/10.1038/s41598-017-07846-w>
- Halje, P., Brys, I., Mariman, J. J., da Cunha, C., Fuentes, R., & Petersson, P. (2019). Oscillations in cortico-basal ganglia circuits: Implications for Parkinson's disease and other neurologic and psychiatric conditions. *Journal of Neurophysiology*, 122(1), 203–231. <https://doi.org/10.1152/jn.00590.2018>
- Harmony, T. (2013). The functional significance of delta oscillations in cognitive processing. *Frontiers in Integrative Neuroscience*, 7, Article e83. <https://doi.org/10.3389/fnint.2013.00083>
- Hartung, T. J., Neumann, C., Bahmer, T., Chaplinskaya-Sobol, I., Endres, M., Geritz, J., Haeusler, K. G., Heuschmann, P. U., Hildesheim, H., Hinz, A., Hopff, S., Horn, A., Krawczak, M., Krist, L., Kudelka, J., Lieb, W., Maetzler, C., Mehner-Theuerkauf, A., Montellano, F. A., . . . Finke, C. (2022). Fatigue and cognitive impairment after COVID-19: A prospective multicentre study. *eClinicalMedicine*, 53, Article e101651. <https://doi.org/10.1016/j.eclim.2022.101651>
- Hassan, M., Chaton, L., Benquet, P., Delval, A., Leroy, C., Plomhause, L., Moonen, A. J. H., Duits, A. A., Leentjens, A. F. G., van Kranen-Mastenbroek, V., Defebvre, L., Derambure, P., Wendling, F., & Dujardin, K. (2017). Functional connectivity disruptions correlate with cognitive phenotypes in Parkinson's disease. *NeuroImage. Clinical*, 14, 591–601. <https://doi.org/10.1016/j.nicl.2017.03.002>
- Heine, J., Schwichtenberg, K., Hartung, T. J., Rekers, S., Chien, C., Boesl, F., Rust, R., Hohenfeld, C., Bungenberg, J., Costa, A. S., Scheibenbogen, C., Bellmann-Strobl, J., Paul, F., Franke, C., Reetz, K., & Finke, C. (2023). Structural brain changes in patients with post-COVID fatigue: A prospective observational study. *eClinicalMedicine*, 58, Article e101874. <https://doi.org/10.1016/j.eclim.2023.101874>

- Heitmann, H., Zebhauser, P. T., Hohn, V. D., Henningsen, P., & Ploner, M. (2023). Resting-state EEG and MEG biomarkers of pathological fatigue – A transdiagnostic systematic review. *NeuroImage: Clinical*, 39, Article e103500. <https://doi.org/10.1016/j.nicl.2023.103500>
- Humphries, M. D., & Gurney, K. (2008). Network ‘Small-World-ness’: A quantitative method for determining canonical network equivalence. *PLOS ONE*, 3(4), Article e0002051. <https://doi.org/10.1371/journal.pone.0002051>
- Ida, F. S., Ferreira, H. P., Vasconcelos, A. K. M., Furtado, I. A. B., Fontenele, C. J. P. M., & Pereira, A. C. (2024). Post-COVID-19 syndrome: persistent symptoms, functional impact, quality of life, return to work, and indirect costs - a prospective case study 12 months after COVID-19 infection. *Cadernos De Saude Publica*, 40(2), Article e00022623. <https://doi.org/10.1590/0102-311XPT026623>
- Jacob, M. S., Roach, B. J., Sargent, K. S., Mathalon, D. H., & Ford, J. M. (2021). Aperiodic measures of neural excitability are associated with anticorrelated hemodynamic networks at rest: A combined EEG-fMRI study. *NeuroImage*, 245, Article e118705. <https://doi.org/10.1016/j.neuroimage.2021.118705>
- Jäncke, L., & Langer, N. (2011). A strong parietal hub in the small-world network of coloured-hearing synaesthetes during resting state EEG. *Journal of Neuropsychology*, 5(2), 178–202. <https://doi.org/10.1111/j.1748-6653.2011.02004.x>
- Jiang, F., Deng, L., Zhang, L., Cai, Y., Cheung, C. W., & Xia, Z. (2020). Review of the clinical characteristics of coronavirus disease 2019 (COVID-19). *Journal of General Internal Medicine*, 35(5), 1545–1549. <https://doi.org/10.1007/s11606-020-05762-w>
- Karch, J. D. (2023). Outliers may not be automatically removed. *Journal of Experimental Psychology: General*, 152(6), 1735–1753. <https://doi.org/10.1037/xge0001357>
- Karimi-Galougahi, M., Yousefi-Koma, A., Bakhshayeshkaram, M., Raad, N., & Haseli, S. (2020). 18FDG PET/CT scan reveals hypoactive orbitofrontal cortex in anosmia of COVID-19. *Academic Radiology*, 27(7), 1042–1043. <https://doi.org/10.1016/j.acra.2020.04.030>

- Karsai, M., Kivelä, M., Pan, R. K., Kaski, K., Kertész, J., Barabási, A.-L., & Saramäki, J. (2011). Small but slow world: How network topology and burstiness slow down spreading. *Physical Review E*, 83(2), Article e025102. <https://doi.org/10.1103/PhysRevE.83.025102>
- Kent-Braun, J. A., & Miller, R. G. (2000). Central fatigue during isometric exercise in amyotrophic lateral sclerosis. *Muscle & Nerve*, 23(6), 909–914. [https://doi.org/10.1002/\(sici\)1097-4598\(200006\)23:6<909::aid-mus10>3.0.co;2-v](https://doi.org/10.1002/(sici)1097-4598(200006)23:6<909::aid-mus10>3.0.co;2-v)
- Kilavik, B. E., Zaepffel, M., Brovelli, A., MacKay, W. A., & Riehle, A. (2013). The ups and downs of  $\beta$  oscillations in sensorimotor cortex. *Experimental Neurology*, 245, 15–26. <https://doi.org/10.1016/j.expneurol.2012.09.014>
- Kopańska, M., Banaś-Ząbczyk, A., Łagowska, A., Kuduk, B., & Szczęgielski, J. (2021). Changes in EEG recordings in COVID-19 patients as a basis for more accurate QEEG diagnostics and EEG neurofeedback therapy: A systematic review. *Journal of Clinical Medicine*, 10(6), Article e1300. <https://doi.org/10.3390/jcm10061300>
- Kopańska, M., Ochojska, D., Muchacka, R., Dejnowicz-Velitchkov, A., Banaś-Ząbczyk, A., & Szczęgielski, J. (2022). Comparison of QEEG findings before and after onset of Post-COVID-19 brain fog symptoms. *Sensors*, 22(17), Article e6606. <https://doi.org/10.3390/s22176606>
- Kopańska, M., Rydzik, Ł., Błajda, J., Sarzyńska, I., Jachymek, K., Pałka, T., Ambroży, T., & Szczęgielski, J. (2023). The use of quantitative electroencephalography (QEEG) to assess Post-COVID-19 concentration disorders in professional pilots: An initial concept. *Brain Sciences*, 13(9), Article e1264. <https://doi.org/10.3390/brainsci13091264>
- Koutroumanidis, M., Gratwicke, J., Sharma, S., Whelan, A., Tan, S. V., & Glover, G. (2021). Alpha coma EEG pattern in patients with severe COVID-19 related encephalopathy. *Clinical Neurophysiology*, 132(1), 218–225. <https://doi.org/10.1016/j.clinph.2020.09.008>
- Krupp, L. B., LaRocca, N. G., Muir-Nash, J., & Steinberg, A. D. (1989). The Fatigue Severity Scale: Application to patients with Multiple Sclerosis and Systemic Lupus Erythematosus.

- Archives of Neurology*, 46(10), 1121–1123.  
<https://doi.org/10.1001/archneur.1989.00520460115022>
- Kubota, T., Gajera, P. K., & Kuroda, N. (2021). Meta-analysis of EEG findings in patients with COVID-19. *Epilepsy & Behavior*, 115, Article e107682.  
<https://doi.org/10.1016/j.yebeh.2020.107682>
- Kuppuswamy, A., Clark, E. V., Turner, I. F., Rothwell, J. C., & Ward, N. S. (2015). Post-stroke fatigue: A deficit in corticomotor excitability? *Brain*, 138(1), 136–148.  
<https://doi.org/10.1093/brain/awu306>
- Lamoš, M., Bočková, M., Goldemundová, S., Baláž, M., Chrastina, J., & Rektor, I. (2023). The effect of deep brain stimulation in Parkinson's disease reflected in EEG microstates. *NPJ Parkinson's Disease*, 9(1), Article e63. <https://doi.org/10.1038/s41531-023-00508-x>
- Langer, N., Pedroni, A., & Jäncke, L. (2013). The problem of thresholding in Small-World network analysis. *PLOS ONE*, 8(1), Article e53199. <https://doi.org/10.1371/journal.pone.0053199>
- Letko, M., Marzi, A., & Munster, V. (2020). Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. *Nature Microbiology*, 5(4), 562–569. <https://doi.org/10.1038/s41564-020-0688-y>
- Li, L., Cui, Z., & Wang, L. (2022). A more female-characterized resting-state brain: Graph similarity analyses of sex influence on the human brain intrinsic functional network. *Brain Topography*, 35(3), 341–351. <https://doi.org/10.1007/s10548-022-00900-5>
- Lindsley, D. B., Bowden, J. W., & Magoun, H. W. (1949). Effect upon the EEG of acute injury to the brain stem activating system. *Electroencephalography and Clinical Neurophysiology*, 1(1-4), 475–486. [https://doi.org/10.1016/0013-4694\(49\)90221-7](https://doi.org/10.1016/0013-4694(49)90221-7)
- Ludwig, K. A., Miriani, R. M., Langhals, N. B., Joseph, M. D., Anderson, D. J., & Kipke, D. R. (2009). Using a common average reference to improve cortical neuron recordings from microelectrode arrays. *Journal of Neurophysiology*, 101(3), 1679–1689.  
<https://doi.org/10.1152/jn.90989.2008>

- Lynch, S., Ferrando, S. J., Dornbush, R., Shahar, S., Smiley, A., & Klepacz, L. (2022). Screening for brain fog: Is the montreal cognitive assessment an effective screening tool for neurocognitive complaints post-COVID-19? *General Hospital Psychiatry*, 78, 80–86.  
<https://doi.org/10.1016/j.genhosppsych.2022.07.013>
- Magnusson, K., Kristoffersen, D. T., Dell'Isola, A., Kiadaliri, A., Turkiewicz, A., Runhaar, J., Bierma-Zeinstra, S., Englund, M., Magnus, P. M., & Kinge, J. M. (2022). Post-covid medical complaints following infection with SARS-CoV-2 Omicron vs Delta variants. *Nature Communications*, 13(1), Article e7363.  
<https://doi.org/10.1038/s41467-022-35240-2>
- Makeig, S., Bell, A. J., Jung, T.-P., & Sejnowski, T. J. (1995). Independent component analysis of electroencephalographic data. *Proceedings of the 8th International Conference on Neural Information Processing Systems*, 145–151.
- Malik, P., Patel, K., Pinto, C., Jaiswal, R., Tirupathi, R., Pillai, S., & Patel, U. (2022). Post-acute COVID-19 syndrome (PCS) and health-related quality of life (HRQoL)-A systematic review and meta-analysis. *Journal of Medical Virology*, 94(1), 253–262.  
<https://doi.org/10.1002/jmv.27309>
- Manning, J. R., Jacobs, J., Fried, I., & Kahana, M. J. (2009). Broadband shifts in local field potential power spectra are correlated with single-neuron spiking in humans. *The Journal of Neuroscience*, 29(43), 13613–13620.  
<https://doi.org/10.1523/JNEUROSCI.2041-09.2009>
- Marino, M., & Mantini, D. (2024). Human brain imaging with high-density electroencephalography: Techniques and applications. *The Journal of Physiology*, 0(0), 1–30. <https://doi.org/10.1113/JP286639>
- Maris, E., & Oostenveld, R. (2007). Nonparametric statistical testing of EEG- and MEG-data. *Journal of Neuroscience Methods*, 164(1), 177–190.  
<https://doi.org/10.1016/j.jneumeth.2007.03.024>

- Marshall, M. (2020). The lasting misery of coronavirus long-haulers. *Nature*, 585(7825), 339–341. <https://doi.org/10.1038/d41586-020-02598-6>
- Martin, E. M., Rupprecht, S., Schrenk, S., Kattlun, F., Utech, I., Radscheidt, M., Brodoehl, S., Schwab, M., Reuken, P. A., Stallmach, A., Habekost, T., & Finke, K. (2023). A hypoarousal model of neurological post-COVID syndrome: The relation between mental fatigue, the level of central nervous activation and cognitive processing speed. *Journal of Neurology*, 270(10), 4647–4660. <https://doi.org/10.1007/s00415-023-11819-7>
- Matschke, J., Lütgehetmann, M., Hagel, C., Sperhake, J. P., Schröder, A. S., Edler, C., Mushumba, H., Fitzek, A., Allweiss, L., Dandri, M., Dottermusch, M., Heinemann, A., Pfefferle, S., Schwabenland, M., Sumner Magruder, D., Bonn, S., Prinz, M., Gerloff, C., Püschel, K., . . . Glatzel, M. (2020). Neuropathology of patients with COVID-19 in Germany: A post-mortem case series. *The Lancet Neurology*, 19(11), 919–929. [https://doi.org/10.1016/S1474-4422\(20\)30308-2](https://doi.org/10.1016/S1474-4422(20)30308-2)
- Mayeli, A., Al Zoubi, O., Misaki, M., Stewart, J. L., Zotev, V., Luo, Q., Phillips, R., Fischer, S., Götz, M., Paulus, M. P., Refai, H., & Bodurka, J. (2020). Integration of simultaneous resting-state electroencephalography, functional magnetic resonance imaging, and eye-tracker methods to determine and verify electroencephalography vigilance measure. *Brain Connectivity*, 10(10), 535–546. <https://doi.org/10.1089/brain.2019.0731>
- McKeown, D. J., Finley, A. J., Kelley, N. J., Cavanagh, J. F., Keage, H. A. D., Baumann, O., Schinazi, V. R., Moustafa, A. A., & Angus, D. J. (2024). Test-retest reliability of spectral parameterization by 1/f characterization using SpecParam. *Cerebral Cortex*, 34(1), 1–11. <https://doi.org/10.1093/cercor/bhad482>
- Meinhardt, J., Radke, J., Dittmayer, C., Franz, J., Thomas, C., Mothes, R., Laue, M., Schneider, J., Brünink, S., Greuel, S., Lehmann, M., Hassan, O., Aschman, T., Schumann, E., Chua, R. L., Conrad, C., Eils, R., Stenzel, W., Windgassen, M., . . . Heppner, F. L. (2021). Olfactory transmucosal SARS-CoV-2 invasion as a port of central nervous system entry in

- individuals with COVID-19. *Nature Neuroscience*, 24(2), 168–175.  
<https://doi.org/10.1038/s41593-020-00758-5>
- Meinhardt, J., Streit, S., Dittmayer, C., v Manitius, R., Radbruch, H., & Heppner, F. L. (2024). The neurobiology of SARS-CoV-2 infection. *Nature Reviews Neuroscience*, 25(1), 30–42.  
<https://doi.org/10.1038/s41583-023-00769-8>
- Mercier, M. R., Molholm, S., Fiebelkorn, I. C., Butler, J. S., Schwartz, T. H., & Foxe, J. J. (2015). Neuro-oscillatory phase alignment drives speeded multisensory response times: An electro-corticographic investigation. *Journal of Neuroscience*, 35(22), 8546–8557.  
<https://doi.org/10.1523/JNEUROSCI.4527-14.2015>
- Merello, M., Bhatia, K. P., & Obeso, J. A. (2021). SARS-CoV-2 and the risk of Parkinson's disease: Facts and fantasy. *The Lancet Neurology*, 20(2), 94–95.  
[https://doi.org/10.1016/S1474-4422\(20\)30442-7](https://doi.org/10.1016/S1474-4422(20)30442-7)
- 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>
- Mishra, S. S., Gandhi, T. K., & Biswal, B. B. (2023). Structural connectomes of COVID-survivors show disruption in Global Integration and Small-Worldness. *Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, 2023, 1–4.  
<https://doi.org/10.1109/EMBC40787.2023.10340776>
- Mohammadi, S., & Ghaderi, S. (2024). Post-COVID-19 conditions: A systematic review on advanced magnetic resonance neuroimaging findings. *Neurological Sciences*, 45(5), 1815–1833. <https://doi.org/10.1007/s10072-024-07427-6>
- Montan, I., Löwe, B., Cell, 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>

- Morawa, E., Krehbiel, J., Borho, A., Herold, R., Lieb, M., Schug, C., & Erim, Y. (2023). Cognitive impairments and mental health of patients with post-COVID-19: A cross-sectional study. *Journal of Psychosomatic Research*, 173, Article e111441. <https://doi.org/10.1016/j.jpsychores.2023.111441>
- 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>
- Niepel, G., Bibani, R. H., Vilisaar, J., Langley, R. W., Bradshaw, C. M., Szabadi, E., & Constantinescu, C. S. (2013). Association of a deficit of arousal with fatigue in multiple sclerosis: Effect of modafinil. *Neuropharmacology*, 64, 380–388. <https://doi.org/10.1016/j.neuropharm.2012.06.036>
- Nolte, G., Bai, O., Wheaton, L., Mari, Z., Vorbach, S., & Hallett, M. (2004). Identifying true brain interaction from EEG data using the imaginary part of coherency. *Clinical Neurophysiology*, 115(10), 2292–2307. <https://doi.org/10.1016/j.clinph.2004.04.029>
- 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, Article e156869. <https://doi.org/10.1155/2011/156869>
- Ortelli, P., Ferrazzoli, D., Sebastianelli, L., Engl, M., Romanello, R., Nardone, R., Bonini, I., Koch, G., Saltuari, L., Quartarone, A., Oliviero, A., Kofler, M., & Versace, V. (2021). Neuropsychological and neurophysiological correlates of fatigue in post-acute patients with neurological manifestations of COVID-19: Insights into a challenging symptom. *Journal of the Neurological Sciences*, 420, Article e117271. <https://doi.org/10.1016/j.jns.2020.117271>
- Ortelli, P., Ferrazzoli, D., Sebastianelli, L., Maestri, R., Dezi, S., Spampinato, D., Saltuari, L., Alibardi, A., Engl, M., Kofler, M., Quartarone, A., Koch, G., Oliviero, A., & Versace, V.

- (2022). Altered motor cortex physiology and dysexecutive syndrome in patients with fatigue and cognitive difficulties after mild COVID-19. *European Journal of Neurology*, 29(6), 1652–1662. <https://doi.org/10.1111/ene.15278>
- 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), Article e2228. <https://doi.org/10.3390/biomedicines11082228>
- Papo, D., Zanin, M., Martínez, J. H., & Buldú, J. M. (2016). Beware of the Small-World neuroscientist! *Frontiers in Human Neuroscience*, 10, Article e96. <https://doi.org/10.3389/fnhum.2016.00096>
- 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), Article e1545. <https://doi.org/10.3390/jcm9051545>
- Pernet, C. R., Appelhoff, S., Gorgolewski, K. J., Flandin, G., Phillips, C., Delorme, A., & Oostenveld, R. (2019). EEG-BIDS, an extension to the brain imaging data structure for electroencephalography. *Scientific Data*, 6(1), Article e103. <https://doi.org/10.1038/s41597-019-0104-8>
- Perrin, F., Pernier, J., Bertrand, O., & Echallier, J. F. (1989). Spherical splines for scalp potential and current density mapping. *Electroencephalography and Clinical Neurophysiology*, 72(2), 184–187. [https://doi.org/10.1016/0013-4694\(89\)90180-6](https://doi.org/10.1016/0013-4694(89)90180-6)
- Petermann, F. (2011). Hospital Anxiety and Depression Scale, Deutsche Version (HADS-D). *Zeitschrift für Psychiatrie, Psychologie und Psychotherapie*, 59(3), 251–253. <https://doi.org/10.1024/1661-4747/a000077>

- Pion-Tonachini, L., Kreutz-Delgado, K., & Makeig, S. (2019). ICLLabel: An automated electroencephalographic independent component classifier, dataset, and website. *NeuroImage*, 198, 181–197. <https://doi.org/10.1016/j.neuroimage.2019.05.026>
- 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>
- Pogosyan, A., Gaynor, L. D., Eusebio, A., & Brown, P. (2009). Boosting cortical activity at beta-band frequencies slows movement in humans. *Current Biology*, 19(19), 1637–1641. <https://doi.org/10.1016/j.cub.2009.07.074>
- Porges, E. C., Woods, A. J., Edden, R. A. E., Puts, N. A. J., Harris, A. D., Chen, H., Garcia, A. M., Seider, T. R., Lamb, D. G., Williamson, J. B., & Cohen, R. A. (2017). Frontal Gamma-Aminobutyric Acid concentrations are associated with cognitive performance in older adults. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, 2(1), 38–44. <https://doi.org/10.1016/j.bpsc.2016.06.004>
- Rahimi, F., Saadat, M., Hessam, M., Ravanbakhsh, M., & Monjezi, S. (2024). Post-COVID-19 physical and cognitive impairments and associations with quality of life: A cross-sectional study. *Frontiers in Sports and Active Living*, 6, Article e1246585. <https://doi.org/10.3389/fspor.2024.1246585>
- Reitan, R. M. (1958). Validity of the Trail Making Test as an indicator of organic brain damage. *Perceptual and Motor Skills*, 8, 271–276. <https://doi.org/10.2466/PMS.8.7.271-276>
- Rossiter, H. E., Davis, E. M., Clark, E. V., Boudrias, M.-H., & Ward, N. S. (2014). Beta oscillations reflect changes in motor cortex inhibition in healthy ageing. *NeuroImage*, 91(100), 360–365. <https://doi.org/10.1016/j.neuroimage.2014.01.012>
- Rubega, M., Ciringione, L., Bertuccelli, M., Paramento, M., Sparacino, G., Vianello, A., Masiero, S., Vallesi, A., Formaggio, E., & Del Felice, A. (2022). High-density EEG sleep correlates of cognitive and affective impairment at 12-month follow-up after COVID-19. *Clinical Neurophysiology*, 140, 126–135. <https://doi.org/10.1016/j.clinph.2022.05.017>

- Rubin, R. (2020). As their numbers grow, COVID-19 “Long Haulers” stump experts. *JAMA*, 324(14), 1381–1383. <https://doi.org/10.1001/jama.2020.17709>
- Rubinov, M., & Sporns, O. (2010). Complex network measures of brain connectivity: Uses and interpretations. *NeuroImage*, 52(3), 1059–1069.  
<https://doi.org/10.1016/j.neuroimage.2009.10.003>
- Russo, M., Calamuneri, A., Cacciola, A., Bonanno, L., Naro, A., Dattola, V., Sessa, E., Buccafusca, M., Milardi, D., Bramanti, P., Calabro, R. S., & Quartarone, A. (2017). Neural correlates of fatigue in multiple sclerosis: A combined neurophysiological and neuroimaging approach (R1). *Archives Italiennes De Biologie*, 155(3), 142–151.  
<https://doi.org/10.12871/00039829201735>
- Schandry, R. (2016). Methoden der Biologischen Psychologie. In *Biologische Psychologie* (4th ed., pp. 513–542). Beltz Verlagsgruppe.
- Schoffelen, J.-M., & Gross, J. (2009). Source connectivity analysis with MEG and EEG. *Human Brain Mapping*, 30(6), 1857–1865. <https://doi.org/10.1002/hbm.20745>
- Sfera, A., Thomas, K. G., Sasannia, S., Anton, J. J., Andronescu, C. V., Garcia, M., Sfera, D. O., Cummings, M. A., & Kozlakidis, Z. (2022). Neuronal and non-neuronal GABA in COVID-19: Relevance for psychiatry. *Reports*, 5(2), 22.  
<https://doi.org/10.3390/reports5020022>
- Sherlin, L., Budzynski, T., Kogan Budzynski, H., Congedo, M., Fischer, M. E., & Buchwald, D. (2007). Low-resolution electromagnetic brain tomography (LORETA) of monozygotic twins discordant for chronic fatigue syndrome. *NeuroImage*, 34(4), 1438–1442.  
<https://doi.org/10.1016/j.neuroimage.2006.11.007>
- Shine, J. M. (2019). Neuromodulatory influences on integration and segregation in the brain. *Trends in Cognitive Sciences*, 23(7), 572–583. <https://doi.org/10.1016/j.tics.2019.04.002>
- Shinn, M., Hu, A., Turner, L., Noble, S., Preller, K. H., Ji, J. L., Moujaes, F., Achard, S., Scheinost, D., Constable, R. T., Krystal, J. H., Vollenweider, F. X., Lee, D., Anticevic, A., Bullmore, E. T., & Murray, J. D. (2023). Functional brain networks reflect spatial and

- temporal autocorrelation. *Nature Neuroscience*, 26(5), 867–878.  
<https://doi.org/10.1038/s41593-023-01299-3>
- Silva-Passadouro, B., Tamasauskas, A., Khoja, O., Casson, A. J., Delis, I., Brown, C., & Sivan, M. (2024). A systematic review of quantitative EEG findings in Fibromyalgia, Chronic Fatigue Syndrome and Long COVID. *Clinical Neurophysiology*, 163, 209–222.  
<https://doi.org/10.1016/j.clinph.2024.04.019>
- Sinha, S., Mittal, S., & Roy, R. (2021). Parkinson's disease and the COVID-19 pandemic: A review article on the association between SARS-CoV-2 and  $\alpha$ -synucleinopathy. *Journal of Movement Disorders*, 14(3), 184–192. <https://doi.org/10.14802/jmd.21046>
- Smith, K., Azami, H., Parra, M. A., Starr, J. M., & Escudero, J. (2015). Cluster-span threshold: An unbiased threshold for binarising weighted complete networks in functional connectivity analysis. *Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, 2015, 2840–2843. <https://doi.org/10.1109/EMBC.2015.7318983>
- Solomon, I. H., Normandin, E., Bhattacharyya, S., Mukerji, S. S., Keller, K., Ali, A. S., Adams, G., Hornick, J. L., Padera, R. F., & Sabeti, P. (2020). Neuropathological features of Covid-19. *The New England Journal of Medicine*, 383(10), 989–992.  
<https://doi.org/10.1056/NEJMc2019373>
- Soriano, J. B., Murthy, S., Marshall, J. C., Relan, P., & Diaz, J. V. (2022). A clinical case definition of post-COVID-19 condition by a Delphi consensus. *The Lancet Infectious Diseases*, 22(4), e102–e107. [https://doi.org/10.1016/S1473-3099\(21\)00703-9](https://doi.org/10.1016/S1473-3099(21)00703-9)
- Sporns, O., & Betzel, R. F. (2016). Modular brain networks. *Annual Review of Psychology*, 67, 613–640. <https://doi.org/10.1146/annurev-psych-122414-033634>
- Srinivasan, R., Winter, W. R., Ding, J., & Nunez, P. L. (2007). EEG and MEG coherence: Measures of functional connectivity at distinct spatial scales of neocortical dynamics. *Journal of Neuroscience Methods*, 166(1), 41–52.  
<https://doi.org/10.1016/j.jneumeth.2007.06.026>

- Stumme, J., Jockwitz, C., Hoffstaedter, F., Amunts, K., & Caspers, S. (2020). Functional network reorganization in older adults: Graph-theoretical analyses of age, cognition and sex. *NeuroImage*, 214, Article e116756. <https://doi.org/10.1016/j.neuroimage.2020.116756>
- Sumner, P., Edden, R. A. E., Bompas, A., Evans, C. J., & Singh, K. D. (2010). More GABA, less distraction: A neurochemical predictor of motor decision speed. *Nature Neuroscience*, 13(7), 825–827. <https://doi.org/10.1038/nn.2559>
- Tadel, F., Baillet, S., Mosher, J. C., Pantazis, D., & Leahy, R. M. (2011). Brainstorm: A user-friendly application for MEG/EEG analysis. *Computational Intelligence and Neuroscience*, 2011, Article e879716. <https://doi.org/10.1155/2011/879716>
- Tanaka, M., Shigihara, Y., Ishii, A., Funakura, M., Kanai, E., & Watanabe, Y. (2012). Effect of mental fatigue on the central nervous system: An electroencephalography study. *Behavioral and Brain Functions*, 8(1), 48. <https://doi.org/10.1186/1744-9081-8-48>
- Tanaka, M., & Watanabe, Y. (2012). Supraspinal regulation of physical fatigue. *Neuroscience & Biobehavioral Reviews*, 36(1), 727–734. <https://doi.org/10.1016/j.neubiorev.2011.10.004>
- Tang, D., Comish, P., & Kang, R. (2020). The hallmarks of COVID-19 disease. *PLOS Pathogens*, 16(5), Article e1008536. <https://doi.org/10.1371/journal.ppat.1008536>
- Tombaugh, T. N., & McIntyre, N. J. (1992). The mini-mental state examination: A comprehensive review. *Journal of the American Geriatrics Society*, 40(9), 922–935. <https://doi.org/10.1111/j.1532-5415.1992.tb01992.x>
- Van Schependom, J., Gielen, J., Laton, J., D'hooghe, M. B., De Keyser, J., & Nagels, G. (2014). Graph theoretical analysis indicates cognitive impairment in MS stems from neural disconnection. *NeuroImage: Clinical*, 4, 403–410. <https://doi.org/10.1016/j.nicl.2014.01.012>
- van Wijk, B. C. M., Stam, C. J., & Daffertshofer, A. (2010). Comparing brain networks of different size and connectivity density using graph theory. *PLOS ONE*, 5(10), Article e13701. <https://doi.org/10.1371/journal.pone.0013701>

- Vecchio, F., Miraglia, F., Porcaro, C., Cottone, C., Cancelli, A., Rossini, P. M., & Tecchio, F. (2017). Electroencephalography-derived sensory and motor network topology in Multiple Sclerosis fatigue. *Neurorehabilitation and Neural Repair*, 31(1), 56–64.  
<https://doi.org/10.1177/1545968316656055>
- Venkatesan, P. (2021). NICE guideline on long COVID. *The Lancet Respiratory Medicine*, 9(2), 129. [https://doi.org/10.1016/S2213-2600\(21\)00031-X](https://doi.org/10.1016/S2213-2600(21)00031-X)
- Verger, A., Kas, A., Dudouet, P., Goehringer, F., Salmon-Ceron, D., & Guedj, E. (2022). Visual interpretation of brain hypometabolism related to neurological long COVID: A French multicentric experience. *European Journal of Nuclear Medicine and Molecular Imaging*, 49(9), 3197–3202. <https://doi.org/10.1007/s00259-022-05753-5>
- Versace, V., Sebastianelli, L., Ferrazzoli, D., Romanello, R., Ortelli, P., Saltuari, L., D'Acunto, A., Porrazzini, F., Ajello, V., Oliviero, A., Kofler, M., & Koch, G. (2021). Intracortical GABAergic dysfunction in patients with fatigue and dysexecutive syndrome after COVID-19. *Clinical Neurophysiology*, 132(5), 1138–1143.  
<https://doi.org/10.1016/j.clinph.2021.03.001>
- VoytekLab. (2018/2023). 07: Tuning & Troubleshooting — fooof 1.1.0 documentation. Retrieved August 19, 2024, from  
[https://fooof-tools.github.io/fooof/auto%5C\\_tutorials/plot%5C\\_07-TroubleShooting.html](https://fooof-tools.github.io/fooof/auto%5C_tutorials/plot%5C_07-TroubleShooting.html)
- Waschke, L., Donoghue, T., Fiedler, L., Smith, S., Garrett, D. D., Voytek, B., & Obleser, J. (2021). Modality-specific tracking of attention and sensory statistics in the human electrophysiological spectral exponent (M. Chait, B. G. Shinn-Cunningham, B. R. Postle, & J. Z. Simon, Eds.). *eLife*, 10, Article e70068. <https://doi.org/10.7554/eLife.70068>
- Watts, D. J., & Strogatz, S. H. (1998). Collective dynamics of ‘small-world’ networks. *Nature*, 393(6684), 440–442. <https://doi.org/10.1038/30918>
- Westner, B. U., Kujala, J., Gross, J., & Schoffelen, J.-M. (2024). Towards a more robust non-invasive assessment of functional connectivity. *Imaging Neuroscience*, 2, 1–19.  
[https://doi.org/10.1162/imag\\_a\\_00119](https://doi.org/10.1162/imag_a_00119)

- 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, Article e1019778. <https://doi.org/10.3389/fnins.2023.1019778>
- Wong, T. L., & Weitzer, D. J. (2021). Long COVID and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)-A systemic review and comparison of clinical presentation and symptomatology. *Medicina*, 57(5), 418. <https://doi.org/10.3390/medicina57050418>
- World Health Organization. (2021). A clinical case definition of post COVID-19 condition by a Delphi consensus, 6 October 2021. *World Health Organization*.
- Wu, C.-H., De Doncker, W., & Kuppuswamy, A. (2023). Electroencephalography-derived functional connectivity in sensorimotor networks in post stroke fatigue. *Brain Topography*, 36(5), 727–735. <https://doi.org/10.1007/s10548-023-00975-8>
- Yachou, Y., El Idrissi, A., Belaparov, V., & Ait Benali, S. (2020). Neuroinvasion, neurotropic, and neuroinflammatory events of SARS-CoV-2: Understanding the neurological manifestations in COVID-19 patients. *Neurological Sciences*, 41(10), 2657–2669. <https://doi.org/10.1007/s10072-020-04575-3>
- Yan, Y., Zhao, A., Ying, W., Qiu, Y., Ding, Y., Wang, Y., Xu, W., & Deng, Y. (2021). Functional connectivity alterations based on the weighted Phase Lag Index: An exploratory electroencephalography study on Alzheimer's disease. *Current Alzheimer Research*, 18(6), 513–522. <https://doi.org/10.2174/1567205018666211001110824>
- Yao, D. (2001). A method to standardize a reference of scalp EEG recordings to a point at infinity. *Physiological Measurement*, 22(4), 693–711. <https://doi.org/10.1088/0967-3334/22/4/305>
- Yellen, S. B., Celli, 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](https://doi.org/10.1016/s0885-3924(96)00274-6)

- Yong, S. J. (2021a). Long COVID or post-COVID-19 syndrome: Putative pathophysiology, risk factors, and treatments. *Infectious Diseases*, 53(10), 737–754.  
<https://doi.org/10.1080/23744235.2021.1924397>
- Yong, S. J. (2021b). Persistent brainstem dysfunction in Long-COVID: A hypothesis. *ACS Chemical Neuroscience*, 12(4), 573–580. <https://doi.org/10.1021/acschemneuro.0c00793>
- Zanin, M. (2015). On alternative formulations of the small-world metric in complex networks. *ArXiv*.
- 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>
- Zinn, M. A., Zinn, M. L., Valencia, I., Jason, L. A., & Montoya, J. G. (2018). Cortical hypoactivation during resting EEG suggests central nervous system pathology in patients with chronic fatigue syndrome. *Biological Psychology*, 136, 87–99.  
<https://doi.org/10.1016/j.biopsych.2018.05.016>
- Zinn, M. L., Zinn, M. A., & Jason, L. A. (2016). Intrinsic functional hypoconnectivity in core neurocognitive networks suggests central nervous system pathology in patients with Myalgic Encephalomyelitis: A pilot study. *Applied Psychophysiology and Biofeedback*, 41(3), 283–300. <https://doi.org/10.1007/s10484-016-9331-3>
- Zinn, M. A., Zinn, M. L., & Jason, L. (2017). Small-World network analysis of cortical connectivity in Chronic Fatigue Syndrome using quantitative EEG. *NeuroRegulation*, 4, 125–137. <https://doi.org/10.15540/nr.4.3-4.125>

## Appendix A

### Additional Tables

**Table A1**

*Statistical Prerequisites of All Relevant Variables*

Variable	Shapiro Wilks-Test				Levene Test	
	with PCS		without PCS		<i>F</i> value	<i>Pr(&gt;F)</i>
	W	<i>p</i>	W	<i>p</i>		
FACIT-F [0-50]	.97	.670	.84	<b>.002</b>	2.41	.128
HADS-D [0-21]	.94	.194	.77	<b>&lt;.001</b>	0.09	.761
TMT A [0-200]	.94	.156	.91	<b>.047</b>	0.05	.827
TMT B-A	.75	<b>&lt;.001</b>	.75	<b>&lt;.001</b>	1.52	.224
MoCA	.94	.153	.92	.074	1.77	.191
$\delta$ power	.86	<b>.004</b>	.88	<b>.010</b>	0.20	.659
$\beta$ power	.76	<b>&lt;.001</b>	.83	<b>.001</b>	0.15	.703
$\beta 1$ power	.71	<b>&lt;.001</b>	.71	<b>&lt;.001</b>	0.12	.728
$\beta 2$ power	.72	<b>&lt;.001</b>	.68	<b>&lt;.001</b>	0.09	.769
Aperiodic exponent	.88	<b>.011</b>	.97	.587	2.15	.150
Aperiodic offset	.96	.391	.96	.438	4.25	<b>.045</b>
$\delta$ FC	.90	<b>.017</b>	.90	<b>.030</b>	0.00	.971
$\beta$ FC	.93	.135	.96	.567	2.22	.144
$\beta$ SWI (30%)	.93	.117	.95	.281	1.47	.232
$R^2$ frontal	.79	<b>&lt;.001</b>	.60	<b>&lt;.001</b>	0.46	.498
$R^2$ central	.70	<b>&lt;.001</b>	.69	<b>&lt;.001</b>	2.58	.11

*Note.* Significant Wilcox Test means not a normal distribution and significant Levene Test means non equal variances.

FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue, HADS-D = Hospital Anxiety and Depression Scale – Deutsche Version, TMT = Trail Making Test, MoCA = Montreal Cognitive Assessment. FC = functional connectivity, SWI = Small World Index,  $R^2$  is a measure for goodness of fit of specparam model fit.

**Table A2**

*SWI Delta and Beta Values for All Thresholds (10% - 90%) as well as Correlation Values of SWI Delta and Beta With Clinical Tests*

SWI	group		Spearman's $\rho$			
	with PCS	without PCS	FACIT-F	HADS-D	TMT A	TMT B-A
$\beta$ 10%	2.22 $\pm$ 0.71	2.04 $\pm$ 0.59	-.24	.21	.27	<b>-.32*</b>
$\beta$ 20%	1.48 $\pm$ 0.27	1.43 $\pm$ 0.21	-.26	.21	.23	<b>-.34*</b>
$\beta$ 30%	1.28 $\pm$ 0.16	1.21 $\pm$ 0.11	<b>-.32*</b>	.25	.27	-.22
$\beta$ 40%	1.16 $\pm$ 0.11	1.11 $\pm$ 0.07	-.29	.20	.20	-.25
$\beta$ 50%	1.08 $\pm$ 0.07	1.06 $\pm$ 0.04	-.25	.22	.24	-.21
$\beta$ 60%	1.04 $\pm$ 0.05	1.03 $\pm$ 0.03	-.28	.24	.28	-.20
$\beta$ 70%	1.02 $\pm$ 0.04	1.01 $\pm$ 0.02	-.18	.12	.19	-.26
$\beta$ 80%	1.00 $\pm$ 0.03	1.01 $\pm$ 0.02	.04	.03	.19	-.19
$\beta$ 90%	1.00 $\pm$ 0.02	1.00 $\pm$ 0.02	-.15	.22	.17	-.10
$\delta$ 10%	1.91 $\pm$ 0.60	2.22 $\pm$ 0.74	<b>.34*</b>	-.05	.14	-.01
$\delta$ 20%	1.48 $\pm$ 0.27	1.52 $\pm$ 0.34	.14	.20	.21	.10
$\delta$ 30%	1.25 $\pm$ 0.14	1.29 $\pm$ 0.20	.18	.19	.17	.07
$\delta$ 40%	1.15 $\pm$ 0.09	1.18 $\pm$ 0.12	.18	.15	.15	.04
$\delta$ 50%	1.10 $\pm$ 0.07	1.11 $\pm$ 0.09	.03	.19	.04	.09
$\delta$ 60%	1.05 $\pm$ 0.04	1.07 $\pm$ 0.05	.09	.03	.16	.01
$\delta$ 70%	1.03 $\pm$ 0.04	1.03 $\pm$ 0.05	.05	-.03	.21	.08
$\delta$ 80%	1.02 $\pm$ 0.03	1.01 $\pm$ 0.04	-.08	.12	.02	-.04
$\delta$ 90%	1.00 $\pm$ 0.02	1.01 $\pm$ 0.02	-.11	.06	-.12	-.05

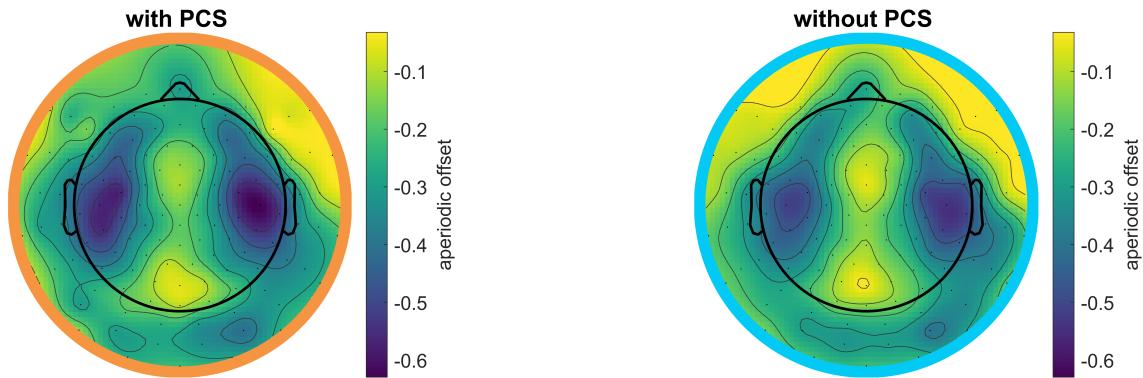
*Note.* None of the group differences were significant in the permutation tests. FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue, HADS-D = Hospital Anxiety and Depression Scale – Deutsche Version, TMT = Trail Making Test. 10% means, that the threshold for establishing this SWI was at 10% and so on.

## Appendix B

### Additional Plots

**Figure B1**

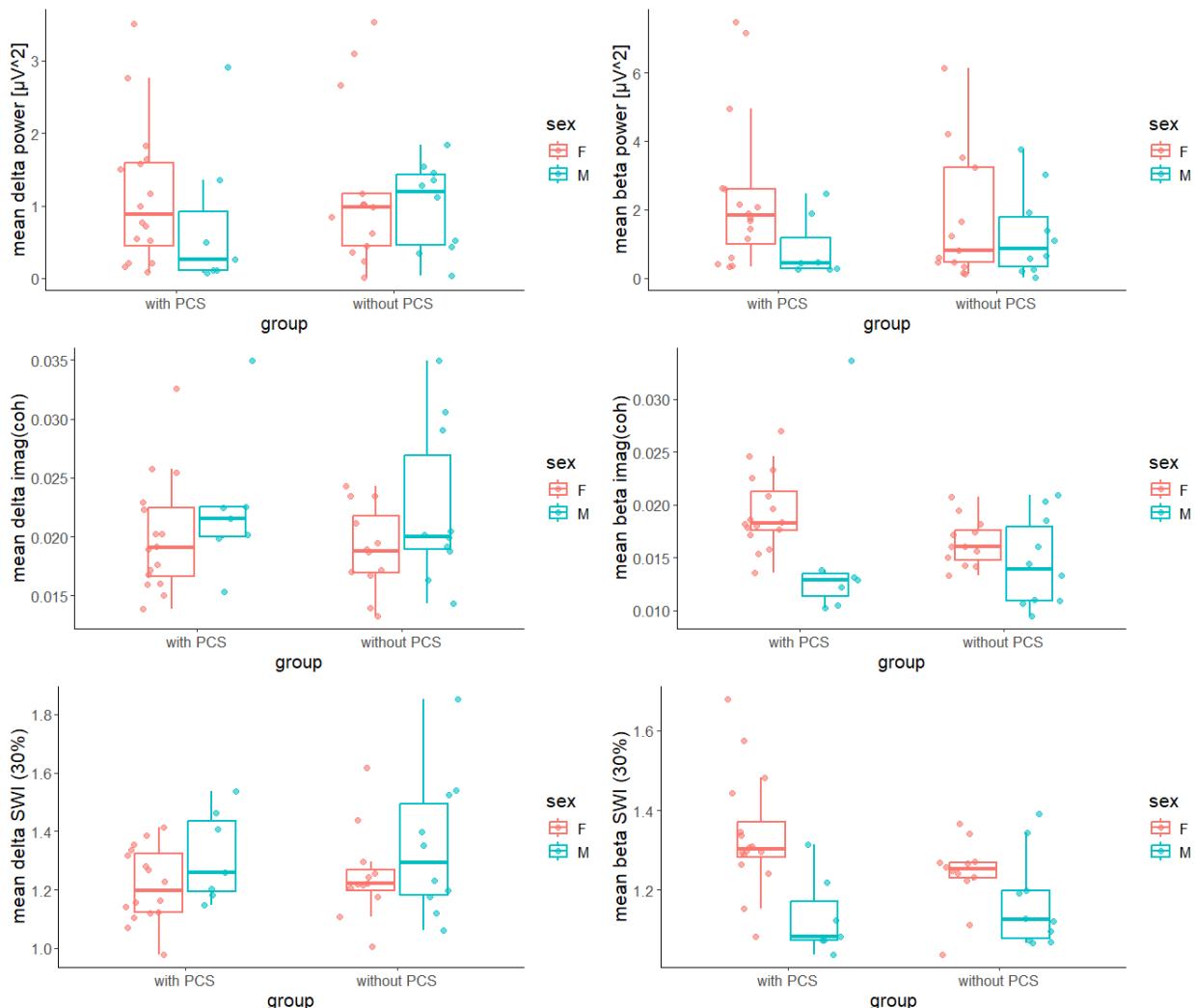
*Topoplot of the Aperiodic Offset per Group*



*Note.* There are no white dots in this plot compared to the aperiodic exponent, because there were no differences between the groups in any channels, with a  $p < .05$  in a permutation test.

**Figure B2**

*Descriptive View on Sex Differences in Our Measures of Importance*



*Note.* Measures of importance are the delta power in a frontal ROI, beta power in a central ROI, delta coherence in a frontal ROI, beta coherence in a central ROI and lastly, delta SWI at 30% threshold in a frontal ROI and beta coherence at 30% in a central ROI. F = female, M = male.

**Appendix C****Eigenständigkeitserklärung**

Ich bestätige, dass ich die vorliegende Arbeit selbstständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet habe. Die vorliegende Masterarbeit habe ich nicht bereits in derselben oder einer ähnlichen Fassung an einer anderen Fakultät oder in einem anderen Fachbereich zur Erlangung eines akademischen Grades eingereicht.

Mit der Einstellung dieser Arbeit in die Institutsbibliothek des Institutes für Psychologie bin ich einverstanden.

A handwritten signature in black ink, appearing to read "Axel Godberson".

Kiel, 25.11.2024

Unterschrift