How do individuals with different cognitive performance levels differ in their self-reported limitations after SARS-CoV-2 infection, their well-being and their resting state neural activity?

We've all walked into a room, only to have forgotten exactly why we are there. Or maybe our ability to recall names of long-lost friends or classmates isn't quite what it used to be. These are normal signs of aging. But, if such events begin to happen more frequently or escalate, then it could be something called mild cognitive impairment, often called MCI. Mild cognitive impairment is an early stage of memory—or cognitive ability—loss in people who can still independently perform most daily activities.

Cognition is a combination of processes in the brain that includes the ability to learn, remember, and make judgements (1). When cognition is impaired, it can have a profound impact on an individual's overall health and well-being (1).

Cognitive impairment in young adults
DSM5 – MCI nachschlagen

One part about MCI
EEG Frequency bands in psychiatric disorders:
Newson & Thiagarajan (2019): https://doi.org/10.3389/fnhum.2018.00521
Depression: The dominant result for depression was an increase in the absolute power in both theta and beta bands for both eyes open and eyes closed conditions (eyes closed consistency 1.8, validation 880; eyes open consistency 2.0, validation 337) with average magnitudes of 48%. However, these increases were no longer visible when considering relative power where most studies failed to find any significant differences across any band (Knott et al., 2001b; Morgan et al., 2005; Korb et al., 2008; Cook et al., 2014). The largest study (Arns et al., 2015) consisting of 1,344 participants showed increases in theta power across frontal regions of the brain using the eLORETA source localized signal which is methodologically different from most other depression studies identified for this review which perform their analysis in electrode space.

Other disorders such as bipolar disorder (Clementz et al., 1994; El-Badri et al., 2001; Bas¸ar et al., 2012; Kam et al., 2013; Narayanan et al., 2014; Moeini et al., 2015), anxiety (Sachs et al., 2004; Oathes et al., 2008; Xing et al., 2017) and panic disorder (Knott et al., 1996; Gordeev, 2008; Wise et al., 2011; de Carvalho et al., 2015) are included here for completeness. However generally there was no more than one or two studies for any one condition (eyes closed, eyes open, relative power, absolute power), which was too few for the inference of any trends or for the calculation of consistency scores. Nonetheless we show these results as part of our table with the caveat that they are generally poorly validated.

Cogntive impairment:

Millán-Calenti, Tubío, Píta-Fernández, González-

Subjective cognitive decline (SCD) – A public health issue:

SCD is the self-reported experience of worsening or more frequent confusion or memory loss (1,2). It is a form of cognitive impairment and one of the earliest noticeable symptoms of Alyheimer's disease and relared dementias (2,3). Self-reported, therefore not imply a diagnosis of cognitive decline by a health care professional.

Cognition is a combination of processes in the brain that includes the ability to learn, remember, and make judgements (1). When cognition is impaired, it can have a profound impact on an individual's overall health and well-being (1). Cognitive decline can range from mild cognitive impairment to dementia, a form of decline in abilities severe enough to interfere with daily life (1). Alzheimer's disease is the most common form of dementai (1-3).

Prevalence: 11,1% or 1 in 9 adults; aged 65 and older 11,7% and 10,8% among adults 45-64 years of age. Lower prevalence of SCD is reported in adults with more years of formal education

Jessen et al. (2014): https://doi.org/10.1016/j.jalz.2014.01.001

There is increasing evidence that subjective cognitive decline (SCD) in individuals with unimpaired performance on cognitive tests may represent the first symptomatic manifestation of Alzheimer's disease (AD).

Research criteria for pre-MCI SCD: 1. Self-experienced persistent decline in cognitive capacity in comparison with a previously normal status and unrelated to an acute event. 2. Normal age-, gender-, and education-adjusted performance on standardized cognitive tests,

which are used to classify MCI or prodromal AD. -> 1 and 2 must be present. Exclusion criteria: MCI, prodromal AD, or dementia; can be explained by psychiatric or neurological disease (apart from AD), medical disorder, medication, or substance uses.
Cognitive referse to any cognitive domain.
Studies on SCD have often used the term *impairment* (subjective cognitive impairment) instead of *decline*. The term *impairment* does not immediately reflect the temporal course of subjective cognitive change because impairment may also be of a chronic and stable nature. Thus, it requires an additional definition of onset. In contrast, the term *decline* already includes the fact that an onset has occurred.

Petersen (2016): https://doi.org/10.1212/CON.0000000000000313

MCI, a state of cognitive function between that seen in normal aging and dementia. estimating its prevalence to be between 15% and 20% in persons 60 years and older. MCI memory concern beyond what was expected for age. Memory impairment. <- Historical
But not only memory disturbance, multiple cognitive domain can be impaired (MCI with and without memory impairment is possible). MCI could result from a variety of etiologies and not just AD.
In DSM5 -> now include a predementia phase called mild neurocognitive disorder
MCI reflects a change in cognitive functioning for this individual person, not a lifelong low cognitive function
If time allows can MoCA be used for assessment, but clinican must be mindful that these screening instruments are insufficient to make the diagnosis; nevertheless they can be important to isolate domains of impairment and advise the clinician on further assessments (32,33).

Commented [JH1]: Interesting for discussion, that we just have total score of cognitive impairment. So I don't knnow in which domaine patients are better or worse

Daily function is largely preserved in MCI.
In addition, some aspects of psychiatric conditions such as major depression or generalized anxiety disorder can have cognitive components, and consequently, in the early stages of these disorders, cognition may be impaired. The clinician must always consider other medical conditions such as uncompensated heart failure, poorly controlled diabetes mellitus, or chronic obstructive pulmonary disease as contributors to cognitive impairment.

Petersen (2004): https://doi.org/10.1111/j.1365-2796.2004.01388.x

The concept of cognitive impairment intervening
between normal ageing and very early dementia has
been in the literature for many years. Recently, the
construct of mild cognitive impairment (MCI) has

been proposed to designate an early, but abnormal, state of cognitive impairment.

As the field matures, we will learn more about the various subtypes of MCI and their ability to predict various forms of cognitive impairment. Hopefully, as therapeutic interventions become available, we will be able to tailor treatments for specific prodromal forms of cognitive impairment and dementia

Bischkopf, Busse & Angermeyer (2002): https://doi.org/10.1034/j.1600-0447.2002.01417.x

Mild cognitive impairment is associated with an increased risk of developing dementia: patients develop dementia at a rate of 10–15%/year compared with healthy controls who develop dementia at a rate of 1–2%/year (6–8). In the ICD-10 the category Ômild cognitive disorderÕ (MCD) (F 06.70) has been included as a provisional definition (44). Although the definition is slightly narrower than the one in the DSM-IV (45), weak correlations among its components call an underlying presence of a syndrome into question (46). In contrast to the constructs mentioned above, the category MCD includes cases with impairment caused by medical or psychiatric conditions. However, a prevalence rate of only 4% for people 70 years and older has been reported (46) and people with a diagnosis of MCD are more distinguished by anxiety, depression and neuroticism than by cognitive deficits (47). The authors went as far as to relate MCD to neurotic, stress-related and somatoform disorders. One population-based study revealed that 12% of MCD-classified cases according to ICD-10 developed dementia after a follow-up period of approximately 4 years (47).

The term
MCI, for example, is used by several research
Bischkopf et al.
406
centres (6, 63–65). The definitional criteria include complaint of memory, normal activities of daily living, normal general cognitive function, abnormal memory function for age and education (1–2 SD), and absence of dementia (4). Prevalence rates of 15% for people 75 years and older (66) and only 3% for people 60 years and older have been reported (38). Finally, a term that often appears in research reports is the category Ôcognitively impaired, not dementedÕ (CIND) (70, 71), classifying all cognitively impaired cases, which do not satisfy the criteria for dementia. The CIND- classification usually includes cases with impairment caused by medical or psychiatric conditions. Mild cognitive impairment as discussed above is then treated as a subcategory among these cases. Problems arise, when prevalence and incidence rates are not calculated according to the different subcategories covered by the broad term of Ôcognitive impairment, no dementiaÕ

Roberts & Knopman (2013): 10.1016/j.cger.2013.07.003

Mild cognitive impairment (MCI) is the widely used term that describes an intermediate stage from normal cognitive function to dementia. The concept of MCI is highly significant and important to the field of aging and dementia for several reasons. Subjects with MCI have a high rate of progression to dementia over a relatively short period. Even among subjects who revert to normal cognition, the rate of subsequent MCI or dementia is higher than among those who never develop MCI.

The concept of CIND is a broader definition of impairment that encompasses subjects who meet criteria for MCI as well as others who are cognitively impaired but do not meet all the criteria for MCI.[8–10] The criteria for CIND include participant or informant-reported

significant decline in cognition or function; physician-detected significant impairment in cognition; cognitive test score (s) at least 1.5 SD below the mean compared to normative data; no clinically important impairment in activities of daily living assessed by physician/informant; absence of dementia.

MCI is an important public health concern due to the increased risk of progression to dementia and increased mortality. In particular, cognitive and functional severity within the MCI definition varies over a wide range, so that the syndrome of MCI is not homogeneous.

Pais, Ruano, Carvalho & Barros (2020): https://doi.org/10.3390/geriatrics5040084

This systematic review reports that the global prevalence of cognitive impairment ranged from 5.1% to 41% with a median of 19.0%. The incidence of cognitive impairment ranged from 22 to 76.8 per 1000 person-years, with a median of 53.97 per 1000 person-years

Resting state EEG power differences

Notes:

Freeman (2004): https://doi.org/10.1016/j.clinph.2004.02.029

Mantini, Perrucci, Del Gratta, Romani & Corbetta (2007): https://doi.org/10.1073/pnas.0700668104

Resting state rerefers to the functional imaging usage of this term, which indicates activity that is spontaneous and not dependent on a study-related task or stimulus. Resting state investigations have implications on cognitive neuroscience, sleep physiology, and resting state brain networks.

Neo, Foti, Keehn & Kelleher (2023): https://doi.org/10.1038/s41398-023-02681-2

First, similar to other neural-based measures , resting state EEG yields objective metrics that may be more sensitive in detecting subtle neurophysiological changes that percede behavioral manifestations of ASD. Second, EEG is more cost-effective, non-invasive, or portable than other neuroimaging methodologies. Third, resting state EEG data may be collected from individuals with a wide range of developmental and functioning levels, including children, which is of paramount importance fir early diagnosis of ASD (23).

EEG in cognitive impairment!

D'Atri et al. (2021): https://doi.org/10.1016/j.isci.2021.102386

The hallmark of the resting state EEG in patients with AD is the slowing of cortical rhythms, consisting of increased low-frequency (0.5-7.0 Hz) and decreased high-frequency activity (Babiloni et al., 2015; Jeong, 2004). Similar EEG features affect mild cognitive impairment (MCI) subjects, a condition being prodromal to AD in more than half of cases (Babiloni et al.,

Commented [JH2]: The EEG index that showed the strongest correlation with cognitive deterioration is the synthetic index of the EEG slowing during REM sleep. This result confirms previous findings (Montplaisir et al., 1996), and it also suggests that this composite index may be better suited as a disease marker than others based on cortical activity in a single frequency band measured during REM and NREM sleep or resting state, as well as than the same index evaluated during wakefulness.

2006; Galluzzi et al., 2001; Petersen et al., 2001; Scheltens et al., 2002). The EEG slowing correlates with the functional, structural, and cognitive changes in the disease progression (Babiloni et al., 2006; Claus et al., 2000; Jelic et al., 1996) and has been considered an EEG expression of the neurodegenerative process (Dringenberg, 2000).

Results: The waking EEG activity recorded in the evening hours displayed significant differences at the prefrontal and right frontotemporal sites for the delta band and at the right occipital derivation only for the alpha band. Prefrontal delta power was significantly higher in the AD compared to the HC group, while the right frontotemporal delta activity increased in the AD compared to both the HC and MCI groups. As expected, the occipital alpha power was reduced in the AD and MCI groups compared to the HC group. In the morning EEG, the three groups showed differences only in the delta band with a prevalence of the delta activity in AD compared to both HC and MCI groups. On the other hand, the EEG activity of the MCI group differed from that of HC only at the frontal sites. greater EEG slowing was associated with worse cognitive impairment, as indicated by lower MMSE scores.

Jelic, Shigeta, Julin, Almkvist, Winblad & Wahlund (1996):

https://doi.org/10.1159/000106897

MCI presenting as objective or subjective disturbances in cognition which do not fulfil the established diagnostic criteria for dementia syndrome (1-4).

A significant difference between the AD group and groups with objective and subjective memory disturbances was found for delta, theta, and alpha relative power. AD group significantly higher theta relative power in all investigated regions, and significantly lower alpha relative power in all investigated regions, in relation to the rest of the study population. For delta relative power, a lower level of significance ($p<0.05$) was observed in the left and right temporal and parieto-occipital, and left frontal regions. No significant difference was found for beta relative power in the groups studied, but a tendency towards higher values was observed in frontal regions in groups with objective memory disturbance and subjective memory complaints, as well as an increase in the left and right temporal and perieto-occipital regions in the AD group. A significant difference was found between the AD group and the other groups for mean frequency in the 4- to 20- Hz range in all regions, except for the left temporal region where the AD group was significantly different compared to controls and the group with subjective memory disturbances. There was no significant difference in the mean frequency between AD patients and the group with objective memory disturbances in that region. All 4 spectral ratios were significantly lower in all investigated regions in the AD

group. Significantly lower temporoparietal alpha band coherence was found in the AD group. A tendency towards a decrease in temporofrontal coherence was observed in the AD group. No significant differences between the groups with subjective or objective memory impairment when compared to the controls. The lack of clear qEEG changes in the present study in subjects with MCI can have at least two explanations. 1. Group is heterogeneous and, according to some follow-up studies, only a proportion if them will show further cognitive decline and develop manifest disease (4,9). 2. Some of these subjects have preclinical AD with pathology still restrictred to medial temporal lobes, which cannot be detected as changes in EEG power.

In conclusion, using complementary qEEG power

Claus et al. (2000): https://doi.org/10.1159/000017219

Slowing on the electroencephalogram (EEG) in patients with Alzheimer's disease (AD), compared to normal control subjects, evidenced by increase of theta activity and decrease of beta or alpha power, is a uniform finding in previous studies [1–5].

More impairment in overall cognitive function was most strongly reflected in loss of parieto-occipital and fronto-central alpha activity.

Detailed analysis of cognitive domains in relation to localized EEG values also revealed most consistently associations with decrease in alpha activity. Lower temporal and parietal rCBF were significantly associated with lower parieto-occipital alpha activity, while presence of leukoaraiosis was significantly associated with lower relative beta activity and higher absolute delta and theta activity.

General level of cognitive function, assessed in several previous studies with the MMSE, is most consistently related to alpha activity on EEG in AD patients [8, 13, 16 17, 46], in agreement with our findings. However, also correlations between overall cognitive function and delta and theta activity were observed in our study and in previous reports [13–16].

Alpha power as strongest correlate of cognitive

domains finds support in the study of Jelic et al. [19], where visuospatial functions were strongly related to alpha power in left parieto-occipital and right temporal regions. In the study by Jelic et al. [19] measures of frontal lobe function, including attention and abstraction, were significantly related to fronto-central theta activity. We also found that, in addition to alpha activity, fronto-central theta activity was selected as a significant predictor of performance in attention and abstraction.

Interestingly, our relative beta activity, but also absolute theta and delta activity, were significantly related to leukoaraiosis on CT. This analysis may demonstrate that increase of absolute theta and delta power is sometimes less clearly reflected in the relative power values. This is probably due to the fact that theta and also delta power determine the main part of the total power. As, for instance, theta or delta increases, the total power more or less increases proportionally. An increase in theta or delta may then be reflected by the absolute power, rather than by the relative EEG values. The preclinical finding that beta activity is found in subcortical or lower cortical structures [51–53] may either suggest that neuronal function of these brain structures is compromised by the presence of leukoaraiosis or that leukoaraiosis results in disconnection of subcortical and cortical structures.

Thus, the results suggest that leukoaraiosis in AD patients is related to slowing of the EEG, evidenced mainly by increase of theta and loss of beta activity.

In conclusion, alpha activity may be closely associated with cognitive function and rCBF, while beta and theta activity are related to lower cortical or subcortical changes. Our study therefore suggests that the EEG bands reflect differential pathophysiologic changes in AD.

Duffy, McAnulty & Albert (1995): https://doi.org/10.1093/cercor/5.3.215

These results demonstrate that there are significant and topographically consistent alterations in qEEG in mild to moderately impaired AD patients. The qEEG differences between patients and controls were bet reflected by increased theta, decreased beta, and reducted amplitude in the long-latency VER and AER. Spectral findings were basically the same for both absolute and relative measures.

By EEG spectral analysis, theta was increased and beta decreased for the AD patients (abstract).

Wada, Nanbu, Jiang, Koshino, Yamaguchi & Hashimoto (1997):
https://doi.org/10.1016/0006-3223(95)00651-6

Compared with the normal controls, the AD patients had a significantly lower alpha-2 and beta band power in the resting EEG as well as a significant increase in delta and theta band power.

In addition, our patients were found to have a significantly lower EEG power for the alpha-2, beta-1 and beta-2 bands in the resting condition. These findings are in general agreement with those of earlier studies showing that AD patients had background EEG slowing with a reduction in alpha and fast activity (Liddell 1958; Swain 1959; Horie et al 1990; Miyauchi et al 1989, 1994).

Topographic analyses of the resting EEG showed a significant increase in delta band power at the frontal regions. This finding is consistent with that of previous EEG studies both with visual inspection (Liddell 1958; Swain 1959) and with significant probability mapping (Miyauchi et al 1989, 1994), in which delta activity was observed predominantly at the frontal areas.

Previous studies showed the relationships between cognitive impairment and EEG abnormalities in AD patients (Johannesson et al 1979; Sulkava 1982) although these studies evaluated EEG by visual inspection. Although in our AD patients the MMS score was positively correlated with alpha and beta band power of the resting EEG, no significant correlations were found with delta or theta

band power.

Schreiter-Gasser, Gasser & Ziegler (1993) : https://doi.org/10.1016/0013-4694(94)90144-9

he degree of dementia is strongly reflected by an increase of power in the delta frequency band, accentuated on the
left hemisphere, as well as a decrease of alpha activity. Longer duration of disease is associated with a decrease of power in the alpha frequency
band, earlier age at onset with an additional increase of power in the theta frequency band. Visual EEG evaluation correlates highly with the
degree of dementia, in contrast to visually assessed CCT.
The quantitative E E G shows a surprising power in
reflecting stages of AIzheimer's disease and indeed the
most striking associations occurred between the degree
of dementia and delta power. Correlations of absolute
delta power with MMSE scores ranged typically from
0.6 to 0.9 at different locations. The delta band is by
far the best indicator for the degree of dementia. The
theta band, which best separated patients from con-
trols (Schreiter-Gasser et al. 1993), separates poorly
different stages of dementia. This can be explained by
the fact that theta activity is greatly increased already
in mild to moderate cases. In the delta band, on the
other hand, mild to moderate cases are intermediate
between severe cases and controls. Thus, progression
of Alzheimer's disease goes along with gradual in-
crease of delta power. This is in general agreement
with the literature (Cohen et al. 1985; Penttilfi et al.
1985; Soininen and Partanen 1988; Soininen et al.
1991), but the relationships are more clear-cut in our
Study. This may be attributed to using absolute rather than relative power and also to L O G artifact correction.

Elmståhl, Rosen & Gullberg (1994): https://doi.org/10.1159/000106706

Commented [JH3]: akzent

The control subjects showed increasing theta activity with age but the EEG changes did not correlate significantly with psychometric features. The AD patients showed highly significant increases in delta and theta activity and decreases in beta activity compared with controls. Our finding of a steadily increasing
relative theta power with age is in accordance with earlier
studies [20, 21], but at variance with other studies which
indicate a continuous decline in delta and theta activity
with age [10, 22].
Not
only theta power but also delta power is significantly increased. This is most likely due to the fact that our
patient sample is one o f late-onset AD in a rather
advanced stage. In studies of the progress of the FEG with
increasing severity of AD theta power is increased, fol
lowed by a decrease in beta power and later by an increase
in delta power and a decrease in alpha power (3. 25]. Our
group of elderly institutionalized patients had obviously
reached a stage of marked delta power increase.
The topographical analysis showed a widespread in
crease in delta and theta power over most cortical areas,
whereas the decrease in beta power was more restricted to
posterior temporoparietal areas. Delta waves are consid
ered to reflect primarily abnormalities of connections
between subcortical and cortical areas whereas the beta power decrease is considered to reflect cortical degenera
tive changes [26, 27]. The results of our study would
therefore indicate a profound derangement of subcortical
function in combination with degeneration of posterior
cortical areas.

Dierks, Frölich, Ihl & Maurer (1994): https://doi.org/10.1007/BF01271469

Summarizing the present investigation, we demonstrated a) an increase of
dipole strength in the slow frequency bands, b) a more anterior equivalent
dipole of alpha- and beta-activity, and c) a slowing of the EEG with increasing
cognitive deterioration. The results support the assumption that cognitive de-

cline in dementia can be assessed by measuring the electrical activity of the brain.

Kuskowski, Mortimer, Morley, Malone & Okaya (1993): https://doi.org/10.1016/0006-3223(93)90108-P

Log-absolute EEG power in the alpha bandwidth (8–12 Hz) was found to be correlated with the computed rate of MMSE decline. This association was present for electrode sites across all regions of the scalp and remained significant when the effects of current cognitive severity were partialled out. These data suggest that a quantitative EEG measure (absolute alpha power) is related to the rate of cognitive decline in patients with Alzheimer's disease.

The data presented here suggest that a quantitative EEG measure (absolute alpha power) is correlated with the rate of cognitive decline in patients with AD. This association was present for electrode sites across all regions of the scalp and remained significant when the effects of current cognitive severity were partiailed out.

Dringenberg (2000): https://doi.org/10.1016/S0166-4328(00)00261-8

The generalized slowing of the neocortical EEG is a characteristic symptom in AD and refers to a reduction in desynchronized, activated EEG patterns that are replaced by deactivated, synchronized activity. Typical EEG changes in AD include a loss of beta (13–30 Hz) activity, a decrease in power and mean frequency of alpha activity (8–12 Hz), and increased power in the theta (4–7 Hz) and delta (B4 Hz) bands [21,39,71,74]. Also, alpha EEG coherence decreases while delta coherence increases in patients with clinically probable AD [56]. These quantitative EEG changes provide a sensitive index of the cognitive status of AD patients; McAdam and Robinson [59] reported a positive correlation of 0.79 between EEG abnormalities and the severity of dementia in a population of demented patients, and Pentilla¨ et al. [71] noted a significant positive correlation between occipital peak (alpha) frequency and neuropsychological test scores in AD patients (i.e.

lower frequency was associated with lower test scores). Some EEG changes, such as the increase in theta power, occur together with the earliest signs of cognitive deterioration, while others are associated with more advanced cognitive decline (e.g. increased delta power [71,74]). The close relation between EEG slowing and the severity of cognitive symptoms suggests that a disruption of processing in cortical networks contributes importantly to the behavioral disorganization present in AD.

Babiloni et al. (2006): https://doi.org/10.1016/j.clinph.2005.09.019

In the present study, low-band (8–10.5 Hz) alpha sources in parietal, occipital, temporal, and limbic areas had an intermediate magnitude in MCI subjects when compared to mild AD and Nold subjects. Furthermore, magnitude of these five EEG sources showed positive linear and non-linear (i.e. correlations with MMSE score (global cognitive level) across all Nold, MCI, and mild AD subjects as a single group. These results suggest that the global neurophysiological variables (posterior cortical rhythmicity) were linearly and not linearly correlated with global clinical and cognitive status (MMSE score) across the shadow region between physiological and pathological aging.

The present results extend in spatial detail previous EEG evidence showing a decrease of alpha power in MCI compared to normal subjects (Frodl et al., 2002; Grunwald et al., 2001; Huang et al., 2000; Jelic et al., 1996; 2000). Furthermore, they complement previous evidence of early atrophy signs in limbic, precuneus, and posterior cingulate areas of MCI subjects (Baron et al., 2001; Callen et al., 2001).

In our MCI group, the alpha findings paralleled those in occipital delta (2–4 Hz), which had an intermediate

magnitude compared to mild AD and Nold subjects. Furthermore, magnitude of these EEG sources showed
negative linear and non-linear correlations with MMSE score (global cognition) across all subjects. These results are
compatible with previous EEG evidence showing increased
slow rhythms in MCI compared to normal controls
(Grunwald et al., 2001; Jelic et al., 2000; Prichep et al.,
1994; Wolf et al., 2003). Furthermore, previous evidence
have shown that the increase of slow EEG rhythms in AD is
secondary to progressive cortical hypoperfusion (Brenner
et al., 1986; Dossi et al., 1992; Kwa et al., 1993;
Niedermeyer, 1997; Nobili et al., 1998; Passero et al.,
1995; Rae-Grant et al., 1987; Stigsby et al., 1981; Steriade
et al., 1994; Rodriguez et al., 1999a; Young, 1987). From a physiological viewpoint, delta rhythms have been
intensively studied during slow wave sleep. These rhythms
are then replaced by fast (beta and gamma) cortical
oscillations induced by the depolarizing effects of meso-
pontine cholinergic neurons acting on thalamocortical
neurons and by the depolarizing effects of nucleus basalis
cholinergic neurons acting on cortical neurons (Steriade,
2003). Therefore, it can be speculated that the increment of
delta oscillations in MCI and AD subjects might be related
to loss of hippocampal and posterior cortical neurons, which
are impinged by cholinergic inputs. Indeed, it has been
demonstrated that early degeneration in mesial temporal
cortex of MCI and AD subjects can affect functional
connectivity between hippocampal formation and tempor-
oparietal cortex (Killiany et al., 1993). Furthermore, a
bilateral reduction of gray matter volume in the hippocam-
pal formation and entorhinal cortex of AD subjects was
correlated with an increment of delta rhythms in posterior
cortex (Fernandez et al., 2003).
In the present study, the theta sources in parietal,

occipital, temporal and limbic areas had a stronger magnitude in mild AD subjects than MCI and Nold subjects. These results extend in spatial detail previous EEG evidence showing an increase of theta power in mild AD compared to normal subjects (Coben et al., 1983; Huang et al., 2000; Mattia et al., 2003; Ponomareva et al., 2003).

The results of the present study showed that cortical sources of EEG rhythms changed across Nold, MCI, and mild AD subjects, as a function of the global cognitive level. This was true for occipital delta and alpha 1 sources in parietal, occipital, temporal, and limbic areas, which had an intermediate magnitude in MCI subjects compared to mild AD and Nold subjects and were correlated with MMSE score across all subjects.

Jeong (2004): https://doi.org/10.1016/j.clinph.2004.01.001

Since Hans Berger, the discoverer of the electroencephalogram (EEG), first observed pathological EEG sequences in a historically verified AD patient (Berger, 1931, Berger, 1932), a large number of studies about the EEG of AD have been performed. The hallmark of EEG abnormalities in AD patients is slowing of the rhythms and a decrease in coherence among different brain regions. An increase in theta and delta activities and a decrease in alpha and beta activities are repeatedly observed (Brenner et al., 1986, Coben et al., 1983, Coben et al., 1985, Giaquinto and Nolfe, 1986), and a reduced coherence of the alpha and beta bands is frequently found (Dunkin et al., 1994, Leuchter et al., 1987, Locatelli et al., 1998). Furthermore, these abnormalities are correlated with the severity of the disease (Hughes et al., 1989, Kowalski et al., 2001). For the last 2 decades, the EEG has been utilized as a useful tool for diagnosing dementias.

There is a good correlation between the degree of the EEG abnormality and cognitive impairment (Brenner et al., 1988; Erkinjuntti et al., 1988; Johannesson et al., 1979; Kaszniak et al., 1979; Liddle, 1958; Merskey et al., 1980; Obrist et al., 1962; Rae-Grant et al., 1987; Roberts et al., 1978; Soininen et al., 1982; Wiener and Schuster, 1956).

It is of clinical interest to find that the EEG abnormality

Commented [JH4]: Here more information about delta, theta, beta and alpha waves in AD

is associated with cognitive deficits. A good correlation is found between EEG spectral measures and cognitive deterioration scores, such as the Folstein (Mini-mental) score (Brenner et al., 1986; Elmsta¨hl et al., 1994; Filipovitch et al., 1989; Leuchter et al., 1987; Leuchter et al., 1993; Schreiter-Gasser et al., 1994; Strijers et al., 1997), the global deterioration score (Helkala et al., 1991; Passero et al., 1995; Prichep et al., 1994), and a composite neuropsychological test score (Penttila¨ et al., 1985). There are, however, some studies reporting only a weak correlation or no correlation between EEG changes and the cognitive decline in AD (Hughes et al., 1989; Prinz and Vitiello, 1989).

Babiloni (2015): **https://doi.org/10.1016/j.ijpsycho.2015.02.008**

Results showed abnormalities of the EEG power density at specific frequency bands (< 12 Hz) in the MCI and AD populations, associated with an altered functional and effective EEG connectivity among long range cortical networks (i.e. fronto-parietal and fronto-temporal). These results suggest that resting state EEG rhythms reflect the abnormal cortical neural synchronization and coupling in the brain of prodromal and overt AD subjects, possibly reflecting dysfunctional neuroplasticity of the neural transmission in long range cortical networks.

The human brain is composed of about 100 billion neurons interconnected through a complex and intricate network of synapses. A combination of several factors is responsible for brain aging, typically the synaptic pruning, the neuronal apoptosis, and the loss of cortico-cortical connections, bringing to a decline of cognitive **functions (D'Amelio and Rossini, 2012).** Neural and synaptic redundancy, as well as plastic remodeling of brain networking, promotes maintenance of brain functions and cognitive status in late life (D'Amelio and Rossini, 2012). The absence of objective cognitive impairment at the onset of AD motivates the use of instrumental markers of altered functional connectivity and neutral transmission across long-range neural networks together with “paper and pencil” neuropsychological batteries to assess the cognitive functions (Rossini et al., 2007).

To this aim, digital electroencephalography (EEG) has very interesting features to provide useful information on the functioning of neutral transmission and cortical neuronal synchronization and coupling across long-range neural networks when compared to other classical neuroimaging techniques (Babiloni et al., 2009a).

Of note, EEG is characterized by a low spatial resolution (centimeters) compared to other neuroimaging relatively non-invasive techniques, such as structural MRI and PET, producing "in vivo" brain anatomy images with high spatial resolution (millimeters to a few centimeters). On the other hand, EEG can rely on a high temporal resolution (i.e. milliseconds; Rossini et al., 2004), compared to structural MRI, which does not provide any functional information about the brain, and PET scan of brain glucose metabolism/rCBF (seconds to minutes for PET). High temporal resolution of EEG is considered crucial for the study of the spontaneous and event-related oscillatory gross electromagnetic activity at different frequency ranges (1–4 Hz, delta, 4–8 Hz, theta, 8–13 Hz, alpha, 13–30 Hz, beta, and > 30 Hz, gamma). Any EEG frequency band conveys particular physiological information on brain functional activity in wake and wake (Nunez et al., 1999).

In the last two decades, the evaluation of quantitative EEG (qEEG) and/or event-related potentials (ERPs) as clinical markers of the early stages of AD has been considered (Celesia et al., 1987, Rossini et al., 2007, Rossini, 2009, Yener et al., 2008, Yener et al., 2009). In particular, the recording of resting state eyes-closed EEG represents a simple standardized procedure that may be carried out rapidly in a clinical environment. The recording of the EEG rhythms at rest does not require stimuli or assessment of subject's behavior, and it does not induce fatigue or anxiety typically associated with common task performance. Also, the recording of the EEG rhythms can be repeated countless times along the disease progression and the EEG markers are virtually not affected by meta-learning relative to task processes. These are ideal requisites when EEG recordings are performed in elderly vulnerable or diseased subjects. Furthermore, EEG rhythms can be recorded in highly comparable experimental conditions in normal subjects, individuals with subjective memory complaints, objective mild cognitive impairment (MCI), and overt AD (Rossini et al., 2007). Moreover, resting state EEG rhythms have been found to partially restore together with patients' cognitive performance after the administration of AchetylCholinesterase inhibitors licensed for the symptomatic treatment of AD (Kogan et al., 2001; Rodriguez et al., 2002, Rodriguez et al., 2004, Reeves et al., 2002, Onofrj et al., 2003, Brassen and Adler, 2003, Babiloni et al., 2006e).

The word EEG refers to the measurement of brain electrical activity
211 recorded from electrodes placed on the surface of the head. In 1929,
212 Hans Berger reported a dominant 10-Hz oscillating voltage difference
213 between two electrodes placed on the scalp in healthy subjects during
214 a wakeful eyes-closed relaxed state (the so-called alpha rhythm).

215 Berger showed that the 10-Hz oscillations (10–50 microvolts) are
216 reduced in amplitude when subjects open their eyes or perform a cog-
217 nitive task. Nowadays, EEG is largely employed for basic scientific re-
218 search and clinical applications since it is easy to use, non-invasive,
219 cheap, and totally safe.
220 As an important limitation, the EEG voltage measured depends on
221 the position of the reference electrode. Furthermore, EEG is character-
222 ized by a low spatial resolution as compared to other measures of
223 brain function such as functional magnetic resonance imaging (fMRI).
224 Indeed, different conductivities of head tissues (brain, meninges, skull,
225 and scalp) attenuate and blur the spatial distribution of neural currents
226 from brain to scalp electrodes. As a consequence, scalp EEG data present
227 enhanced low-spatial components and negligible values of high-
228 frequency brain oscillations (N40 Hz, gamma rhythms). To minimize
229 these effects of head volume conduction, mathematical procedures
230 have been developed to obtain reference-free measurements with
231 attenuated head volume conductor effects, namely estimation of com-
232 mon average reference, source current density, and inverse EEG source
233 solutions (Q12 Babiloni et al., 2009a, 2009b, 2009c).
Technical requirements make the EEG equipment a non-invasive
235 and non-expensive device, with an overall present price of few tens of
236 thousands of Euro needed for high-resolution EEG recording. EEG sig-
237 nals are derived from electric activity of neurons in the cerebral cortex.
238 Specifically, these signals are mainly produced by post-synaptic ionic
239 currents of synchronously active cortical pyramidal neurons reflecting
240 the integrative information processing of signals coming from thalamus,
241 brainstem, and other cortical modules. EEG signals are very large-scale
242 measures of brain source activity, reflecting synaptic activity synchro-
243 nized over macroscopic (centimeter) regional spatial scales (Nunez
244 et al., 2001). Synchrony among neural populations in compact regions
245 of the brain produces localized dipole current sources. Synchrony
246 among neural populations distributed across the cortex results in re-
247 gional or global networks consisting of many dipole sources.
248 EEG signals have a high temporal resolution (b 1 ms) ideal to inves-

tigate an important property of brain physiology, namely brain rhythms during passive wakefulness and task performance. Spectral analysis methods allow the estimation of EEG dynamics in terms of the dominant frequencies, power (or amplitude), phase, and coherence of EEG rhythms. The background spontaneous oscillatory activity of brain neurons at about 10 Hz generates the dominant alpha rhythm of resting-state EEG activity first described by Berger. In the classical studies by Jasper and Penfield (1949), alpha rhythms ranging from about 8 to 12 Hz were recorded from nearly the entire upper cortical surface (including the frontal and prefrontal areas) in a large population of patients awake during surgery.

In the condition of slow-wave sleep, cortico-fugal slow oscillations (b1 Hz) are effective in grouping thalamic-generated delta rhythms (1–4 Hz) and spindling activity (7–14 Hz) rhythms (Steriade, 2003). In the condition of brain arousal, spindles as well as high and low components of the delta rhythms are blocked by the inhibition of oscillators within, respectively, reticulo-thalamic (7–14 Hz), thalamo-cortical (1–4 Hz), and intracortical (b1 Hz), neuronal circuits. These rhythms are replaced by fast (beta and gamma) cortical oscillations, which are mainly induced by forebrain (nucleus basalis) cholinergic inputs to hippocampus and cortex as well as by thalamo-cortical projections (Steriade, 2003; Steriade et al., 1996). In the condition of awake rest, low frequency (8–10.5 Hz) alpha would be mainly related to subject's global attentional readiness (Klimesch, 1996; Klimesch et al., 1997, 1998; Rossini et al., 1991; Q13Steriade and Llinas, 1998). Noteworthy, there is consensus that alpha rhythms represent the dominant resting oscillations of the adult, awake human brain (Rossini et al., 1991; Q14Steriade and Llinas, 1998; Klimesch, 1996; Klimesch, 1997, 1998), and have been linked to intelligence quotient, memory, and cognition (Klimesch, 1999). This background activity is desynchronized during sensory and cognitive-motor events (Q15Babiloni et al., 2005, Q16Babiloni et al., 2006a, 2006b, 2006c, 2006d, 2006e, 2008a, 2008b; Pfurtscheller and Lopes da Silva, 1999). Oscillations in other frequency bands, e.g., delta (1–4 Hz), theta

(4–7 Hz) and gamma bands (30–70 Hz) also exhibit complex patterns of power that are modulated by cognitive processes such as working memory and perceptual binding (Srinivasan et al., 2006). Unless otherwise specified, spontaneous EEG activity during resting state condition is indexed by spectral power density in given narrow frequency bands (per electrode, scalp region of interest or cortical source).

Resting state EEG power density differed between AD patients and amnesic MCI subjects, who were considered to be at high risk of suffering from prodromal AD. There was an "intermediate" power density of low-frequency alpha rhythms (8–10.5 Hz) in the parietal and occipital regions in MCI compared to mild AD and Nold subjects (Babiloni et al., 2006b). Furthermore, maximum alpha and beta power density shifted more anteriorly in AD patients compared to Nold and MCI subjects (Huang et al., 2000). Moreover, longitudinal studies have shown that increased delta or theta power density, decreased alpha and beta power density, and slowing of mean EEG frequency were in some way predictors of the progression from MCI to dementia at about 1-year follow-up (Huang et al., 2000; Jelic et al., 1996, 2000; Grunwald et al., 2001; Kwak, 2006; Rossini et al., 2006). High power density of the posterior alpha rhythms also predicted a stable global cognitive function in MCI subjects at 1-year follow-up (Babiloni et al., 2010a).

n the MCI subjects, the EEG markers of disease progression included an increase of the power density at the theta and delta rhythms in the temporal and occipital regions as well as a decrease of the power density at beta rhythms in temporal and occipital regions (Jelic et al., 2000).

In the AD patients with global cognitive impairment, hippocampal atrophy was associated with increased power density at delta and theta rhythms in the temporal and parietal regions (Helkala et al., 1996), in line with recent magnetoencephalographic (MEG) evidence (Fernandez et al., 2003).

Furthermore, a volume decrement of hippocampus was related to the decreased power density at alpha rhythms in the temporal, pari-

388 etal, and occipital regions in MCI and AD subjects (Babiloni et al.,
389 2009b).
Furthermore, the
399global delta and alpha power density was related to the total amount
400of atrophy of cortical gray matter in the amnesic MCI and in the AD sub-
401jects, as revealed by MRI voxel-to-voxel volumetry of lobar brain vol-
402ume; the higher the total gray matter volume, the lower the global
403delta power density and the higher the global alpha power density
404(Babiloni et al., 2012).
The power density of the resting state eyes-closed EEG rhythms was
412repeatedly found to be correlated to cognitive status in MCI and AD sub-
413jects. It has been shown that the posterior alpha power density was pos-
414itively correlated to the subjects' global cognitive status, as measured by
415ADAS-cog in the MCI or AD subjects; namely, the lower the alpha power
416density, the lower the cognitive status (Luckhaus et al., 2008). This rela-
417tionship can be extended to the cognitive health condition. Further-
418more, the posterior delta and alpha power density was correlated to
419the MMSE score in the Nold, MCI and AD subjects; namely, the lower
420the alpha power, the higher the delta power and the lower the cognitive
421status (Babiloni et al., 2006b).
It has
440been shown that in the MCI subjects, the markers of disease progression
441included an increase of the power density at theta and delta rhythms in
442the temporal and occipital lobes as well as the reduction of the beta
443power density in the temporal and occipital lobes (Jelic et al., 2000).
AD patients were characterized by an increase of theta and delta power
445density and by a reduction of the alpha and beta power density in the
446parieto-occipital lobes (Coben et al., 1985). Furthermore, half of the AD
447patients showed an increase of the theta and delta power density in
448the temporal-occipital lobe (Soininen et al., 1989).
Power density of the resting state EEG rhythms does not capture one
456of the main features of the AD process, namely the impairment of functional or effective connectivity within long range brain networks
458 underlying the cognitive dysfunction in prodromal and manifest AD

459 patients. Indeed, the majority of the cognitive processes are highly
460 distributed and dynamic processes, depending on the selective inter-
461 play among many neural populations distributed across several cortical
462 and sub-cortical regions. In the same line, it is expected that temporally-
463 coordinated brain networks underpinning cognitive functions do be-
464 come more and more abnormal along the progression of AD neurode-
465 generation, so that AD can be viewed as a disconnection syndrome
466 (Bokde et al., 2009). An ideal methodological approach is, therefore,
467 the extraction of some functional indexes of the abnormalities of the
468 functional brain connectivity across long term neural networks
469Q24 (Varela et al. 2001;Q25 Le Van Quyen et al. 2003; Börner et al. 2007).
1057 conclusion, the resting state EEG makers are promising to unveil abnor-
1058 mal functional connectivity and neuroplasticity of neurotransmission in
1059 the brain of AD patients.

Commented [JH5]: Discussion (further research)

Sun, Sun, Chen, Wang & Gao (2024): https://doi.org/10.1186/s12916-024-03481-1

Commented [JH6]: Very important

The eruption of the SARS-CoV-2 pandemic has instigated a global public health crisis, posing significant threats to respiratory health [1–3]. Significantly, this crisis has not only posed a substantial menace to the respiratory system [4, 5] but has also sparked concerns regarding its impact on the central nervous system [6–8]. A wealth of empirical research has confirmed that SARS-CoV-2 can induce a range of neurological issues, notably affecting cognitive functions [9, 10]. Amidst various methodologies employed for cognitive function assessment, electroencephalography (EEG) techniques emerge as pivotal tools [11] for evaluating cognitive function and quantifying the detrimental effects of SARS-CoV-2 infection on cognitive performance [12, 13].

However, existing research predominantly focuses on EEG studies involving elderly and severely affected patients [10, 14–16]. Recent shifts in focus explore the effects on younger, more diverse populations. For instance, in 2024, researchers employed EEG to analyze sleep patterns in chil-

dren post-SARS-CoV-2 infection [17]. Although numerous comparative EEG studies have targeted younger demographics [18–20], these investigations often involve limited participant numbers and age ranges. Therefore, it is critical to expand EEG studies to more comprehensively assess the long-term cognitive impacts of SARS-CoV-2.

The primary aim of this study is to bridge the gap in understanding the cognitive effects of SARS-CoV-2 in individuals presenting mild symptoms, with a focus on EEG patterns across different age groups, especially in children and adolescents. We gathered resting EEG data from a diverse cohort of 185 individuals who experienced mild symptoms related to SARS-CoV-2, both before infection and after full recovery. Utilizing advanced analytical techniques such as source connectivity and microstate analysis, this study explores the subtle cognitive changes induced by SARS-CoV-2, analyzing both spatial and temporal aspects.

Against the backdrop of the globally reported tally of more than 770 million confirmed cases of SARS-CoV-2 infection as of September 29, 2023 [21], it is of paramount importance to fathom the cognitive implications wrought by SARS-CoV-2 infection upon the substantial proportion of individuals who exhibit mild symptoms. Such an endeavor is indispensable not only for enhanced comprehension of the virus itself but also for the formulation of healthcare strategies and support systems, with a specific focus on the child and adolescent demographics alongside other vulnerable segments of the population. Our investigation serves to elucidate the intricacies surrounding the cognitive ramifications of SARS-CoV-2 infection in mildly symptomatic populations across varying age groups, thereby contributing to the foundation of rehabilitation strategies geared towards ameliorating the afflictions of SARS-CoV-2 and mitigating the challenges

posed by long COVID or post-COVID-19 syndrome [22].

A preprocessing protocol was implemented to maintain data integrity. During the recording phase, a specialist flagged any segments where significant body movements caused electrode dislodgement. To mitigate the impact of ocular and muscular artifacts, the independent component analysis (ICA) was employed. Additionally, direct current (DC) and instrumental frequency (IF) interferences were eliminated using a bandpass filter ranging from 0.5 to 45 Hz. These preprocessing steps were critical to ensuring the reliability and validity of the study's findings. In the analytical phase, the EEG data was segregated into six distinct frequency bands using a specialized filter bank, covering the full frequency spectrum: full band (0.5–45 Hz), delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–30 Hz), and gamma (30–45 Hz). An averaging reference operation was subsequently applied across all datasets to ensure analytical consistency and accuracy.

Commented [JH7]: methode

Commented [JH8]: methode

Commented [JH9]: methode

Brain network source connectivity analysis in the spatial domain

Source connectivity analysis is a critical technique using neuroimaging data for examining complex interactions between brain regions [23]. Its main goal is to identify functional or effective linkages among cerebral sources that reflect cognitive shifts in conditions like depression and schizophrenia [24, 25]. Among various functional connectivity metrics, coherence is a key measure, calculating the linear correlation between two signals in the frequency domain. However, coherence measurements can be affected by volumetric conduction, causing misleading pseudo-coherent values [26, 27].

Commented [JH10]: discussion

Commented [JH11]: Connectivity

Statistical test methods

In this study, statistical analyses were conducted to

ensure the robustness and validity of the findings. First and foremost, normality testing was performed using the Shapiro–Wilk normality test, a fundamental step in validating the assumptions underlying parametric statistical methods. Subsequently, for datasets adhering to a normal distribution ($P > 0.05$), a paired t-test was employed, a method widely acknowledged for its appropriateness in comparing means under normal conditions. In cases where the data did not conform to a normal distribution ($P \leq 0.05$), the analysis was conducted using the Wilcoxon signed-rank test, a non-parametric test known for its effectiveness in evaluating differences between paired samples without relying on the assumptions of normality. All statistical procedures were executed with the SCIPY. STATS toolkit for Python.

Commented [JH12]: methode

Age-related differences in the impact of SARS-CoV-2 were also apparent. Young adults showed the most significant cognitive impact, followed by adults and adolescents, while children under 10 exhibited the least effect, with significantly fewer link reductions compared to young adults. These findings suggest that the cognitive resilience varies with age, with the brain networks of young adults being notably more vulnerable to disruption by SARS-CoV-2. This vulnerability could be influenced by factors such as the stage of brain development, lifestyle, or pre-existing health conditions. Adults and adolescents displayed moderate resilience, while the minimal impact on children could indicate more robust brain networks or compensatory mechanisms that protect against connectivity loss.

Significantly, the young adult group demonstrated the highest prevalence of cognitive dysfunctions, closely followed by the adult cohort. In contrast, the adolescent and child groups showed a lower

probability of exhibiting cognitive-related symptoms.

The outcomes of this study distinctly highlight the amplified susceptibility of young adults to cognitive deficits following a SARS-CoV-2 infection, a demographic that has traditionally not been considered as high risk.

Our findings propose a more profound impact of SARS-CoV-2 on young adults in comparison to adolescents and children. This insight can potentially steer the formulation of rehabilitation strategies tailored for long COVID patients.

The diminished connectivity in specific brain regions, such as electrode T5, which in temporal lobe, may reflect disruptions in neural networks that are crucial for cognitive functions [54]. This aligns with existing studies that link changes in brain connectivity to various cognitive impairments [55]. The persistence of connectivity reductions primarily within hemispheres further underscores the targeted impact of SARS-CoV-2 on brain function. The increase in the HA parameter within the theta band post-infection in adults suggests subtle yet discernible changes in EEG activity, potentially reflecting alterations in cognitive states. The heightened complexity in EEG patterns post-recovery, particularly in the delta band, might indicate a compensatory neural mechanism or an altered state of brain activity in response to the infection.

The observed concentration of alterations within the delta frequency band presents a pioneering insight, proposing that this band may be particularly susceptible to the neurological impacts of SARS-CoV-2 [56]. Traditionally, it is recognized that delta wave activity is diminished when the eyes are open. However, the findings of this study suggest that delta waves can also

reflect changes in subject states to a certain degree. lthough none of the participants in this study was clinically diagnosed with “brain fog,” the EEG changes noted bear resemblance to those associated with “brain fog,” hinting at a potential underlying neurological impact of the infection [58].

Results indicate a gradation in susceptibility to cognitive impacts post-SARS-CoV-2 infection across different age groups. The most substantial cognitive changes were observed in young adults, a demographic that is not typically considered at high risk for severe COVID-19 implications. While previous studies have also shown that infection has a greater impact on young adults [59], the results of the present study provide additional evidence at the electrophysiological level for this conclusion.

We endeavored to include as broad a population as possible, yet our study did not encompass all age groups, particularly the elderly. This omission means that the effects of the coronavirus on the neurological systems of older individuals remain unknown, given that some studies suggest this demographic may be more susceptible to such impacts [60].

In essence, this research furthers the existing knowledge on the neurological implications of SARS-CoV-2, underscoring the urgent requirement for a more profound understanding of the virus’s enduring effects on cognition. Particularly, it focuses on its impact on younger demographics, encompassing children and adolescents. The results intimate that the influence of SARS-CoV-2 is amplified within the younger populace. Although children and adolescents were relatively less affected, they exhib-

ited noteworthy neurophysiological markers of abnormality, suggesting possible risk. This study, therefore, serves as a groundwork for more extensive research into potential therapeutic interventions and strategies to alleviate these cognitive alterations.

Perez, Duque, Hidalgo & Salvador, 2024:

https://doi.org/10.1016/j.biopsycho.2024.108823

As the older population continues to expand, there is a growing prevalence of individuals who experience subjective cognitive decline (SCD), characterized by self-reported failures in cognitive function and an increased risk of cognitive impairment. Recognizing that preventive interventions are typically more effective in preclinical stages, current research endeavors to focus on identifying early biological markers of SCD using resting-state electroencephalogram (rsEEG) methods. The review emphasizes patterns in frequency band activity, revealing that individuals classified as SCD exhibited increased theta power than healthy controls, but decreased than MCI. However, findings for the alpha, delta, and beta bands were inconsistent, demonstrating variability across studies and highlighting the need for further research.

Subjective cognitive decline (SCD) has become particularly noteworthy because it is considered a prodromal stage of cognitive impairment (Jessen et al., 2014). A meta-analysis of longitudinal studies on SCD with a follow-up period of at least four years revealed an estimated conversion rate to Mild Cognitive Impairment (MCI) of 27 %, and 14 % to dementia (Mitchell et al., 2014).

Commented [JH13]: Very important for my thesis - Introduction

However, in 2012, researchers and clinicians in the field of Alzheimer's Disease (AD) proposed the term SCD (Jessen et al., 2014), which has been extensively accepted. SCD is characterized by two key features: (1) a self-reported decline in cognitive capacity across various cognitive domains, rather than being restricted to memory, and (2) normal performance on standardized tests used to classify MCI. Although individuals with SCD perform within normal limits on neuropsychological tests, this group is a heterogeneous population with diverse possibilities and outcomes. On the one hand, SCD has been associated with an

objective cognitive performance similar to that of individuals without SCD and no progression to dementia (Sohrabi et al., 2019). On the other hand, SCD has been linked to a higher risk of objective cognitive impairment (Li et al., 2022; Numbers et al., 2023; Rivas-Fern´andez et al., 2023) and a reduction in functional connectivity (Yasuno et al., 2015). Additionally, individuals with SCD have been found to exhibit neurological changes similar to those observed in AD, including differences in both grey and white matter structures (Munro et al., 2023) and a smaller bilateral hippocampus and right amygdala compared to controls (Striepens et al., 2010). Jessen et al. (2020) also established different trajectories from SCD, such as complete remission of SCD when the underlying conditions are depression, medication side effects, or intermittent sleep disturbance. Additionally, there can be a persistent continuation of SCD due to normal aging or a progression to dementia. Therefore, it would be beneficial to investigate early and reliable biomarkers for the detection and treatment of SCD in an attempt to maintain cognitive health and delay or prevent the progression to AD (Abdulrab & Heun, 2008). Currently, the use of electroencephalographic (EEG) measures is promising because they provide direct, non-invasive, and relatively inexpensive assessments of brain neuronal activity (Babiloni et al., 2021; Biasiucci et al., 2019). EEG measures the electrical field obtained from the summations at scalp electrodes of the oscillatory component generated by postsynaptic potentials in pyramidal cortical neurons (Babiloni et al., 2021; Biasiucci et al., 2019). Additionally, EEG offers a time resolution of ≤ 1 ms, enabling it to provide neurophysiological data that cannot be obtained from other neuroimaging techniques (Biasiucci et al., 2019). In recent years, resting state EEG (rsEEG) measurements have emerged as a reliable tool for quantifying brain neurophysiological dysfunction. rsEEG is typically recorded from subjects during brief periods under both eyes-open and eyes-closed conditions, capturing spontaneous brain activity during periods of cognitive disengagement. This method captures neural activity independent from the cognitive task, making it resilient to factors such as fatigue, movements, anxiety, or meta-learning, as Babiloni et al. (2021) highlighted. The most com-

mon way to characterize rsEEG is by breaking down oscillatory signals into the spectral power of a frequency band. Spectral power is proportional to the rate of energy change at a specific frequency or frequency band (Ward, 2003), and it is involved in various cognitive processes. Alpha power is linked to heightened attention and task engagement, whereas theta power is associated with memory encoding and retrieval. Gamma-theta interactions may support short-term memory, and gamma oscillations are linked to processing attended stimuli (Ward, 2003). The predominant approach in the literature focuses on the analysis of broad frequency bands in the EEG power spectrum, from slow bands, delta (δ: 0.1–<4 Hz) and theta (θ:4–<8 Hz), to faster bands, alpha (α: 8–13 Hz), beta (β:14–30 Hz), and gamma (γ: >30–80 H) (Babiloni, et al., 2020). In normal aging, there may be a gradual slowing of EEG rhythms and subtle changes in neural oscillations across different frequency bands (Babiloni et al., 2006; Barry & De Blasio, 2017). However, in pathological aging, as in AD, these alterations are often more pronounced and disruptive, with significant changes in frequency bands (Lejko et al., 2020). Over the years, a substantial body of research has amassed compelling evidence pointing to a progressive alteration in brain electrical activity in neurodegenerative disorders such as MCI or AD. This alteration is characterized by an increase in theta power and a decrease in beta power, followed in subsequent stages by a decrease in alpha power and an increase in delta power (Gouw et al., 2017; Jeong et al., 2021; Prichep et al., 2006). Although there has been extensive recent research on the use of frequency bands in individuals with SCD to investigate and understand changes in brain activity associated with early MCI and the risk of progression to neurodegenerative diseases such as AD, the findings have not yet been fully integrated. This is probably due to the heterogeneity of the methodological approaches and criteria used to characterize SCD. Four studies documented alterations in the rsEEG delta frequency band in people with SCD. Sibilano et al. (2023), Iliadou et al. (2021), and Gouw et al. (2017) conducted a thorough investigation of frequency band changes by comparing individuals with SCD to those with MCI. Additionally, Sibiliano included a group of healthy controls in their

analysis. In Iliadou's study, the MCI group exhibited a significant increase in overall delta power compared to the SCD group, highlighting distinctive spectral alterations. Moreover, in their spectral analysis comparing SCD and MCI, Sibilano et al. (2023) identified higher spectral power in the delta band that was associated with the clinical progression from SCD to MCI. In a longitudinal study exploring the gradual progression towards AD, Gouw et al. (2017) identified alterations in spectral power in individuals with SCD who eventually advanced to MCI. The study reported heightened delta activity throughout the cortex. Finally, Jeong et al. (2021) reported increased delta activity in the frontal cortex in individuals with SCD compared to healthy controls. Six studies reported an abnormal rsEEG of theta power in people with SCD compared to MCI and healthy control groups. Three studies specifically explored rsEEG in individuals with SCD along the MCI continuum. Iliadou et al. (2021) observed lower spectral power in theta in SCD compared to individuals with MCI. Sibilano et al. (2023) utilized rsEEG to discriminate between SCD and MCI, identifying the delta and theta bands as discriminating the most between SCD and MCI. We identified six articles that reported alterations in alpha power in individuals with SCD compared to those with MCI and healthy control groups. Iliadou et al. (2021) observed a decrease in alpha spectral power in individuals with SCD compared to those with MCI. Individuals with SCD exhibited decreased alpha1, compared to the healthy control group, and increased alpha2 in the left temporal, central, and parietal cortex compared to those with MCI, as reported in the study by Mazzon et al. (2018). Additionally, a decrease in spectral power across the entire alpha band was noted in individuals with SCD who progressed to MCI in the study conducted by Gouw et al. (2017). When comparing people with SCD to the healthy control group, Jeong et al. (2021) found a decrease in alpha1, specifically in the occipital regions, whereas Prichep et al. (2006) observed a decrease in the alpha band. In contrast, Alexander et al. (2006) reported an increase, rather than a decrease, in the alpha band in individuals with SCD compared to the healthy control group. In the case of the beta band, three studies reported noteworthy

changes. Iliadou et al. (2021) observed a decrease in beta spectral power in individuals with SCD compared to those with MCI. Additionally, Mazzon et al. (2018) identified a decrease in beta power in the left frontal regions when comparing the SCD group to the MCI group. In the study by Alexander et al. (2006), which compared individuals with SCD to a healthy control group, increased beta power was observed in the central, parietal, and frontal regions in individuals with SCD.

None of the studies included in this review reported significant changes in the groups in the gamma frequency band.

Overall, individuals with SCD exhibited a pronounced increase in theta spectral power compared to healthy controls, whereas those with MCI showed a further increment compared to individuals with SCD, indicating alterations across the MCI continuum. Similar alterations across the MCI continuum were observed in alpha spectral power. Specifically, individuals with SCD displayed decreased alpha spectral power compared to healthy controls, but higher levels than in individuals with MCI. However, this trend is inconsistent because two studies reported increases, rather than decreases, in this band in both SCD and MCI. Additionally, findings for the delta and beta frequency bands are rather inconclusive, given that half of the studies did not identify significant effects within these bands. In the studies that did observe effects, an increase in delta was noted in individuals with SCD compared to healthy controls, as well as in individuals with MCI compared to individuals with SCD. The findings related to beta band activity are also unclear. Whereas one study reported an increase in beta band activity when comparing SCD and healthy controls, an examination of the MCI continuum reveals a tendency towards decreased beta band activity in individuals with MCI compared to those with SCD. Despite this overarching trend, variability in the studies' results was evident, probably stemming from variations in measurement and analysis methodologies and discrepancies in the diagnostic criteria used to define SCD.

Overall, most of the consulted studies reported an alteration in the EEG associated with SCD, as evidenced by an increase in

spectral power in the low-frequency bands and a decrease in spectral power in the high-frequency bands.

Most of the analyzed studies reported abnormal rsEEG activity in individuals with SCD compared to healthy control groups. Furthermore, studies contrasting SCD and MCI reveal that rsEEG abnormalities persist and intensify as cognitive decline progresses. Our review revealed the following evidence: 1) increased delta power in individuals with SCD compared to both healthy controls and people with MCI, although these findings were not consistently reported across all the studies; 2) a progressive increase in theta frequency bands in individuals with SCD compared to healthy controls, which intensified when comparing MCI to SCD; 3) a decrease in the alpha frequency band in individuals with SCD compared to healthy controls, with this decrease being more pronounced in those diagnosed with MCI compared to SCD. However, this trend was not observed in two studies that compared individuals with SCD to healthy controls and individuals with MCI, respectively. In these studies, unexpected increases, rather than decreases, in alpha and beta frequency band spectral power were reported in the SCD groups compared to healthy controls, and in the MCI groups compared to the SCD groups; 4) a decrease in beta band activity was only noted in studies that compared MCI with SCD. Conversely, the other two studies reported increases in the frequency of this band.

What is the physiological significance of the changes observed in the spectral power of delta, theta, alpha, and beta rhythms in individuals with SCD? The alterations in the high and low components of the delta rhythms, indicative of a healthy brain, are thought to be influenced by inhibiting oscillators within the reticulo-thalamic (7–14 Hz), thalamo-cortical (1–4 Hz), and intracortical (<1 Hz) neural circuits (Steriade, 2006). Moreover, it has been proposed that thalamo-cortical circuits play a role in the generation and modulation of theta rhythms. Thus, it is plausible to hypothesize that diminished activation of neurons, possibly due to acetylcholine reduction or synaptic damage, can impact inhibitory and excitatory cortical feedback interactions that are crucial for generating cortical rsEEG rhythms. This disruption may influence the

regulation of overall brain arousal, the balance of cortical inhibition/excitation, and vigilance, potentially resulting in a decrease in spectral power across the delta and theta bands. The crucial implication of cholinergic deficiency is further corroborated by EEG investigations using scopolamine, a non-selective antagonist of muscarinic receptors that hinders stimulation of postsynaptic receptors. Following scopolamine administration, healthy subjects show increased delta and theta power, along with decreased alpha and beta power (Ebert et al., 2001). urthermore, beta rhythms may be associated with the regulation of thalamocortical flow, encompassing commands, images, and motor plans through the basal ganglia and motor thalamus (Oswal et al., 2013). As mentioned previously, Alexander et al. (2006) and Iliadou et al. (2021) found distinct alpha and beta rhythm patterns from those found in other studies reviewed. These authors suggested that the psychophysiological changes observed in the SCD in their study may reflect an initial compensatory process in response to early cognitive impairment.

Notably, theta and gamma bands are recognized for their involvement in memory (Klimesch, 1999; Nyhus & Curran, 2010), whereas delta bands play a role in maintaining focused attention (Harmony, 2013). The alpha band has been associated with attention and memory processes (Klimesch, 1999, 2012). Although the role of beta oscillations in the cognitive process has been explored less, some evidence suggests that they are related to the state of attention (Güntekin et al., 2013). hird, because SCD often precedes more severe conditions, such as MCI or AD, analyzing the rsEEG may be crucial in identifying early markers of changes in brain activity, making earlier interventions possible.

However, measuring brain activity at rest has limitations. One of these limitations is continuous cognitive engagement during rest, including processes such as mind wandering and interoception. Moreover, without specific instructions, there is no control over what individuals are actually doing while they are at rest. Addi-

tionally, resting-state brain activity may not entirely reflect the cognitive and functional capacity during active situations or specific tasks.

The incorporation of spectral power measures across frequency bands in rsEEG as enriching neurophysiological biomarkers in the assessment and monitoring of SCD should be based on an initial demonstration that these measures are reliable, consistent, and sensitive.

All the studies under review indicated similar recording settings, and they were conducted in quiet rooms with low light and reduced noise levels while participants were in a comfortable position.

The most commonly used resting condition was eyes closed, which tests the neurophysiological mechanisms involved in maintaining constant low vigilance with the eyes closed (for 3 to 5 min) and moderate vigilance with the eyes open (for 3 to 5 min) (Babiloni et al., 2020).

Addressing these limitations is crucial for the progression of EEG research and its effective application in the study of SCD.

Although the rsEEG frequency bands are universally identified using Greek letters (e.g., delta, theta, alpha, beta, and gamma), different classifications of their frequency limits were observed in the reviewed studies. To address this lack of consensus, on the one hand, the International Pharmaco-EEG Society recommends the following frequency limits: delta (1.5-<6), theta (6-<8.5), alpha1 (8.5-<10.5), alpha2 (10.5-<12.5), beta1 (12.5-<18.5), beta2 (18.5-<21), beta3 (21.0-<30), gamma (30-<40). For gamma, they empirically choose the following ranges: gamma1 (30-<65), gamma2 (65-<90), and gamma3 (90->135) (Jobert et al., 2012). On the other hand, the International Federation of Clinical Neurophysiology (IFCN) proposes another classification, which is the one most commonly used in clinical EEG (Kane et al., 2017): delta (0.1-<4), theta (4-<8), alpha (8 13), beta (14 30), and gamma (>30–80).

In understanding the distribution of electrical activity across different frequency bands, the reviewed studies have presented analyses of power density (the amount of electrical energy in a specific frequency band per unit of frequency), absolute power (the total amount of elec-

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trical energy in a specific frequency band, disregarding other frequencies), and relative power (the proportion of power in a specific frequency band relative to the total power across all frequencies) (Babiloni et al., 2020; Singh & Krishnan, 2023). The choice of each of these measures to assess brain electrical activity depends on the objectives or the specific analyses being conducted. However, when examining the resting state, it would be advisable to employ relative power, given that it provides information about the proportional distribution of electrical activity in different frequency bands in relation to the total EEG activity. This information can yield valuable insights into potential changes in resting-state brain activity in individuals with SCD.

In conclusion, this systematic review reveals a general tendency toward EEG alterations in the context of SCD. However, specific results indicate noteworthy discrepancies that highlight significant variability. This complexity underscores the need for a thorough exploration of the underlying factors that contribute to divergence in the results of frequency bands, even within the context of the overall EEG alteration observed. Despite the promising potential of analyzing resting-state frequency bands, further refinement is required for their implementation as early biomarkers of brain activity changes or as complementary information in the neuropsychological evaluation of SCD cases. Additionally, this review exclusively reports group-level differences. Further research is needed to better understand how these findings would translate into an individual diagnostic context. Adherence to the latest guidelines, such as those of the IFCN (Babiloni et al., 2020) or the American Clinical Neurophysiology Society (ACNS) (Sinha et al., 2016), is recommended for proper implementation. Constant and uniform research on these frequency bands, guided by these established protocols, can facilitate the identification of consistent patterns and provide a robust foundation for early diagnosis and the development of more effective treatment strategies. Ultimately, it is crucial to emphasize the importance of adhering to the SCD-I criteria in order to ensure the comparability and reliability of the results across various studies.

Commented [JH17]: discussion

Farina et al., 2020: https://doi.org/10.1016/j.neuroimage.2020.116795

Among the most promising EEG markers are reduced alpha power and increased theta power, as well as increased theta band functional connectivity (Cassani et al., 2017; Hatz et al., 2015; Musaeus et al., 2018). EEG ratios, such as theta/gamma and high alpha/low alpha, have also been suggested as promising markers (Moretti et al., 2012, 2009).

2.4.1. EEG frequency band and power ratio calculations

Spectral analysis of absolute and relative power across the 30 scalp electrodes was conducted using the multitaper spectral estimation with Hann taper and 0.5 Hz frequency resolution. Power values were calculated separately for EEG recorded with participants' eyes open and eyes closed to explore potential differences between these two arousal states (Barry and De Blasio, 2017). The following seven frequency bands were included: delta (1–4 Hz), theta (4–8 Hz), alpha1 (8–10 Hz), alpha2 (10–13 Hz), beta1 (13–18 Hz), beta2 (18–30 Hz) and gamma (30–45 Hz), based on previous literature (Cassani et al., 2018). The mean number of epochs included in the eyes open condition was 112 (6.36). The mean number of epochs included in the eyes closed condition was 112.5 (4.95). Absolute power values were converted to logarithm base 10 to produce values in dB. For relative power, the values were expressed as a percentage of power in a frequency band divided by the total power across all seven frequency bands. Three additional power metrics were also calculated for the EO condition, based on previous literature (Moretti et al., 2009, 2012; Musaeus et al., 2018). These were: theta/gamma power ratio, alpha2/alpha1 power ratio and global theta power. Theta/gamma ratios were calculated by dividing the absolute power in the theta band with the absolute power in the gamma band to create a ratio for each electrode. Alpha2/alpha1 ratios were calculated in the same way. Global theta was calculated by averaging absolute theta power for all channels. Absolute and relative power were calculated separately for EO and EC conditions.

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2.4.2. EEG weighted phase lag index calculation

Data were epoched into 5-s segments and then filtered in delta (1–4 Hz), theta (4–8 Hz), alpha1 (8–10 Hz), alpha2 (10–13 Hz), beta1 (13–18 Hz), beta2 (18–30 Hz) and gamma (30–45 Hz) bands using a Butterworth filter. Participants with fewer than 21 epochs, corresponding to less than

50% of the individual's data, were excluded from further analyses: 2 from the HC group during EC condition; and 3 from the HC group, 1 from the aMCI group and 1 from the AD group during EO condition. This resulted in 63 HC, 64 aMCI and 60 AD participants in the EC analysis, and 62 HC, 63 aMCI and 59 AD participants in the EO analysis.

The weighted phase lag index (WPLI) between all possible channel pairs (from 30 channels) was calculated (435 pairs). The WPLI provides a measure of the lead/lag (i.e., positive/negative) phase difference between two signals. Phase differences close to the zero-phase lag are weighted with a lower value to diminish the contribution of volume conduction (Vinck et al., 2011). The WPLI per frequency band was calculated per epoch and then averaged across epochs (cf. Kiiski et al., 2020).

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Similar to AD models, the best features for distinguishing aMCI from healthy ageing were increased theta and delta power in left temporo-parietal electrodes, while the best predictor of control status was increased frontal beta2 power. Theta and beta1 power also discriminated aMCI from AD participants; that is, higher theta in left frontal and right parietal electrodes was associated with AD status, and higher temporo-parietal beta1 power was associated with aMCI status.

The EEG markers highlighted here are consistent with the neurophysiological changes typically associated with AD; specifically, increases in slow wave activity (i.e., delta and theta) and decreases in fast wave activity (i.e., alpha and beta), which are thought to reflect loss of cholinergic innervations as the disease progresses (Cassani et al., 2018; Musaeus et al., 2018). Theta power was the best overall predictor of patient status, in line with the suggestion that increased theta is one of the first changes to occur in AD (Musaeus et al., 2018). Differences in theta were most pronounced at temporo-parietal sites, where connectivity between electrodes was increased in AD and aMCI. AD participants were distinguished from aMCI participants by increased theta in frontal and parietal electrodes, likely reflecting widespread changes that occur at advanced stages (Fraga et al., 2013). Higher delta power in left temporo-parietal areas was also indicative of patient status, though to a

lesser degree, consistent with evidence that delta changes occur later (Roh et al., 2011). As expected, healthy ageing was associated with
higher alpha power, both in amplitude (temporo-parietal areas) and
connectivity (with frontal electrodes), and beta power, which was
increased in controls relative to patients, and in aMCI relative to AD.

Fröhlich, Kutz, Müller & Claudia Voelcker-Rehagen (2021):
https://doi.org/10.3389/fnagi.2021.675689

Compared with healthy older adults, patients with Alzheimer's disease show decreased alpha and beta power as well as increased delta and theta power during resting state electroencephalography (rsEEG). Findings for mild cognitive impairment (MCI), a stage of increased risk of conversion to dementia, are less conclusive. Results indicate no rsEEG power differences between healthy individuals and those with MCI.

Also some things about power analysis and also topography, might be relevant for methods, but maybe not

In this study, the synchronized activity at rest while eyes are open and closed in the classical broad bands delta, theta, alpha, and beta was compared between cognitively healthy OA and individuals with MCI of the same age. The sample included OA, 80 years or older, which are often not enough represented in studies on early detection of dementia. Groups were compared with respect to mean absolute power, relative power, and reactivity to eyes opening separately in each band. No significant differences between any of the groups of different cognitive status (CHI, pMCI, naMCI, and aMCI) were detected. Overall, specific topographical patterns were present, which will be compared with results from other age groups later. In addition, EEG reactivity was also present in each of the four frequency bands with overall greater power during EC compared with EO and a few focal increases in the beta band. The topography of reactivity for the most part related to the topography found in the EC condition.

Thus, the hypotheses that MCI is characterized by lower alpha and beta power as well as stronger delta and theta power during EC could not be confirmed in our sample. This is not in complete

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agreement with prior findings of changes in the rsEEG in patients with MCI. For the rest with EC, it was shown that alpha and beta powers were reduced and theta and delta powers were either elevated or reduced in MCI compared with healthy OA (Koenig et al., 2005; Babiloni et al., 2006b, 2010; Kwak, 2006; Ya et al., 2015). In fact, when specifying former studies, each study only showed some of the listed changes, but the overlap between results was often not great even though similar parameters were studied.

Caravaglios et al., 2023: https://doi.org/10.1177/15500594221110036

Amnesic-MCI had: i) increased delta/beta activity in the superior frontal gyrus and decreased alpha1 activity in the paracentral lobule (ie, default mode network); ii) greater delta/theta/alpha/beta in the superior frontal gyrus (i.e, attention network); iii) lower alpha in the left superior parietal lobe, as well as a lower delta/theta and beta, respectively in post-central, and in superior frontal gyrus(ie, attention network).

- ➔ Not that much about power, but other things

Özbek, Fide & Yener, 2021: https://doi.org/10.1016/j.clinph.2021.05.012

Compared to healthy controls individuals with early-onset Alzheimer's disease (EOAD) showed an increase in slow frequency bands and a decrease in fast frequency bands. Frontal alpha/theta power ratio is the best discriminating value between EOAD and young HC with the sensitivity and specificity greater than 80% with area under the curve (AUC) 0.881.

This study is the first to report that resting-state EEG power can be a promising marker for diagnostic accuracy between EOAD and healthy controls.

dditionally, our study showed that resting-state alpha/theta power ratio can accurately discriminate between individuals with EOAD and healthy controls.

Babiloni et al. (2011): https://doi.org/10.3233/JAD-2011-0051

Modern neurophysiological techniques including digital electroencephalography (EEG) allow non-invasive analysis of cortico-cortical connectivity and

neuronal synchronization of firing, and coherence of brain rhythmic oscillations at various frequencies.

Several decades ago, electroencephalogram (EEG) was introduced to allow a direct, on-line view of human “brain at work” in physiological and pathological conditions [1]. Indeed, EEG is a direct correlate of brain function, and it reflects CNS dysfunction including the characterization of significant deviations from the ‘natural’ aging such as Alzheimer’s disease (AD) and other dementias [2]. Starting from the 1970 s, EEG was progressively supplanted for clinical applications on diagnosis of abnormal brain aging.

It should be noted that high temporal resolution of EEG is crucial for the study of an emerging property of brain activity, namely the spontaneous and event-related oscillatory activity at different frequencies ranging at 1–4 Hz (delta), 4–8 Hz (theta), 8–13 Hz (alpha), 13–30 Hz (beta), and >30 Hz (gamma). Each of these frequencies conveys peculiar physiological information on brain functional state during sleep and wake periods.

Recently, greater attention has been focused on the application of quantitative EEG (qEEG) and/or event-related potentials (ERPs) as suitable clinical markers of early stage of disease or its progression [4–6]. It has been reported that a positive ERP peaking 600 ms after the zerotime of stimuli to be encoded (P600) was reduced in patients with AD and mild cognitive impairment (MCI), particularly in those MCI patients who subsequently converted to AD [7, 8]. Furthermore, a positive ERP peaking 300 ms after the zerotime of oddball stimuli (P300) was reduced in amplitude in AD patients [5, 9], even during its early stages [10].

A certain consensus is reached on the fol-

lowing physiological model. During slow-wave sleep, corticofugal slow oscillations (<1 Hz) are effective in grouping thalamic-generated delta rhythms (1–4 Hz) and spindling activity (7–14 Hz) [14]. In this condition, delta rhythms would dominate EEG oscillations, while alpha rhythms (about 8–12 Hz) would be suppressed. In the case of endogenous or exogenous arousing stimuli, spindles, high- and low-frequency components of the delta rhythms are blocked by the inhibition of reticulo-thalamic (7–14 Hz), thalamocortical (1–4 Hz), and intracortical (<1 Hz) oscillators. These rhythms are replaced by fast oscillations in the range of beta (14–30 Hz) and gamma frequencies (>30 Hz) [14, 15]. In the wake resting state condition, alpha rhythms would dominate the human EEG oscillatory activity, while delta rhythms would be quite low in amplitude in physiological conditions [16–18].

Resting state eyes closed cortical EEG rhythms typically change across physiological aging, with gradual modifications in profile and magnitude of the spectra power spectrum. It was observed a marked amplitude decrease of alpha (8–13 Hz) and a global “slowing” of the background EEG, which increases in power and spatial distribution in the slower delta (1–4 Hz) and theta (4–8 Hz) rhythms [58–61]. A recent study in a large sample of healthy subjects (N = 215, 18–85 years) confirmed an age-dependent power decrement of posterior low-frequency alpha (alpha 1; 8–10.5 Hz) and delta rhythms [62].

When compared to the resting state EEG rhythms of healthy normal elderly (Nold) subjects, AD patients showed an amplitude increase of widespread delta and theta sources and an amplitude decrease of

posterior alpha (8–13 Hz) and/or beta (13–30 Hz) sources [45, 55, 56, 76–78]. The observation of these abnormalities of the EEG rhythms could allow discrimination among different dementia diagnoses, for instance a marked decline of posterior slow-frequency alpha power shows peculiar features in mild AD subjects when compared to cerebrovascular dementia, fronto-temporal dementia and normal elderly subjects with similar cognitive impairment. Furthermore, pathological increased amplitude of the theta sources characterized cerebro-vascular dementia patients [56].

Despite the evidence of abnormal cortical rhythms in MCI and AD subjects, EEG analysis alone is unable to allow a diagnosis of disease.

The hypothesis of some strict relationships between brain activity in MCI and AD subjects implies the prediction of similar features of resting state EEG rhythm in MCI and AD subjects as a function of genetic risk factors.

The present review highlights the use of modern EEG techniques that report assessment of physiological and pathological brain aging. Application of these techniques allows the quantification of the power and functional coupling of resting state eyes closed EEG rhythms at scalp electrodes and mathematical cortical sources. The results reviewed in the present article suggest that these quantitative indexes of resting state EEG rhythms might reflect neurodegenerative processes along preclinical and clinical stages of AD, at least at group level.

Liu, Wang, Xin, Wang, Jiang & Meng, 2024: https://doi.org/10.1186/s12877-024-05041-x

Cognitive function refers to the ability to select, process, store, and retrieve information, as well as apply this information to guide behavior [2]. Cognitive impairment refers

to varying degrees of damage to cognitive function caused by various reasons, with an incidence rate that generally reaches 33.59% and increases with age [3].

Mild cognitive impairment (MCI) is considered a transitional stage between normal aging of the brain and dementia, and it has become a significant global public health concern [4]. Electroencephalography (EEG) is an external reflection of the electrical activity of brain neurons, capable of indicating the physiological and pathological states of the brain. As a non-invasive neurophysiological detection method, EEG has advantages such as simplicity, convenience, non-invasiveness, high temporal resolution, and good spatial distribution [5, 6]. EEG can be used as an auxiliary diagnostic tool for cognitive impairment, reflecting not only pathological brain function abnormalities but also abnormalities before reaching pathological diagnostic criteria [7]. Studies have found that EEG signals in older adults with cognitive impairment exhibit specific characteristics, such as a basic rhythm slowdown, manifested by an increase in low-frequency band (delta, theta) power and a decrease in high-frequency band (alpha, beta) power [8, 9]. Slowing of alpha power may be an early sensitive indicator of the brain transitioning from normal physiological function to aging or its pathological state [10], while increased theta power may have a good predictive effect on cognitive decline [11].

In individuals with cognitive impairment, acute exercise effects include decreased delta and theta power and increased beta1 power [18, 20]; longterm exercise appears to result in decreased delta [18, 20, 21] and theta rhythm power [19, 21], and increased alpha and beta rhythm power [18, 20, 22].

Montreal cognitive assessment

Widely used for assessing cognitive function in the older

adults, MoCA consists of 8 aspects: visuospatial/executive function, naming, memory, attention, language fluency, abstraction, delayed recall, and orientation. The total score is 30 points, with higher scores indicating better cognitive function [23]. MoCA scores above or equal to 26 are considered normal, scores between 18 and 26 indicate mild cognitive impairment, scores between 10 and 17 indicate moderate impairment, and scores below 10 indicate severe impairment. To account for the impact of education duration, 1 point is added to the total score for education levels of 12 years or less; if the total score exceeds 30 after adding, no additional points are given. The retest reliability of MoCA used in this study is 0.857 [23].

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The left frontal area, located at the front of the brain, is associated with advanced cognitive functions, decision-making, problem-solving, and personality traits. It plays a role in executive functions, emotional regulation, and modulation of social behavior.

The severity of cognitive impairment is positively correlated with increased theta activity, and an increase in theta waves in EEG serves as a good predictor of cognitive decline [36].

As the activation level of the frontal lobe cortex increases, theta wave power decreases, leading to improved cognitive function. A decrease in theta wave power was observed after both single and prolonged exercise [17].

Finnigan & Robertson, 2011: https://doi.org/10.1111/j.1469-8986.2010.01173.x

We address the degree to which resting EEG bandpower is associated with cognitive performance in 73 healthy older adults (aged 56–70). Relative theta (4–6.5 Hz) power was significantly correlated with immediate and delayed verbal recall, attention, and executive function measures. Relative delta and alpha power and peak alpha frequency did not correlate with any cognitive measures. These data indicate that high resting theta power in healthy

older adults is associated with better cognitive function and may be a marker of healthy neurocognitive aging.

In summary, these outcomes indicate that high resting-state theta power in older adults is associated with relatively greater cognitive impairment; whereby such impairment either may already exist, be developing, and/or may (be predestined to) subsequently manifest or increase (this is from introduction).

Across 73 healthy older adults, relative resting theta power was significantly correlated with performance on numerous cognitive tests, which assess verbal memory, attention, or executive function.

Lejko, Larabi, Herrmann & Aleman, 2020: https://doi.org/10.3233/JAD-200962

We have therefore decided to take the first step by focusing on the alpha band for three main reasons. First, alpha is the most prominent rhythm during quiet wakefulness [33]. Second, it has large amplitudes ranging from 10 to 50 V [34]. This is in contrast to theta, beta, and gamma waves, which have smaller amplitudes at rest [34–36], and can be best identified using tasks with many repetitions. This makes measuring alpha activity in research and clinical practice highly feasible, as it does not require people with cognitive decline to perform challenging and tiresome tasks.

Lastly, lower power and synchronization of alpha oscillations have consistently been associated with neurodegenerative dementias, especially AD [29, 37–39]. These decreases were found to correlate with lower cognitive scores [40, 41], higher atrophy of the hippocampus [42] and higher amyloid burden [43], as well as with genetic susceptibility for AD [44, 45]. Though alpha activity in other neurodegenerative dementias is less well-researched, there is evidence of lower alpha power in people with demen-

tia due to Lewy body disorders [46–49]. Alpha power and synchronization are therefore an important part of the changes in the EEG spectrum associated with cognitive decline.

Musaeus et al., 2018: https://doi.org /10.3233/JAD-180300

Clinical diagnostic criteria for dementia disorders are based mainly on findings from simple assessments. However, most of the clinical criteria are not very helpful in the very early phase of a dementia disorder [1]. The use of magnetic resonance imaging (MRI) techniques, positron emission tomography (PET), and examination of the cerebrospinal fluid (CSF) have proven helpful in diagnosing Alzheimer's disease (AD) in a very early phase [2–6], but these methods are mainly available in academic centers, and are either expensive, require special expertise, or are invasive. Electroencephalography (EEG) is non-invasive, widely available electrophysiological monitoring method to record electrical activity of the brain and has potential also as a diagnostic marker. One approach to analyze the EEG is by using quantitative EEG (qEEG), which is the numerical analysis of the EEG data. One type of qEEG markers is power or squared amplitude of EEG rhythmic signal, which previously has been shown as a promising marker of disease state in patients with AD [7–10].

For any potential classifier, it is essential to consider its relationship with pathophysiological changes. In AD, studies have reported an increase in the slower frequency bands (delta and theta) and a decrease in the faster frequency bands (alpha and beta) compared with HC [8, 9, 14–23] when applying qEEG power. However, the earliest changes in AD have been described as increased theta with a decrease

beta and at the later stages a decrease in alpha power and an increase in delta power [14, 15]. However, the literature in this field is limited.

For patients with mild cognitive impairment (MCI), which is a group that has a high risk of developing AD [24], studies have found that these patients share similar qEEG characteristics as AD [16, 25].

Working memory has been associated with the theta, alpha, and beta bands [14–16] but most studies have investigated the relation to the Folstein score [15], which is a broad score. A newer study has showed that word list recall and word list recognition were correlated to the theta, alpha, and beta2 (22–30 Hz) bands [16], which may due to more advanced disease.

Demographics

For a full description of the demographics and comparisons between groups for AD, MCI, and HC see Table 1.

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In the present study, we found that increased theta power was the most pronounced change in patients with dementia due to AD at the time of diagnosis and this increase may be associated with hippocampal function and the decreases found in the default mode network. Furthermore, the relative theta band was significantly correlated to working memory measures and showed the strongest correlation to total tau, which supports our initial hypothesis. In addition, the beta1 showed more pronounced changes and was better correlated to neuropsychological measures than the broad beta band, which should be considered in future studies. Lastly, we found that the best classification rate for AD and HC was for relative power with

eyes closed with an accuracy of 72.9%. The qEEG power can be a helpful tool when more advanced methods are not available. In addition, future studies may reveal if relative power will be able to show progression of the disease.

Kim et al., 2023: **https://doi.org/10.3389/fpsyt.2023.1231861**

The results revealed no significant difference in EEG spectral power between the HC and MCI groups. owever, we observed significant changes in brain complexity and networks in individuals with MCI compared with HC. Patients with MCI exhibited lower complexity in the middle temporal lobe, lower global efficiency in theta and alpha bands, higher local efficiency in the beta band, lower nodal efficiency in the frontal theta band, and less small-world network topology compared to the HC group. These observed differences may be related to underlying neuropathological alterations associated with MCI progression. The findings highlight the potential of network analysis as a promising tool for the diagnosis of MCI.

Mild cognitive impairment (MCI) is a condition characterized by a noticeable decline in cognitive abilities that goes beyond typical age-related changes but does not meet the criteria for dementia owing to its less severe nature (7, 16, 17). Patients with MCI often have an increased risk of developing AD, and thus detecting MCI is crucial to help delay or even prevent its progression to AD (17–19). Magnetic resonance imaging (MRI) and positron emission tomography are widely used imaging techniques for diagnosing MCI and AD. These methods provide detailed information about the brain's anatomical and network features; however, their usage is restricted owing to the high cost of facilities and the need for specialized expertise. Therefore, electroencephalography (EEG) has increasingly been used to identify biomarkers for MCI diagnosis. EEG is a non-invasive and cost-effective technique that measures postsynaptic potentials of cortical neurons firing synchronously in the brain (20–23). Its relatively safe and quick application makes it particularly suitable for conducting repeated measurements in high-risk older individuals. Several studies have validated the

feasibility and reliability of resting-state EEG (rsEEG) in identifying cognitive impairments caused by AD or MCI (24).

EEG spectral power captures the amplitude of oscillations in each frequency band and can be used as a potential biomarker to differentiate AD from normal aging (25–28). In spectral analysis, it has been predominantly observed that the dementia stages of AD are associated with slowing oscillations caused by increasing low-frequency and decreasing high-frequency band power (24). However, other studies found no or minimal differences between the MCI and healthy control (HC) groups (29–31), suggesting that the neurophysiological changes underlying MCI may not always be apparent in spectral power owing to the complex and heterogeneous conditions of MCI. Therefore, it is important to combine multiple biomarkers such as complexity measures, functional connectivity, and graph-based network analyses, to enhance MCI detection.

3. Results

3.1. Power spectral properties

Topographic plots were computed for the delta (0.1–4 Hz), theta (4-8 Hz), alpha (8–12 Hz), beta (12–30 Hz), and gamma (30–45 Hz) frequency bands in the HC and MCI groups. In both groups, delta oscillations were dominant in the frontal area (Fp1 and Fp2) (Figure 2A). Theta and alpha oscillations were prominent in occipital regions (O1 and O2) in two groups (Figures 2B, C). Beta and gamma activities remained negligible across all brain regions (Figures 2D, E). However, no significant differences were found between the HC and MCI groups in any of the frequency bands and channels after FDR correction.

Our findings indicated that the power spectrum analysis did not yield any significant differences between the HC and MCI groups. However, when analyzing the multiscale SE, we observed that the MCI group exhibited lower complexity. In addition, the MCI group demonstrated higher wPLI values than the HC group. Further examination using graph theory

analysis revealed that the MCI group predominantly displayed lower global efficiency in the theta band and higher local efficiency in the gamma band relative to the HC group. Moreover, nodal efficiency was reduced in the frontal region of the MCI group. Finally, in the small-world analysis, the MCI group exhibited a lower small-world coefficient when compared to the HC group. In the power spectral analysis, no significant differences were found between the HC and MCI groups in any frequency band (delta, theta, alpha, beta, or gamma). This suggests that there were no significant differences in the overall power of the EEG signals between the two groups. These results are consistent with those of the recent studies suggesting that PSD had a limited ability to distinguish between HC and MCI groups (30, 77). However, some prior findings have revealed that MCI can be characterized by lower alpha and beta power as well as stronger delta and theta power (26). This contradiction may be because the neurophysiological changes associated with MCI may not always be apparent in spectral power, suggesting that the power spectral analysis is relatively insensitive to network changes resulting from MCI progression.

Our findings suggest that alterations in functional connectivity and graph theory-based measures, particularly in the theta band associated with memory and attention processes, may serve as important clinical biomarkers for detecting and monitoring cognitive decline in individuals with MCI. Small sample size.

Engedal et al., 2020: https://doi.org/10.1159/000508392

ubjective cognitive decline (SCD), a stage of subjectively experienced impaired cognition, which is not supported by an infor mant or by neuropsychological testing, and mild cog nitive impairment (MCI), which is supported by an in formant and indepth testing. In both stages, the in dividuals are able to perform personal as well as instrumental activities of daily life, but they are at high

risk of developing dementia [5–8].

Electroencephalography (EEG), on the other hand, is a lowcost, noninvasive, simple examination that can be used in most clinics and even in primary care settings, especially if an automatic reading method is applied. In the last decade, studies were published which examined the power of EEG to detect those persons with MCI that will convert to dementia [26–30].

Zheng-yan, 2005: https://doi.org/10.1631/jzus.2005.B1213

Dierks et al.(1991)'s study of the correlation between EEG power in alpha and beta bands at rest and the degree of dementia in AD patients, indicated that topographical EEG power changes may reflect early signs of cortical atrophy and/or compensatory cortical reorganization early during the course of the disease. The present work's experimental results shown in Tables 1 and 2, indicated that the EEG power in theta, alpha-1, alpha-2 and beta-1 bands of MCI patients were significantly higher than those of the controls under experimental conditions of at rest and during working memory task. This finding suggests that MCI patients may be associated with early signs of cortical atrophy and/or compensatory cortical reorganization. As seen in Table 3, MCI group had significantly higher values of EEG power in bilateral parietal (P3, P4) and temporal (T5, T6) lobes in alpha-1 and alpha-2 bands during working memory compared to normal control. The temporal lobe, hippocampus and other related cortexes play an important role in cholinergic activity in the central nerve centre; parietal lobe is responsible for collating all information into an entire perception. Both lobes are physical bases in cognition function. Recent neuroimage studies have also provided experimental evidences that the parietal

lobes are more sensitive during cognitive performance (Xie et al., 2003).

It is known that cognitive performance is supported by a network composed by brain cortical regions (Hogan et al., 2003), therefore, MCI may suffer localized damage and connectional disturbance of cortical regions. The present study shows that compared to the controls, MCI patient had significantly higher EEG coherence values during working memory, although at rest, there were no significant differences between the two groups, which suggests that MCI patients and normal controls had differences in cortical connection, and MCI had cortical connection disturbance. Moreover, MCI patients had higher compensatory connection during active cognition than that at rest.

MCI patients had significantly higher EEG power at rest and significantly higher EEG power and coherence during working memory task, which suggests that MCI may be associated with compensatory processes. Furthermore, failure of normal cortical connections probably exists in MCI patients.

Jelic et al., 2000: https://doi.org/10.1016/S0197-4580(00)00153-6

The most important finding of this study is that qEEG variables could be considered as predictors of dementia in subjects with only MCI. It is interesting that the best predictors were combined alpha and theta relative power Increase of theta power has already been reported in very early stages of the disease [27,33].There are two possible explanations for the reduced alpha power. First, susceptible individuals may have lower values of this main background EEG activity from the beginning. Another possibility is that it is replaced by increasing theta power. The second possi bility seems less likely since there was no strong correlation

between these two variables, suggesting that they yield different information about brain functions, as suggested by Leuchter et al. [22].

It is interesting that alpha power is included in the prediction model, since increased theta power has been described as the earliest change occurring during the course of the disease [27] and some authors have found recently that low beta power [11] predicted further cognitive decline in the elderly. However, a recent study performed by Claus et al. [5] showed that both relative alpha and beta powers were significant and independent predictors of mortality in patients with early AD. An earlier study found that alpha activity, absolute and relative amplitudes, provided the most sensitive indicator of differences among healthy individuals [35]. Alpha activity is the main Godground activity of the normal wakening EEG, which is genetically influenced [37].

Another potential explanation of our results could be that the use of relative power is compromised by the fact that all other bands are interrelated. An increase in, for example, theta power will also cause a decrease in relative alpha power even if there was no change in the amount of alpha absolute power. However, the main interest of this study was to find sensitive neurophysiological indices of disease prediction and progression in subjects at risk and not to draw any stronger inferences about the biological significance of different frequency bands. The separate reliability part of this study, performed as repeated measurements on healthy subjects, showed in general higher intraindividual temporal variability for absolute power values, which was especially marked for the slow frequency bands. Therefore, the use of relative power values was justified.

Commented [JH25]: discussion

In conclusion, the results of the current study support the hypothesis that among patients with MCI there is a sub-

group who develop AD. The dynamics of EEG changes distinguish the subgroup that further deteriorates, and the important predictors of further clinical deterioration are combined alpha and theta relative power and mean frequency.

Siuly et al., 2020: https://doi.org/10.1109/TNSRE.2020.3013429

(MCI) is a degenerative neurological disorder characterized by cognitive decline which is greater than expected for an individual's age, but does not necessarily interfere with daily activities [1].

There are various types of tests to investigate MCI such as Psychological tests (e.g. Mini-Mental State Examinations (MMSE)), blood tests, spinal fluid, neurological examination, and magnetic resonance imaging, positron emission tomography and Electroencephalography (EEG) [6,7, 8]. This study explores the application of EEG signal data to identify MCI patients from healthy control subjects because currently the EEG technique is the most popular as it is relatively inexpensive, non-invasive and portable. EEG signals representing the electrical activity of the brain at the time of recording; frequency and amplitude content vary according to the subject's biological state, mental state, age and disease process etc. [6,9,10].

Perez, Garrido-Chaves, Zapater-Fajarí, Pulopulos, Hidalgo & Salvador, 2022: https://doi.org/10.1016/j.ijpsycho.2022.09.006

In general, the present results confirm previous evidence showing that older people with SMCs are characterized by distinct power resting state EEG rhythms, especially at increased theta power, and a slight loss of EEG reactivity to EO. These findings suggest that neurophysiological markers of brain dysfunction may identify cognitive decline and changes before they are observed in a neuropsychological assessment. Furthermore, these changes could also help us to better understand the neurophysiological mechanisms affected by neurodegeneration.

Coban, Danziger & Storandt, 1985: https://doi.org/10.1016/0013-4694(85)91048-x

This longitudinal study of resting EEGs compared patients with senile dementia of Alzheimer type (SDAT) and
healthy controls at 3 times of testing over a 2.5 year period. Measures included the mean EEG frequency as well as the percentage of
power in alpha, beta, theta, and delta frequency bands obtained from power spectral analysis. The values from occipital to vertex
derivations were averaged for the left and right hemispheres.
In healthy older adults delta increased, and both beta and m e a n frequency decreased over the study period; there was no
significant change in theta or alpha. In the SDAT group, all 5 EEG measures changed significantly; there were increases in delta and
theta, and decreases in beta, alpha and mean frequency. Theta percentage power distinguished between all 4 stages of dementia
(control, mild, moderate and severe). Other EEG measures discriminated only at certain stages. In the mild stage of SDAT theta, beta
and mean frequency were already different from control values. In the moderate stage, these differences persisted, and alpha became
different. Delta was the last to change, and in the present small sample of those with severe S D A T the difference had not yet reached
significance.

Prichep et al., 1993: https://doi.org/10.1016/0197-4580(94)90147-3

Neurometric QEEG measures were found to be a sensitive index of degree of cognitive impairment, especially reflected in increased
absolute and relative power in the theta band, with delta increasing in later stages of deterioration.

Cognitive impairments in depressive and anxiety disorders with a focus on young adults

Castaneda, Tuulio-Henriksson, Marttunen, Suvisaari & Lönnqvist, 2008:
https://doi.org/10.1016/j.jad.2007.06.006

There is growing evidence for cognitive dysfunction in depressive and anxiety disorders. Nevertheless, the
neuropsychological profile of young adult patients has not received much systematic investigation. The following paper reviews

the existing literature on cognitive impairments in depressive and anxiety disorders particularly among young adults. Additionally,
the focus of young adult age group and the effect of confounding variables on study results are discussed.
Cognitive impairments are common in young adults with major depression and anxiety disorders, although their nature
remains partly unclear. Accordingly, executive dysfunction is evident in major depression, but other more specific deficits appear to
depend essentially on disorder characteristics. The profile of cognitive dysfunction seems to depend on anxiety disorder subtype,
but at least obsessive–compulsive disorder is associated with deficits in executive functioning and visual memory. The conflicting
results may be explained by heterogeneity within study participants, such as illness status, comorbid mental disorders, and
medication, and other methodological issues, including inadequate matching of study groups and varying testing procedures.
Cognitive impairments are common in major depression and anxiety disorders. However, more research is needed to
confirm and widen these findings, and to expand the knowledge into clinical practice. Controlling of confounding variables in
future studies is highly recommended

- ➔ But all with objective cognitive impairment and therefore probably not relevant for my discussion

Grant, Thase & Sweeney, 2001: **https://doi.org/10.1016/s0006-3223(00)01072-6**

The most striking finding from the current study was the
absence of significant cognitive impairment on the major-
ity of both standardized neuropsychologic tests and exper-
imental computerized cognitive measures in younger am bulatory adults with major depression. Intact attentional,
memory, and motor functioning were noted across batteries, with some suggestion of impaired executive functioning provided by the WCST. These findings from a large
sample of younger (average age 39.0 years), unmedicated
depressed patients using a comprehensive neurocognitive

assessment indicate that major depressive disorder per se in young ambulatory adults is associated with only minimal cognitive deficits. These findings are consistent with those of several other recent studies of smaller samples of younger medicated depressed patients (Fossati et al 1999; Purcell et al 1997) but are notably different from the more consistent findings of cognitive impairments reported among older depressed patients (Beats et al 1996; Elliott et al 1996; Harvey et al 1997; Palmer et al 1996).

Cognitive impairment in young adults with post COVID-19 syndrome

Herrera et al., 2023: https://doi.org/10.1038/s41598-023-32939-0

Ten to fifteen percent of the patients who have passed COVID-19 report that they continue to experience a wide
range of symptoms even several months after the infection. This disorder, named “post COVID-19 syndrome”,
affects mainly women aged between 40 and 55 years, most of whom have undergone mild or even asymptomatic
COVID-19 1–3 .
In 2021, this syndrome was defined by the World
Health Organization 4 as a condition that “occurs in individuals with a history of probable or confirmed SARS-
CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months
and cannot be explained by an alternative diagnosis”.
Bertuccelli et al. 10 recently conducted a comprehensive review of studies on cognitive impairment in infected

individuals. The review yields interesting results: the cognitive domain reported as impaired in the largest number of studies (8/16) are executive functions. Seven of the 12 studies that evaluated attention found significant impairment in all types of attention with higher error rates and slower reaction times. Memory was evaluated in ten studies, mainly verbal and working memory. Only one of the studies found alterations in immediate recall, while two of them reported impaired delayed recall. As for working memory, significant alterations were found in only two out of seven studies.

Regarding language, only one study included specific tasks to assess this cognitive domain and 97% of the patients obtained normal scores (using the Boston Naming Test). Finally, visuospatial functions were evaluated through specific tasks in 5 studies, although no altered performance of the patients was found in any of them.

Some other studies not included in these reviews show similar results. In the study by Krishnan et al. 11 with 20 patients, alterations in attention, processing speed and executive functions were found. On the other hand, in the study conducted by Delgado-Alonso et al.12 with 50 Spanish patients, impaired performance was found in the cognitive domains of attention, executive functions, episodic memory and visuospatial skills. Dressing et al. 13 , however, failed to find impairments despite the extensive neuropsychological battery they applied to their 31 patients.

Although there is no doubt that these studies are of enormous interest in trying to clarify the cognitive profile of patients with post COVID-19 syndrome, some limitations should be pointed out to treat the results with caution. The main one, in our opinion, is that most of the studies do not differentiate whether the sample

includes only patients with post COVID-19 syndrome, or also patients with sequelae of COVID-19.

The purpose of this study, therefore, is to identify the cognitive features of a large sample of patients with a diagnosis of post COVID-19 syndrome (or compatible symptoms). For this goal, neuropsychological evaluations have been performed on individuals who, after having overcome the acute phase of COVID-19, report cognitive complaints lasting more than 4 months.

Taken together the more semantic verbal fluency tasks (semantic fluency and actions fluency), the effect of age is clearly observed, since 29.12% of patients aged under 50 showed a mild deficit and 7.27% a moderate deficit, while only 5.70% of those aged over 50 showed a mild deficit and none a moderate deficit. In general, language is the most understudied cognitive function in most of the articles 10 , even less when considering the age of the participants, so these data are of special relevance and interest. Similarly as in the case of memory, the results obtained in semantic fluency can be understood as an alteration in the functioning of the temporal lobe 14 , since this region plays an important role in this particular kind of verbal fluency 29 .

In conclusion, the results presented here reveal that at least 85% of the participants exhibit deficits in one neuropsychological test. Also, the youngest patients were those who showed the most marked and heterogeneous cognitive impairment, while the oldest patients maintained their cognitive functions preserved to a greater extent with only a mild impairment in attention and speed processing. Precisely both functions were the cognitive processes that are most deficient and homogeneously identified across the different age subgroups.

In this study, we aimed to examine different cognitive domains in a large sample of patients with

post COVID-19 syndrome. Two hundred and fourteen patients, 85.04% women, ranged 26 to 64 years
(mean = 47.48 years) took part in this investigation. Patients' processing speed, attention, executive
functions and various language modalities were examined online using a comprehensive task protocol
designed for this research. Alteration in some of the tasks was observed in 85% of the participants,
being the attention and executive functions tests the ones that show the highest percentage of patients with severe impairment. Positive correlations were observed between the age of the participants in almost all the tasks assessed, implying better performance and milder impairment
with increasing age. In the comparisons of patients according to age, the oldest patients were found
to maintain their cognitive functions relatively preserved, with only a mild impairment in attention
and speed processing, while the youngest showed the most marked and heterogeneous cognitive
impairment. These results confirm the subjective complaints in patients with post COVID-19 syndrome
and, thanks to the large sample size, allow us to observe the effect of patient age on performance, an
effect never reported before in patients with these characteristics.

I need a new title for submitting thesis!

What is EEG?

Why do I look at resting state and not eeg data while doing cognitive task?

No age matching -> limitation(?)

Correlation test -> cognitive variables

Commented [Janka Hau26]: Electroencephalography (EEG) is a non-invasive, functional brain-activity2 recording modality with high temporal resolution and relatively low cost.
Luca Pion-Tonachini et al.,2019

Commented [Janka Hau27]: https://cambridgecognition.com/what-is-cognition/

Cognition is essential for everyday functioning. Cognition refers to a range of mental processes related to the acquisition, storage, manipulation, and retrieval of information. It underpins many daily activities, in health and disease, across the age span. Cognition can be separated into multiple distinct functions, dependent on particular brain circuits and neuromodulators. The ability to test, measure and monitor cognitive performance across the lifespan opens up the chance for patients to be identified earlier, access treatments faster, and stay healthy for longer, improving quality of life and reducing costs.
Cognition is defined as “the mental action or process of acquiring knowledge and understanding through thought, experience, and the senses.” The modern word “cognition” actually has its roots back to Latin, the word “cognoscere” which is to “get to know”. Cognitive functioning is therefore critical for day-to-day life, governing our thoughts and actions. Need cognition to help us understand information about the word around us and interact safely with our environment, as the sensory information we receive is vast and complicated: cognition is needed to distill all this information down to its essentials.
Cognitive assessment refers to the objective measurement of distinct cognitive abilities, such as working memory, inhibition, cognitive flexibility, psychomotor speed and sustained attention. Cognition can be measured using a variety of methods, each varying in their level of objectivity and sensitivity.

Relation between objective measure of cognition and subjective perception of cognitive functioning reported by …

Patients with … experience a broad range of cognitive impairments affecting domains such as…

(Bland et al. 2024):
Given that subjective and objective cognitive function may be driven by different underlying mechanisms, it is important to explore factors which contribute to objective impairments and subjective feelings of “brain fog” in order to design targeted interventions for individuals living with Post-COVID.

Taken together, understanding the relationship between subjective and objective cognitive impairment and the driving factors underlying these is crucial for the development of tailored rehabilitation programs aimed at improving cognitive function and facilitating recovery in Post-COVID patients. In line with previous literature in other patient groups, we hypothesised that subjective cognitive dysfunction would be associated with increased fatigue and stress whereas objective cognitive function would be most dominantly linked to clinical features of COVID-19.

The present study found that objective and subjective measures of cognitive function were not significantly correlated, and that self-reported experience of cognitive deficits were no longer significant when accounting for heightened stress and fatigue.

Theoretical background

Post-Covid Syndrome

(O'Mahoney et al., 2023)

(Chen et al., 2022)

Cognitive deficits related to Post-Covid Syndrome

Subjective and objective cognitive functions are two distinct measures of cognition. (McWhirter, Ritchie, Stone & Carson, 2020): Cognitive symptoms are common: according to this Review they are present in around a third of the populationm with no clear relation to age.

Subjective

Theoretical background

1. Cognitive Performance as a Key Variable: Introduce cognitive performance as a central factor in your research. Explain its relevance in understanding individual differences in behavior, health, and psychological outcome. Cognitive performance as a key variable that influences many aspects of life, such as well-being, self-reported limitations, and brain function. Cognitive abilities vary across individuals.

Commented [Janka Hau28]: https://www.thelancet.com/pdfs/journals/eclinm/PIIS2589-5370(22)00491-6.pdf

Commented [Janka Hau29]: https://academic.oup.com/jid/article/226/9/1593/6569364?login=true

Commented [Janka Hau30]: Cognitive Performance as a Key Variable
Cognitive performance refers to an individual's ability to carry out mental processes such as attention, memory, executive function, and problem-solving. It plays a crucial role in determining how individuals navigate daily life, affecting everything from decision-making to managing complex tasks. Cognitive performance is not a uniform trait but varies significantly between individuals, influenced by factors like age, education, lifestyle, and health conditions. Understanding these variations is essential in psychological and health research because they are often linked to broader outcomes like well-being, self-reported limitations, and brain activity.
Higher levels of cognitive performance have been associated with better problem-solving skills, greater emotional regulation, and improved mental and physical health outcomes. Conversely, individuals with lower cognitive performance may experience difficulties in these areas, leading to reduced well-being and higher levels of self-reported limitations. Therefore, cognitive performance is a key variable when investigating individual differences in how people experience and report limitations in their daily lives, their well-being, and their underlying neural activity.
Cluster Analysis for Grouping Based on Cognition
Given the variability in cognitive performance across individuals, it is important to group people in ways that reflect meaningful differences in their cognitive abilities. One effective method for achieving this is **cluster analysis**, a statistical technique used to classify individuals into groups (or clusters) based on shared characteristics. In this study, cluster analysis will be used to group participants solely based on their cognitive performance scores. This method allows us to objectively identify subgroups of individuals with similar cognitive profiles, which can then be compared in terms of other variables like self-reported limitations, well-being, and resting-state neural activity.
By forming cognitive clusters, this approach provides a way to explore whether individuals with different levels of cognitive performance report their limitations differently, experience well-being in distinct ways, or exhibit variations in neural activity. The use of cluster analysis in this context is particularly valuable because it captures the natural variation in cognitive functioning, rather than relying on predefined categories. This method thus enhances our understanding of how cognitive differences translate into real-world outcomes.

Introduction (catchy start)

Imagine waking up one day feeling disoriented, unable to concentrate, or struggling to remember simple tasks from the day before. For many individuals recovering from COVID-19, this mental cloudiness, often described as "brain fog," is a persistent reminder of their illness. These cognitive challenges, along with fatigue and other lingering symptoms, affect their daily lives long after the infection has passed.

Cognition is essential for navigating the complexities of everyday life. It encompasses a range of mental processes such as memory, attention, and problem-solving, which are critical for acquiring and processing information. Cognitive functions allow us to understand and interact with the world around us by making sense of vast sensory input and distilling it into actionable knowledge. Whether it's remembering a conversation, concentrating on a task, or making decisions, cognition is the foundation that supports these processes.

This thesis focuses on cognitive impairment in individuals experiencing Post COVID-19 Syndrome (PCS), a condition characterized by the persistence of symptoms such as fatigue and cognitive dysfunction months after recovering from the acute infection. While subjective complaints of cognitive difficulties are common among PCS patients, objective measures often reveal discrepancies between what individuals report and their actual cognitive performance. The goal of this thesis is to explore these differences through a cluster analysis approach, aiming to better understand how objective cognitive measures relate to individuals' self-reported symptoms, their overall well-being, and their neural brain activity.

First, the dopaminergic system, closely related to the basal ganglia, is introduced, as it is centrally involved in reward-based learning and movement generation. Then the concepts of reward, prediction, and reinforcement learning are explained and linked to the dopaminergic system. Next, Parkinson's disease is described as it is a disease affecting the dopaminergic system within the basal ganglia. As this thesis is part of an ongoing research project at the Danish Research Center for Magnetic Resonance (DRCMR), first the overall research questions will be mentioned and then the idea of this thesis will be introduced in details, which is to conceptually show how Bayesian cognitive modeling can be used to model reward-based learning and decision-making in participants diagnosed with parkinson's disease and in healthy control participants.

Theoretical Background

As of September 2024, over 760 million confirmed cases of coronavirus disease 2019 (COVID-19) have been documented by the World Health Organization (WHO) globally, leading to approximately 6.9 million deaths. The actual numbers are likely to be much higher due to underreporting. COVID-19 is an infectious disease caused by the SARS-CoV-2 virus (WHO, 2021). While most patients fully recover, some experience persistent symptoms such as fatigue, shortness of breath, cognitive dysfunction, and other symptoms that generally have an impact on everyday functioning (WHO, 2021). These remaining effects, referred to as Post-COVID-19 Condition or Syndrome (PCS), usually occur three months after the initial infection with the SARS-CoV-2 virus and last for at least two months with no other explanation. Approximately 10-20% of people infected with SARS-CoV-2 meet the criteria for PCS (WHO, 2021).

Cognitive Impairment in PCS

Cognitive impairment is one of the most frequent symptoms of PCS (Davids et al., 2021; WHO) and is therefore of high interest. These impairments are characterized by confusion, memory difficulties, disorientation, and trouble concentrating, which are referred to as experiencing “brain fog” by affected individuals (Bland et al., 2024; Kwan et al., 2024). Around 22% of individuals diagnosed with PCS experience COVID-related cognitive impairment, according to a meta-analysis by Ceban et al. (2022). This finding is based on data from 43 studies, 31 of which used subjective assessments and 12 that employed objective measures. Notably, studies using objective assessments of cognitive function reported significantly greater proportions of individuals with impairment (36%) compared to those relying on subjective modes of ascertainment, which identified 18% as cognitively impaired.

This shows, that subjective and objective measures of cognitive function represent two distinct approaches to assessing cognition. Subjective assessments rely on self-reported experiences and perceptions (Stewart, 2012), while objective assessments use standardized tests and tasks to evaluate cognitive performance in various functional areas. Several studies have illustrated these discrepancies between subjective and objective measures further. In fact, most studies have reported higher rates of cognitive impairment through subjective cognitive complaints than through objective test results (Schild, Scharfenberg, Kirchner et al., 2023). For instance, in a study by Schild, Goereci, Scharfenberg et al. (2023) among 52 patients who self-reported cognitive impairment after SARS-CoV-2 infection, objective cognitive screening tests confirmed impairment in only 25%, while extensive neurological assessment indicated impairments in 60% of these patients. Moreover, Schild, Scharfberg, Kirchner, et al. (2023)

reported that 88% of patients reported persistent self-reported cognitive impairment, with approximately a 40% discrepancy between the subjective reports and objective test results at both follow-up visits, underscoring the discrepancies between patients' self-reports and objective neuropsychological test results. Bland et al. (2024) observed that there was no significant relation between objective and subjective measures of cognitive function, implying that self-reports of "brain fog" may not be reflected by objectively measured cognitive dysfunction.

Subjective cognitive deficits in everyday situations are predicted by elevated anxiety and fatigue levels more than by objective cognitive performance (Zamarian et al., 2024). This lack of alignment highlights the complexity of cognitive impairment and raises questions about which additional factors may influence individuals' perceptions of cognitive difficulties. Recent research has addressed these questions by examining how psychological symptoms influence subjective cognitive and objective cognitive impairment.

Zamarian et al. (2024) discovered that subjective cognitive deficits in everyday situations can be better explained by elevated anxiety and fatigue levels than by objective cognitive performance. In addition to anxiety (Almeria, Cejudo, Sotoca, Deus & Krupinski, 2020; Brück et al., 2019; Costas-Carrera et al., 2022; Hill et al., 2016; Zamarian et al., 2024) and fatigue (Bland et al., 2024; Delgado-Alonso et al., 2023; Zamarian et al., 2024), sleep disturbances (Zamarian et al., 2024) and depressive symptoms (Almeria et al., 2020; Brück et al., 2019; Costas-Carrera et al., 2022; Hill et al., 2016; Zamarian et al., 2024) have been found to be associated with subjective but not objective cognitive impairment (Henneghan, Lewis, Gill & Kesler, 2022). Objective cognitive function, on the other hand, was found to be related to perceived stress (Bland et al., 2024).

These findings highlight the intricate and often discordant relationship between subjective and objective cognitive performance, as well as their complex interactions with psychological factors such as anxiety, fatigue, sleep disturbances, and depressive symptoms. This complexity raises important questions about how these elements interact, particularly in the aftermath of SARS-CoV-2 infection. Understanding these dynamics is crucial for developing effective and personalized rehabilitation programs that aim to improve individuals' perceived cognitive function and assist in their recovery.

Cognition

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

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

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

When starting to talk about EEG: Why is EEG of interest? And why beta and delta frequences?

EEG findings in MCI. Reduced delta power during resting state EEG has been identified in patients with MCI (Liddell et al., 2007). Furthermore, in the study, individuals with MCI demonstrated a significant positive correlation between delta power and immediate memory recall. Liddell et al. (2007) proposed that these findings suggest that delta power may be linked to memory decline in MCI, indicating that it could serve as a sensitive indicator of prodromal or early cognitive decline. However, other studies have shown increased delta power in MCI patients compared to healthy controls, particularly in frontal and centroparietall regions (Adler, Bramesfeld & Jajcevic, 1999; Moretti, Zanetti, Binetti & Frisoni, 2012). A decrease in beta power has been found in individuals with mild AD (Hogan, Swanwick, Kaiser, Rowan & Lawlor, 2003).

Fatigue

Fatigue, alongside cognitive impairment, is the most commonly reported symptom of PCS (WHO, 2021). As mentioned above, subjective perceptions of cognitive performance can be influenced by fatigue. Therefore, a closer examination of fatigue will follow to differentiate between the concepts of fatigue and subjective cognitive impairment.

EEG findings in Fatigue.

EEG findings in PCS patients. Electroencephalography (EEG) is a non-invasive, objective method for assessing neuronal activity and has proven to be a valuable tool in identifying neurophysiological dysfunctions in individuals with cognitive impairment (Koenig, Smailovic & Jelic, 2020; Kubota, Gajera & Kuroda, 2021). Because of this, EEG studies have become increasingly relevant for investigating individuals with COVID-19 and PCS, as they reveal changes in brain neural activity that correlate with fatigue and cognitive deficits in these patients (Antony & Haneef, 2020; Appelt et al., 2022; Cecchetti et al., 2022; Furlanis et al., 2023; Kopańska et al., 2022; Kubota, Gajera & Kuroda, 2021; Pasini et al.,

2020; Pastor, Vega-Zelaya & Abad, 2020; Roberto, Espiritu, Fernandez & Gutierrez, 2020; Wojcik et al., 2023).

Furlanis et al. (2023) found that two-thirds of the 20 participants presenting brain fog were characterized by unexpected abnormal EEG patterns. Ortelli et al. (2023) found that lower performance on cognitive tasks, particularly those assessing executive function, was associated with changes in brain activity in PCS patients.

There are different types of analyses used to evaluate EEG patterns of PCS patients, ranging from common power spectrum and event-related potentials (Cecchetti et al., 2022; Furlanis et al., 2023; Kopańska et al., 2022) to more sophisticated approaches, such as intrinsic mode functions and avalanche analysis (Appelt et al., 2022; Wojcik et al., 2023). However, in this thesis, a power analysis will be conducted, specifically examining delta and beta frequency.

Delta Power in PCS patients. Delta frequency (0.5-3 Hz) is typically absent during the waking state of healthy adults and is associated with deep sleep (Schandry, 2016). Ortelli et al. (2023) reported significant differences in the delta frequency band between PCS and healthy controls, with PCS patients displaying diminished activity compared to healthy controls. Lower delta power was associated with worse cognitive functioning. However, findings regarding delta power in PCS patients are not consistent. For instance, Kopańska et al. (2022) found a decrease in delta in the left hemisphere, similar to Ortelli et al. (2023), but also observed an increase in delta activity in the right hemisphere. In another study of 20 PCS patients, a delta-slowing pattern was revealed in nine of them (Furlani et al., 2022). Furthermore, the relative delta power values in this cohort were higher compared to those reported in the literature for healthy individuals. Similarly, Pastor et al. (2020) demonstrated a significant encephalopathic pattern in PCS patients characterized, among others, by an increase in generalized delta activity.

Beta Power in PCS patients. Beta frequency (14-30 Hz) is typically present when individuals are awake and mentally or physically active, or under psychological stress (Schandry et al., 2016). While Ortelli et al. (2023) found no significant differences in beta frequency bands, Kopańska et al. (2020) reported increased beta2 activity in both hemispheres and elevated beta1 activity in the left hemisphere in PCS patients.

EEG findings conclusion. Those EEG findings discussed above are mainly based on subjective perceived cognitive impairment rather than objective measures of impairment. To illustrate this, the findings of Ortelli et al. (2023) provide relevant insights. The PCS group had a significantly lower MoCA score and higher fatigue score (assessed with the self-

Commented [Janka Hau31]: Why beta and delta power?

Commented [Janka Hau32]: Other literature

Commented [Janka Hau33]: Different reference

evaluation scale measuring perceived fatigue (FSS)), than the control group. However, the global cognitive score assessed with the MoCA was still considered normal, implying that, overall, PCS patients did not have clinically significant cognitive impairment.

Notably, there was no differentiation possible between EEG patterns associated with cognitive impairment and those related to fatigue. This raises an interesting opportunity to examine beta and delta power during resting state in two groups defined solely by objective cognitive measures, allowing for a clearer understanding of the relationship between EEG patterns and cognitive functioning in patients with PCS. This approach would allow potential abnormalities in EEG to be more directly linked to objective cognitive impairment rather than subjective cognitive impairment, which might be influenced by psychological factors, such as fatigue.

Aim of study

The study aims to explore the differences among groups that differ significantly in their objective cognitive performance levels following SARS-CoV-2 infection. This investigation is crucial given the widespread cognitive impairments reported in individuals with PCS and their profound impact on everyday functioning and quality of life. Due to the inconsistent findings in EEG patterns in beta and delta power in patients with PCS, but also in patients with MCI, there is a need for further investigation of this aspect. Specifically, the research will address the following research question: How do individuals with different cognitive performance levels differ in their self-reported limitations after SARS-CoV-2 infection, their well-being, and their resting state neural activity?

By examining the correlations between objective cognitive assessments and self-reported cognitive impairments, as well as the influence of psychological factors, this study aims to provide insights into the complex relationship between cognitive functioning and psychological health in individuals with, and without PCS.

Hypotheses

Following SARS-CoV-2 infection, two distinct groups of individuals will be identified based on objective cognitive assessments, showing significant differences in performance levels between the groups. Suggesting, that one group performs significantly better or worse than the other group. Individuals with objectively assessed lower cognitive performance will report higher levels of self-reported cognitive limitations compared to the group that performed better. Individuals, that have self-reported cognitive impairment, but were not recognized as

Commented [Janka Hau34]: Das sieht alles schon gut aus, aber versuch mal deine Hypothesen richtig hervorzuheben, du kannst ruhig richtig Abstand lassen und sagen

Hypothese 1:

Hypothese 2:

Hypothese 3a: Gruppe B hat weniger Fatigue als Gruppe A
Hypothese 3b: Gruppe B hat weniger Depression als Gruppe A
Hypothese 3c: Gruppe B hat weniger Angst als Gruppe A

und so weiter
WARUM du diese Hypothesen aufstellst, arbeitest du direkt vorher heraus, quasi als Übergang vom theoretischen Hintergrund in deine Fragestellung hinein. Und in den Methoden erklärst du dann WIE du die jeweiligen Hypothesen testest. Also die Hypothese, dass mehr Leute sich subjektiv eingeschränkt fühlen, in der Gruppe die objektiv schlecht abgeschnitten hat, müsstest du dann vielleicht mit einem Chi-quadrat Test überprüfen zum Beispiel

Commented [JH35]: Setzen wir voraus, keine Hypothese

Commented [JH36]: Auf methodischer Ebene haben wir es geschafft zwei Gruppen - Auswerung, ob meine Methode funktioniert.

Commented [JH37]: Nehme ich voweg, wie als wenn ich Voraussetzungen teste. Wir wollen diese Verfahren verwenden. Shapiro Test…. Was kam dabei raus. Danach eigentliches Ergebnis. Ergeben die Gruppen sind, die wir erstellt haben (schon ankündigen in den Methoden) Habe vor zu gucken, ob meine Gruppen sinn ergeben. Ergeben sinn, da sie sich demografisch nicht unterscheiden aber kognitiv schon.

Commented [JH38]: Chi2 test hier. Um das zu überprüfen

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

How do individuals with different cognitive performance levels differ in their self-reported limitations after SARS-CoV-2 infection, their well-being and their resting state neural activity?

Idea: Part What is cognition in methods!?

Why beta and delta and not theta and alpha?

Why is closed eye condition the one I chose?

Methods

Study Design Participants

The current data were collected as part of a larger research project (EPOC), which investigates neurophysiological parameters identified from neuropsychological paradigms using a high-resolution stationary laboratory EEG to reflect cognitive impairments and fatigue. The primary goal of the EPOC study is to find EEG parameters that can serve as neurophysiological markers for progression- and therapy-evaluation concerning cognitive functions in PCS.

Participants for the EPOC study were recruited from COVIDOM, a population-based, prospective multi-centre study to investigate Post-COVID Syndrome (PCS) within the German

Commented [JH39]: Step 1: Wir überprüfen Hypothesen. Nenne Hypothesen die ich habe. Gucken uns aber danach auch die Unterschiede zwischen allen anderen Gruppen an, um ein allgemeines Bild zu kriegen. Und explorativ

Commented [JH40]: Darf mir alles explorativ darstellen. Wie kann ich das interessante auf den Punkt bringen. Alles, wozu ich eine Hypothese habe ist schon auf den Punkt gebracht. Dazu dann auch grafische darstellung.
Wenn explorativ, nicht unbedingt alles interessant. Daher gucke, was ich in Vorderung stelle und was eher in den Hintergrund der vollständigkeits halber. Sämtliche Vergleiche in den Anhang.

Commented [JH41]: Hypothesen müssen abgeleitet sein aus Theoreieteil. Warum vermuten wir das und was würde das bedeuten?

Commented [JH42]: Vorausannahme/Grund für Hypothese: Sie schätzen sich als kognitiv schlechter ein, weil sie andere Symptome haben, die sich auch auf Aufmerksamkeit…. Auswirken können (keine gute Begründung) -> Irgendwann natürlich auch in Diskussion. Das ist das Ergebniss, was ist dahinter. Keine vorher nachher vergleichen, vielleicht vorher extrem gut. Schein cognitive Einschränkungen. Durch depression und anxiety kognitive Einschränkungen geringer sind als bei fatigue post covid.

Commented [JH43]: Mit Fatigue kann ich auch immer viel arbeiten. Nur Fatigue z.B. aber keine kognitive Einschränkung. Wenn sie sich so fühlen, sind sie es vielleicht auch aber die Studie nihct gereicht um fatigue auszulösen. Da ja Fatigue über 7 Tage abgefragt wurde (Quellen)

Commented [Janka Hau44]: What does it stand for? Do I need to name it?

Commented [Janka Hau45]: EEG Post-Covid

Commented [Janka Hau46]: In brief, the experiment consisted of neuropsychological tests (TMT, n-back, PVT, Oddball, RTE), restingstate recording and questionnaires regarding fatigue, sleep quality, depression and anyiety. The study was conducted at the University Medical Center Schleswig-Holstein (UKSH), Campus Kiel.

Commented [Janka Hau47]: Or COVIDOM study?

Commented [Janka Hau48]: Well I say in sentence after, that it is a study

Commented [Janka Hau49]: Do I need to mention full name or is COVIDOm enough?

National Pandemic Cohort Network (NAPKON). COVIDOM participants had been recruited through public health authorities in Kiel, Berlin, and Würzburg. Patients were assessed between November 15, 2020, and September 19, 2021, at University Medical Center Schleswig-Holstein, Campus Kiel, and University Hospital Würzburg in Germany (Bahmer et al., 2022; Horn et al., 2021; Schons et al., 2022).

The participants were included based on the following criteria: A polymerase chain reaction (PCR) confirmed SARS-CoV-2 infection at least 6 months before study visit, a primary residence in one of the three study regions, age ≥ 18 years at the time of recruitment (Berlin) or infection (Würzburg, Kiel). Participants with acute reinfection of SARS-CoV-2 at the time of the scheduled study visit were excluded (Horn et al., 2021).

In the EPOC study, a subset of individuals from Schleswig-Holstein who participated in COVIDOM was selected, constituting of those with PCS and a control group without PCS. As EPOC is still ongoing at the time of writing, the analysis was conducted based on a preliminary subset of 79 participants (mean age 48.52, range 22–78, female 48, male 31, diverse 0, years of education mean 15.27 years min 9 to 24 years) withPCS (49 participants, age mean 50.29 years min 22–78, F=32 M=17, education: mean 15.04 9–23) and withoutPCS (30 participants, age mean 45.63 years min 22–77, f=16,m=14 d 0, education mean 15.63 min 10–24). The study was conducted at the University Medical Center Schleswig-Holstein (UKSH), Campus Kiel. Participants did not receive payment/financial compensation for their participation. Transportation and parking costs were reimbursed.

Ethics statement

The study was approved by the Ethics Committee of the medical faculty of the Christian-Albrechts-University of Kiel, Germany (record identification: D 446/23). In accordance with the Declaration of Helsinki, informed written consent was obtained from all participants.

Procedure/Study Design

In brief, the experiment consisted of neuropsychological tests, assessing cognitive domains such as working memory, attention, preprocessing speed, cognitive flexibility, executive functions, and multisensory integration, EEG recordings, and questionnaires assessing

Commented [Janka Hau50]: Might be bit to specific

Commented [Janka Hau51]: COVIDOM is a population-based cohort study of polymerase chain reaction (PCR) confirmed cases of
SARS-CoV-2 infection, recruited through public health authorities in three German regions (Kiel, Berlin, W€urzburg) between November 15, 2020 and September 29, 2021

Commented [Janka Hau52]: With und without als Tabelle. Gesammte Stichprobe im Text beschreiben

Commented [Janka Hau53]: Table?

Commented [Janka Hau54]: Table here -> see Lara

Commented [Janka Hau55]: Here, or should I inser it after the inclusion criteria?

Commented [Janka Hau56]: All participants gave their written
133 informed consent and were compensated for their participation. The experiment was
134 carried out in accordance with the ethical standards of the Declaration of Helsinki and
135 was approved by the local ethical committee.

Commented [Janka Hau57]: The study was conducted monocentrically at the UKSH, Campus Kiel. A maximum duration of 3 hours was allocated for each participant's visit. The eligibility of participants was determined based on their medical history and MoCA tests, which had been previously conducted as part of the COVIDOM study. Participants were then asked to complete questionnaires on demographic data (e.g., age, education) and psychological and neurological conditions. This initial part of the examination took up to 20 minutes. If deemed eligible for the study, all participants underwent neuropsychological testing. This assessment covered cognitive domains such as working memory, attention, processing speed, cognitive flexibility, executive functions, and multisensory integration. First, three neuropsychological tests were conducted without EEG (TMT, n-back task, PVT). These tests took up to 25 minutes in total. Subsequently, EEG was recorded while two additional neuropsychological tests were performed (Oddball task, RTE). At the end, a resting-state EEG was recorded, during which the participant was not required to perform any task. Finally, three short questionnaires on fatigue, depression, anxiety, and sleep were completed. This last part of the examination took up to 2.25 hours. The data were stored in a pseudonymized manner. The study information disclosed that there was no commuting accident insurance for this study. Data collection was scheduled to be completed by the end of September 2023.

Commented [Janka Hau58]: Participants first completed demographic and psychological questionnaires, followed by neuropsychological testing to assess cognitive domains such as working memory, attention, and executive functions. EEG recordings were conducted during specific tasks, with a resting-state EEG recorded at the end. The entire session lasted up to three hours, with data stored pseudonymousl

Commented [Janka Hau59]: Need to add, that two were there to place EEG cap, and else one person. Here, or at EEG part?

fatigue, sleep quality, depression, and anxiety. All data were collected at the University Medical Center Schleswig-Holstein (UKSH), Campus Kiel.

Participants first filled out a questionnaire on demographic data (e.g., age, education) and psychological and neurological conditions, followed by neuropsychological testing to assess cognitive domains such as working memory, attention, preprocessing speed, cognitive flexibility, executive functions, and multisensory integration. The first test administered was the Trial Marking Test. Following this, the EEG cap was placed, and participants completed a series of other neuropsychological tests, starting with the redundant target effect (RTE), followed by an oddball paradigm, an n-back task, and lastly the psychomotor vigilance task (PVT). Electroencephalographic activity was recorded continuously throughout these tests. Finally, resting state was measured, 5 minutes with eyes open and 5 minutes with eyes closed. During EEG recordings, participants were seated comfortably and instructed to minimize movement, and to focus on a fixation cross displayed on the screen in front of them to reduce eye movements, while the light was turend off. After completing the resting state measurement, the EEG cap was removed, and participants filled out three questionnaires assessing fatigue (FACIT-F), sleep quality (PSQI), depression (HADS-D), and anxiety (HADS-A). The participants got then the chance to wash their scalp/hair. In all, the experiment took up to 3 hours.

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

Cognitive tasks

MoCA

The Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) is a widely used, validated screening tool originally designed to detect mild cognitive impairment (MCI) (Hauffe, 2024). It assesses several cognitive domains, including visuospatial skills/ability, executive function, naming, memory (short-term and delayed recall), working memory, attention and concentration, language, abstraction, and orientation (Freitas, Simões, Alves & Santana, 2013; Hobson, 2015; Kang et al., 2018; Nasreddine et al., 2005). The MoCA has a

Commented [Janka Hau60]: Not sure if nessecary, I like to give an overview but I'm repeating myself

Commented [Janka Hau61]: Already wrote that

Commented [Janka Hau62]: Where does it fit better? Before? Or here?

Commented [Janka Hau63]: Then several neuropsychological tests to assess cognitive domains such as working memory, attention, preprocessing speed, cognitive flexibility, executive functions, and multisensory integration, followed, starting with the Trial Marking Test A and B.

Commented [Janka Hau64]: Or: The first tests used were the Trial Marking Tests A and B.
Or should it be The first test used was the Trial Marking Test A and B?

Commented [Janka Hau65]: Better way to start this sentence?

Commented [Janka Hau66]: Do I need to provide more information here? Which gel etc. ; Two people...

Commented [Janka Hau67]: On what? Should I say specific on participants head?

Commented [Janka Hau68]: Kind of screen and lights off

Commented [Janka Hau69]: Lilly: 27-Zoll-Bildschirm

Commented [Janka Hau70]: The or an?

Commented [Janka Hau71]: Should I already introduce the abbreviation here?

Commented [Janka Hau72]: Maybe a bit informal. Can't think of a better word right now

Commented [Janka Hau73]: Bei dem Ruhe-EEG sollen die Versuchspersonen lediglich auf einen Fixationspunkt gucken. Nach 5
Minuten teilt ein Audiosignal der Versuchsperson mit, dass sie nun für die nächsten 5 Minuten die
Augen schließen sollen. Mit einem letzten Audiosignal wird der Versuch beendet.

Commented [Janka Hau74]: Resting state was measured next.

Commented [Janka Hau75]: Keep their gaze (is that better?)

Commented [Janka Hau76]: What kind of screen? Need to as Christian and add information

Commented [Janka Hau77]: I'm repeating myself. Is that okay in this case?

Commented [Janka Hau78]: Delete sentence?

Commented [Janka Hau79]: And will be of interest in this thesis

Commented [Janka Hau80]: Das

Commented [Janka Hau81]: I like to start with the full name, but maybe dump since I already used it before... or

Commented [Janka Hau82]: literature

Commented [Janka Hau83]: Is that correct written? Or wrong?

total possible score of 30 points, with a score of ≥ 26 considered normal (Nasreddine et al., 2005. Cognitive performance on the MoCA is influenced by sociodemographc factors such as age and education (Kang et al., 2018; Larouche et al., 2016). To account for educational backgroundm the MoCA test manual specifies that one additional point is added for individual with ≤ 12 years of formal education, allowing for a maximum score of 30 points (Nasreddine et al., 2005). Additionally, to address variations in performance related to age, normative data for the MoCA are available for precise interpretation of scores (Larouche et al., 2016).

TMT Part A and B

Originally, developed as part of the Army Individual Test Battery (AITB) in 1944, the Trail Marking Test (TMT) was later integrated into the Halstead-Reitan Battery (Reitan & Wolfson, 1985; Tombaugh, 2004). It is now one of the most popular and widely used neuropsychological assessments, included in most test batteries (Tombaugh, 2004). Its widespread use is supported by strong evidence of its validity (Arbuthnott & Frank, 2000; Sánchez-Cubillo et al., 2009). The TMT assesses cognitive processing speed and executive functioning (Lezak, 1995; Mitrushina et al., 2005; Reitan, 1992; Sánchez-Cubillo et al., 2009; Strauss et al., 2016; Tombaugh, 2004), as well as visual search/scanning, and mental flexibility (Sánchez-Cubillo et al., 2009; Tombaugh, 2004).

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

In TMT-A, participants were instructed to connect consecutively numbered circles from 1 to 25 on an A4 page by drawing lines between them, aiming to complete the task as quickly and accurately as possible. In TMT-B, the task becomes more complex (Gaudino, Geisler & Squires, 1995). Participants were instructed to draw lines alternating between numbered circles from 1 to 13 and lettered circles from A to L in sequential order (e.g, 1 to A, to 2, to B, etc.) on an A4 page. The aim, again, was to complete the task as quickly and accurately as possible.

Commented [Janka Hau84]: See methods1209 for more information on TMT!

Commented [Janka Hau85]: The Trail Making Test (TMT) was originally developed as part of the Army Individual Test Battery (1944) and is one of the most commonly used tests in neuropsychological practice due to its high sensitivity in diagnosing brain impairment (Armitage, 1946; Lewinsohn, 1973; Reitan, 1958; Spreen & Benton, 1965).

Commented [Janka Hau86]: Der Trail Making Test (TMT, Reitan, 1958) ist ein neuropsychologisches Testverfahren zur Erhebung von Aufmerksamkeitsstörungen und exekutiven Dysfunktionen. Der Test besteht aus zwei Abschnitten (TMT A und TMT B). Bei dem TMT A müssen Zahlen in aufsteigender Reihenfolge verbunden werden. Im TMT B müssen Zahlen und Buchstaben alternierend verbunden werden, die Buchstaben in alphabetischer Reihenfolge.

Commented [Janka Hau87]: I think it's fine to write either search or scanning. Which is better?

Commented [Janka Hau88]: Visual search, perceptual/motor speed, speed of processing, working memory, and general intelligence are among the most frequently cited constructs thought to contribute to TMT performance (Sánchez-Cubillo et al., 2009).

The administration of the TMT began with TMT-A, followed by TMT-B. For each part, participants were first given an example to familiarize themselves with the task. After completing the example, they proceeded to the actual test. If participants made a mistake, the experimenter immediately pointed it out, and the participant was required to correct it before continuing. The experimenter timed each part, with the time of completion for each part representing its direct score. In addition to the direct scores, the difference between TMT-B and TMT-A (TMT-B – TMT-A) was calculated.

N-Back Part A and B

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

(Jaeggi, Buschkuehl, Perrig & Meier, 2010) extensively used in literature as a working memory paradigm. Increasingy used as a measure of individual differences.

(Jacola et al., 2014) In particular, we found N-back reaction time during fMRI scanning to be most strongly correlated with measured intelligence, as opposed to clinical measures of working memory

Introduced by Kirchner (1958). Widely used tool for assessing working memory in the field of neuroscience. N-back has grown in use in neuroimaging techniques and progressively adopted (Pelegrina et al., 2015). Reliability varies greatly depending on the study (Van Leeuwen et al., 2007 to Friedman et al., 2008). More complex levels, 2-back and 3-back produce higher reliability coefficients (Jaeggi et al., 2010 stolen from (Pelegrina et al., 2015).). Reason: high variety of WM tasks and different contents that they include. N-back relies on recognition processes. Working memory task. Working memory is a system that enables one to actively maintain and regulate a limited amount of task-relevant information (Baddeley & Logie, 1999) (stolen from Pelegrina et al., 2015) Working memory is traditionally measured using processing-and-storing dual tasks that involve performing a cognitive task

Commented [Janka Hau89]: Why?

Commented [Janka Hau90]: Figure!

Commented [Janka Hau91]: The N-back task is used extensively in literature as a working memory (WM) paradigm and it is increasingly used as a measure of individual differences. However, not much is known about the psychometric properties of this task and the current study aims to shed more light on this issue. We first review the current literature on the psychometric properties of the N-back task. With three experiments using task variants with different stimuli and load levels, we then investigate the nature of the N-back task by investigating its relationship to WM, and its role as an inter-individual difference measure. Consistent with previous literature, our data suggest that the N-back task is not a useful measure of individual differences in WM, partly because of its insufficient reliability. Nevertheless, the task seems to be useful for experimental research in WM and also well predicts inter-individual differences in other higher cognitive functions, such as fluid intelligence, especially when used at higher levels of load

Commented [Janka Hau92]: Looking at the data relating the N-back task to other measures of WMC, the N-back task does not seem to be a useful measure of individual differences in WMC, due to its low reliability. Nevertheless, it is a very useful tool for the experimental investigation of WM processes because it allows load to be manipulated in a very simple, straightforward way. Further, there is converging evidence that N-back performance can well predict individual differences in Gf and other higher cognitive functions, at least when used at higher levels of load

Commented [Janka Hau93]: See: Conway et al., 2005; Kane & Engle, 200

Commented [Janka Hau94]: Our findings of limited validity between N-back performance and clinical measures of working memory

Commented [Janka Hau95]: Our results provide evidence for reliability of N-back accuracy during fMRI scanning; however, reliability of reaction time data is affected by order of task presentation. Data regarding construct validity are inconsistent and emphasize the need to consider clinical utility of behavioral measures in the design and interpretation of functional neuroimaging studies.

while certain information has to be maintained in memory (Pelegrina et al., 2015). N-back does not involve a processing-and-storing dual task and in which individuals are not asked to recall any information but to recognize it (Pelegrina et al., 2015). This study employed an N-back continuous recognition task to assess working memory function.

N-back continuous recognition task in which participants must decide whether a stimulus was previously presented in certain conditions. “n” trials back. Letters were shown. Each item is compared to item presented immediately before, prior letter.
In this study, participants completed two blocks of the n-back task: a 1-back task followed by a 2-back task, with a paus between blocks for additional instructions. The task was programmed using … and presented on a 27-inch computer screen.
In both conditions, participants were shown a series of 60 linguistic stimuli, consisting of 16 different consonants (**B, C, D, F, G, H, J, K, M, Q, R, S, T, V, X, Z**) presented individually in the center of the screen. Each block contained 20 target trials and 40 non-target trials. A trial began with a 250 ms fixation period (a red dot was shown on screen, for the participant to fixate), followed by a 150 ms black screen. The stimulus letter then appeared for 500 ms, succeeded by a variable inter-trial interval of 180 to 220 ms (black screen). Total trial duration ranged from 1080 to 1120 ms.
For the 1-back task, participants were instructed to press the spacebar when the current letter matched the previous one. For example, in the sequence “B, C, C, D,” participants were supposed to respond to the second “C” as it matches the previous letter. In the 2-back task, they were instructed to press the spacebar when the current letter matched the letter presented two trials prior. For instance, in the sequence “B, B, D, F, D,” participants should press the spacebar when the second “D” occurred, as it matches the letter presented two trials before. The response window was limited to the 500 ms stimulus presentation period. Reaction time, hits, misses, and false alarms were recorded. In total, the experiment took around 5 minutes. During the experiment, the light was turned off.

Red circle as fixation point. Two blocks, first 1-back task, sencond a 2-back task (condition) (two positions prior). Between those two blocks is a pause and instructur explaines the new task again, before starting the second block. One trial consist of a fixation period of 250 ms (red dot is displayed), followed by a black screen shown for 150 ms. The stimulus in form of a

Commented [Janka Hau96]: Look at numbers again here

Commented [Janka Hau97]: Is it clear what I mean with that or should I specify it a bit more?

single letter is presented for 500 ms on screen. Inter-trial interval (1800-2200 ms) Black screen. Reaction time window 0.5 seconds (stimulus presentation). In total 2.3 to 2.7 seconds per trial. Press, when detecting a target, a target is. 1-back task: Participants press spacebar when current letter matches the previous one. 2-back task, participants press spacebar when current letter matches the letter presented two trials ago/before. Reaction time, missing and fals hits measured. Response accuracy and response time was measured. In each condition 60 stimuli presented. 20 targets in both conditions. In total the experiment took around 5 minutes. One can easily manipulate the level of difficulty depending on greater or lesser memory loads as well as the timing of stimulus presentation. N-back task programmed by …. In … (program name) Was used in this study. Task applied consisted of two levels: 1-back and 2-back. Items were letters, that is, linguistic material. The following consonants were used as stimuli in all blocks M, C, K, S, R, V, H, X, T, Q, J, B, Z, G, D, F . Presented one by one in center of the screen. 20 target trials and 40 non-target trials, right? Each stimulus appeared on screen for 500 ms, followed by a screen that remained black for another 180 ms to 220 ms. Response time, number of hits, correct rejection, misses, false alarms, and non-responses were recorded. Age-related changes that might be related to different cognitive processes involved in updating information in working memory (Pelegrina et al., 2015).

PVT

The Psychomotor Vigilance Task (PVT) is a widely used reaction time test originally developed in 1985 to measure sustained attention (Drummond et al., 2005). Sustained attention and cognitive functions, particularly in contexts involving fatigue and sleep deprivation.

Reaction time task

(Drummond et al., 2005) Originally developed in 1985 as a measure of sustained attention. Studies have demonstrated its sensitivity to sleepiness in clinical and experimental settings. (Molina, Sanabria, Jung & Correa, 2019)

The monotonous and unpredictable target presentation in the PVT makes subjects highly prone to lapses of attention. Moreover, the PVT has minimal learning effects, minimizing the variability due to participants different abilities and experience (Basner and Dinges, 2011) (stolen from Molina et al., 2019)

(Jakobsen, Sorensen, Rask , Jensen & Kondrup, 2011) Reaction time was related to cognitive function in both healthy subjects and patients. it is valid.

Commented [Janka Hau98]: If I calculated right shortest time: 3.75 minutes, longest 5.8 without instructions

Commented [Janka Hau99]: Give example

Commented [Janka Hau100]: This sentence is not true in my case

Commented [Janka Hau101]: Der Psychomotor Vigilance Test (PVT), die Oddball Aufgabe, der Redundant Target Effect (RTE) und
die n-back Aufgabe sind Reaktionsaufgaben, die an einem Computer im EEG-Labor durchgeführt
werden. Bei dem PVT müssen die Versuchspersonen so schnell wie möglich einen Knopf drücken,
sobald ein Timer aus roten Zahlen erscheint. Sobald die Reaktion stattgefunden hat, stoppt der Timer
14
und zeigt somit die Reaktionszeit der Versuchsperson an. Die Oddball Aufgabe besteht aus einem
Zielreiz, einem Distraktorreiz und einem Standardreiz. Die Aufgabe der Versuchsperson ist es, bei
Erscheinen des Zielreizes so schnell wie möglich einen Knopf zu drücken. Beim RTE kann ein visueller
oder auditiver Reiz erscheinen oder auch beides gleichzeitig. Sobald einer der Reize erscheint
(unabhängig von der Bedingung), soll so schnell wie möglich ein Knopf gedrückt werden. Die n-back
Aufgabe besteht aus zwei Teilen. Auf dem Bildschirm erscheinen Buchstaben. Im ersten Teil sollen
die Versuchspersonen per Knopfdruck reagieren, wenn ein Buchstabe erscheint, der mit dem
vorherigen Buchstaben übereinstimmt. Im zweiten Teil sollen die Versuchspersonen per Knopfdruck
reagieren, wenn ein Buchstabe erscheint, der mit dem vorletzten Buchstaben übereinstimmt.

Commented [Janka Hau102]: figure

Commented [Janka Hau103]: Dinges DF, Powell JW. Microcomputer analyses of performance on
a portable, simple visual RT task during sustained operations. Beh
Res Meth Instr Comp 1985;17:652-5.

Commented [Janka Hau104]: Dorrian J, Rogers NL, Dinges, DF. Psychomotor vigilance performance:
a neurocognitive assay sensitive to sleep loss. In: Kushida C, ed. Sleep Deprivation: Clinical Issues, Pharmacology and Sleep …

Commented [Janka Hau105]: is a straightforward and reliable tool for measuring
fatigue in humans.

Commented [Janka Hau106]: Might be interesting, when comparring with fatigue score

Commented [Janka Hau107]: Research on the relationship between EEG signals and PVT performance showed that an increment in delta power on frontal and occipital …

Commented [Janka Hau108]: It is interesting
to note that frontal and parietal areas have been often related
to sustained attention and, despite the scarce extant evidence with this …

This study employed a 5-minute version of the PVT, which has been established as a valid alternative to the traditional 10-minute PVT-192 (for assessing fatigue) (Lamond et al., 2008). The dynamic stimulus appeared as a red number, counting up in milliseconds, representing the participant's reaction time. Participants were instructed to respond immediately, when the stimulus/red number occured, by pressing the spacebar. Between trials, a white fixation cross was displayed on a black screen for a variable interval ranging from 2 to 10 seconds. Participants were required to maintain their gaze on this fixation cross. Each trial concluded when a response was made. Following each response, the participant's reaction time was displayed on the screen for 50 ms as feedback before the next trial began.
After receiving instructions, participants underwent a training block of 8 trials to familiarize themselves with the task. Following the training, participants proceeded to the main experiment, which consisted of 50 stimulus presentations. The light was turned off during the experiment.

Commented [Janka Hau109]: After receiving instructions, participants underwent a training block of 8 trials to familiarize themselves with the task. Following the training, participants proceeded to the main experiment, which consisted of 50 stimulus presentations.

or should that be here, before describing the experiment in details?

Commented [Janka Hau110]: The PVT was run on an Intel Core 2 Duo PC and a 17" CRT screen
with a 60 Hz refresh rate, using E-Prime software (Schneider et al.,
2001). The target stimulus was a black circle with a red edge (diameter:
9.15 ° of visual angle at a viewing distance of 50 cm).

Commented [Janka Hau111]: (Basner & Dinges, 2011)

Commented [Janka Hau112]: Bei dem Ruhe-EEG sollen die Versuchspersonen lediglich auf einen Fixationspunkt gucken. Nach 5
Minuten teilt ein Audiosignal der Versuchsperson mit, dass sie nun für die nächsten 5 Minuten die
Augen schließen sollen. Mit einem letzten Audiosignal wird der Versuch beendet.

Resting state

Do I even need to write something here?

Maybe to investigate delta and beta frequence eyes closed condition and why?

Questionnaires

PSQI

The Pittsburgh Sleep Quality Index (PSQI), developed by Buysse, Reynolds, Monk, Berman, and Kupfer in 1988 is a self-rated questionnaire that assesses sleep quality and disturbance over the past month. The PSQI is the most commonly used sleep health assessment tool in both clinical and research settings. Its reliability and validity have been consistently demonstrated in multiple studies (e.g. Carpenter & Andrykowski, 1998; Manzar et al., 2018; Mollayeva et al., 2016). The questionnaire consists of 24 items in total, 19 of which are self-repoRTEd by the patient and 5 of which require input from a room or bed partner. Only the 19 self-repoRTEd items are used for the quantitative evaluation of sleep quality, as perceived by the patient (Buysse et al., 1989; Manzar et al., 2018). The response formats across the items vary, including the recording of usual bed and wake times, number of hours slept, minutes taken to fall asleep, as well as forced-choice Likert-type responses (Buysse et al., 1989). The items are categorized into seven components, which are sleep quality, sleep

latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping medications, and daytime dysfunction, for each component given a score. Together, these component scores generate a global sleep quality score ranging from 0 to 21, with scores >5 indicating poor sleep quality (Buysse et al., 1989; Hinz et al., 2017).

HADS

The self-assessment Hospital Anxiety and Depression Scale (HADS) was originally developed by Zigmond & Snaith in 1983 to identify the presence of anxiety and depression states among patients in nonpsychiatric hospital clinics. HADS is an extensively used, reliable, and valid instrument to measure anxiety and depression, not only in psychiatric, and clinical patients (Herrmann, 1997) but in general populations (Bjelland, Dahl, Haug & Neckelmann, 2002; Herrero et al., 2003; Spinhoven et al., 1997). The questionnaire assesses anxiety and depression symptoms during the past week, excluding symptoms also related to physical disorders, e.g., headache, dizziness, or insomnia (Bjelland et al., 2002; Hinz & Braehler, 2011; Zigmond & Snaith, 1983). The scale consists of 14 items, divided into a 7-item anxiety (HADS-A), and a 7-item depression subscale (HADS-D). Both subscales are rated on a four-point Likert scale, giving subscale scores ranging from 0 to 21 (Zigmond & Snaith, 1983). There is no universally accepted cut-off score for the HADS (Herrero et al., 2003; Spinhoven et al., 1997). In this study, the cut-off point was set to eight, indicating elevated/caseness anxiety and depression for scores ≥8, following the recommendations by Zigmond and Snaith (1983), as well as Bjelland et al. (2002) and Herrero et al. (2003).

Zigmond and Snaith (1983), as well as Bjelland, Dahl, Haug, and Neckelmann (2001) and Herrero et al. (2003) recommended a cut-off score of 8 for both subscales,while a score of ≥8 indicates caseness.

(Bjelland, Dahl, Haug & Neckelmann, 2001)

In this study the German Version (HADS-D) of the scale was used.

FACIT-F

The 13-item Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale (FACIT-F; Version 4) was used to assess self-reported fatigue and its impact on daily activities and functions (Cella, Lai, Chang, Peterman & Slavin, 2002; Yellen et al., 1997) during the last 7

Commented [Janka Hau113]: Though in some studies the original cut-off scores (8+ and 11+) failed to be optimal,
until now there is no convention concerning the use of other cut-offs.
- Hinz & Brähler 2011

Commented [Janka Hau114]: Symptoms relating also to physical disorder, such as dizziness, headache or
insomnia were not included

Commented [Janka Hau115]: Zeitform

Commented [Janka Hau116]: Time interval (one week)

Commented [Janka Hau117]: Or maybe literature already here? And then maybe again after cancer-related fatigue!?

days. While it was originally developed for cancer-related fatigue (Cella et al., 2002; Yellen et al., 1997), it has been shown, that the FACIT-F is a reliable and valid measure of fatigue across various health conditions (Cella et al., 2002), making it a widely used tool for both clinical practice and research (Cella et al., 2022; Butt et al., 2013; Montan, Löwe, Cella, Mehnert & Hinz, 2018; Tinsley, Macklin, Korzenik & Sands, 2011). This questionnaire utilizes a five-point Likert scale, with total scores ranging from 0 (severe fatigue) to 52 (no fatigue). Based on general population data, scores ≤30 indicate clinically significant fatigue (Piper & Cella, 2010).

Cluster Analysis

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

Data Preprocessing. All participant data was imported from a TSV file (participants.tsv) into R (using read.delim()), where preprocessing and analysis of the data was conducted. Specific variables of interest were selected and stored as subset including demographic information, cognitive test scores and clinical/questionnaire measures. The MoCA variable was converted to a binary variable: scores ≤25 indicate cognitive impairment, while scores >25 indicate no impairment. Missing values were added for nback task, if participant mentioned that they did not understand the task. Rows with missing values in cone of the relevant cognitive test variables (pvt….) were removed. Missing values in the relevant cognitive test variables (PVT reaction time, n-back miss 1, n-back miss 2, TMT a time, TMT b time (need to mention earlier)) were detected/checked is.na() and rows (participants) with missing values in key cognitive variables were removed using drop_na(), to ensure complete cases for analysis. 9 rows have been delted because of missing values, leaving the dataset with 70 participants. Winzorising was used to replace outliers by capping extreme values beyond 1.5 times the interquartile range (IQR). Outliers are identified and winsorized for the before mentioned cognitive variables. A function winsorize_variable is defined to perform winsorization, replacing values beyond 1.5 * IQR with the values at Q1 – 1.5 * IQR or Q3 + 1.5 * IQR.

Commented [Janka Hau118]: Again literature here? Not quite sure where exactly it should be

Commented [Janka Hau119]: Again „uses“ maybe there is a better/other word I could use instead

Commented [Janka Hau120]: Do I need to mention the literature here again?

Commented [Janka Hau121]: Check checklist from thesis_2711 to see if I mentioned everything important

Commented [Janka Hau122]: Later deleted

Commented [Janka Hau123]: Maybe: Why did I chose those?

Commented [Janka Hau124]: Further down it's written in much more details

Commented [Janka Hau125]: Happened in past!

Commented [Janka Hau126]: Quote (program number, etc.)

Commented [Janka Hau127]: Indicate or indicated?

Commented [Janka Hau128]: Potential cognitive impairment?

Commented [Janka Hau129]: Indicate or indicated?

Commented [Janka Hau130]: Align with what I wrote in MoCA section. Maybe literature here

Commented [Janka Hau131]: If comment said..

Commented [Janka Hau132]: For how many participants

Commented [Janka Hau133]: How many?

Commented [Janka Hau134]: Literature?

Commented [Janka Hau135]: See Lilys BA

Commented [Janka Hau136]: Why?

Winsorized versions of variables were created with _w suffix. 4 outliers were detected for PVT reaction time and winsorized. 2 outliers for TMT_a_time. 4 outliers TMT_b_time. A custom function winsorize_variable() was implemented to replace extreme values beyound 1.5 times the interquartile range (IQR) with the nearest non-outlier values (Q1 - 1.5 * IQR or Q3 + 1.5 * IQR). New variable TMT_diff was calculated as the difference between TMT B and A (B-A).

Variable transformation

To account for the influence of age on cognitive performance, participants were divided into age groups, and z-scores were calculated within each group to adjust the data.

Two functions were defined to categorize participants into age groups. Age groups were created. Age groups added to the dataset. Participants were divided into four distinct age groups, 18-34 years (12 participants), 35-49 years (19 participants), 50-64 years (33 participants), and 65-80 years (6 participants). Age groups orientated from TMT norms. Why decided for this age groups? A separate categorization was used specifically for the TMT difference score. Also 4 age groups but 18-24 years (2 participants), 25-54 years (34 participants), 55-64 years (28 participants), and 65-80 years (6 participants). Why different age groups for TMT difference and all other variables?

After age groups were created, mean and standard deviation for each cognitive variable (PVT and TMTa, TMTb and TMT difference) were calculated within each age group. The function calculate_z_scores_individual() was used to compute z-scores for each participant based on age group norms, adjusting for age-related differences in cognitive performance. Creating new variables with _z suffix. Additionally n-back miss scores (miss 1 and miss 2) are standardized using the scale() function, creating new variables with _s suffix. When looking at the n-back means in each age groups, no age related trent could be detected, therefore no z-score was calculated for the n-back values, instead was standardized. N-back miss scores were standardized using the scale() function to ensure comparability across variables.

The final cleaned and processed dataset was saved for further use as a file named "clean_data.Rdata" in the cluster analysis. Saved as an R data file named clean_data.Rdata.

Cluster Analysis/hierarchical clustering. A hierarchical cluster analysis was performed on the preprocessed test data to identify clusters among participants. Hierarchical cluster analysis was performed on the preprocessed cognitive test data to identify (potential) subgroups/clusters within the participant pool/among participants. Which packages were loaded? Tidyverse, dplyr, dendextend, ggplot2, gridExtra, purrr, vroom. This approach was

Commented [Janka Hau137]: Is that detailed enough or do I need to provide even more information? Or maybe an example?

Commented [Janka Hau138]: Those I need to mention

Commented [Janka Hau139]: Which age groups and why those age groups

Commented [JH140]: Provide mean here

Commented [Janka Hau141]: Do I need to mention the specific age group means for pvt and tmt?

Commented [Janka Hau142]: Probably table here

Commented [Janka Hau143]: Why no age groups for this variable?

Commented [Janka Hau144]: Prove might be needed here

Commented [Janka Hau145]: Since it's explorative investigated k-means and hierarchical. Why then hierarchical? Better fitting

Commented [Janka Hau146]: Why hierarchical and not a different one? I also did k-means but didn't give that much meaning. But I should probably still mention that

Commented [Janka Hau147]: That would mean that I already gave an introduction on cluster analysis

Commented [Janka Hau148]: What is my goal? But I guess I will explain that earlier, so no worries

employed to uncover/reveal patterns in cognitive performance of the participants. Cognitive variables were compared as winsorized, standardized, as well as the original scores were compared.

Only include if good reason to think they will define the clusters. First all cognitive variables, after reduced, why?

At first PVT reaction time, TMT A, TMT B, n-back miss 1 and n-back miss 2, MoCA were used as variables within the clustering. Explorative approach. Using n-back let to bad clustering results. Because everyone performed quite bad. Therefore n-back was excluted from the cluster analysis. TMT difference was not used, since it would double information (not independent). Too high correlation. Why did I choose the variables I chose? Where do I need to write that? Why not used MoCA?

As the hierarchical

The first step in the hierarchical cluster analysis process was to compute a distance matrix. In this approach Euclidean distance method wa used Proximitätsmaß/Distanzmaß bevorzugt bei WARD. All values continuous numerical values that is why used euclidean. Tried different kind of linkage methods and than decided which one performed best, based on. Why? Ward methods was choosen as the algortithm. Specified linkage method via method argument. Dendrogram was build by plotting hierarchical cluster object with hclust. Created desired number of clusters. Cut_mean <- cutree (hclust_median, k = 2) In consideration of the research question and the two groups, withPCS and withoutPCS, a two-cluster solution was chosen. K-means/elbow measure suggested 4 clusters. Therefore a 4-cluster solution was also looked at. As validation, the 2-cluster solution was compared to their self repoRTEd group assignments (withPCS or withoutPCS. Do I here need to mention, how many people are in which cluster? Or is that already result? To visualize cluster on dendrogram abline function used. Stability tested, different proximity measures have been used. But with eucledean best result. Also different algorithms have been tested. Also non-hierarchical clustering was compared to the hierarchical clustering (k-means). Why did I do the analysis with ward and not with k-means? What was my decision there? For the selected number of cluster, three additional analyses were performed using the complete, sigle, and weighted-average linkage methods. The agreement(Übereinstimmung) was assessed using the adjusted Rand index (Hubert and Arabie, 1985). Change of algorithm and alteration of

Commented [Janka Hau149]: Might need to mention that earlier

Commented [Janka Hau150]: Irrelevant or masking variables should be excluded if possible

Commented [Janka Hau151]: Quadriert?

Commented [Janka Hau152]: How detailed? Do I also need to write how I cut the three?

Commented [Janka Hau153]: Maybe for now write and maybe later than delete

Commented [Janka Hau154]: I think in results

number (which numbers where tested?) of clusters was variated. For adjusted rand index: library(fossil) adjusted rand index calculated with rand.index function.

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

Inhaltlich, da zwei verschiedene Gruppen. Later 4 because of k-means

DurchgefühRTE Stabilitätsprüfung

Für ausgewählze Clusteranzahl noch drei weitere Analysen mit dem Complete-, Single- und Weighted-Average-Linkage gerechnet. Die Übereinstimmung wurde mittels des adjustieRTEn Randindex (Hubert und Arabie 1985) beuRTEilt.

Auch: Wechsel des Algorithmus und Veränderung Gruppenzahl (Ein Cluster bleibt gleich)

DurchgefühRTE Validitätsprüfung

Zur Validitätsprüfung wurde auf Variablen Z1, Z2 usw. zurückgeriffen

Statistical analysis. The two clusters were compared in several aspects. First, the two clusters were compared in their cognitive performance levels to validate whether significant differences exist between clusters. Clusters were then compared across demographic variables and results in questionnaires. Of particular interest was to examine how those two clusters differ from or align with the self-reported perception of cognitive performance level. To investigate differences between objective and subjective cognitive performance levels, comparisons occured not only between two clusters but also within the clusters between the subjective groups with PCS and without PCS. Additionally, to maximize the insights from the

Commented [Janka Hau155]: One cluster stayed the same, no matter which cluster numer was chosen.

Commented [Janka Hau156]: Didn't I already mention that?

Commented [Janka Hau157]: Why?

Commented [Janka Hau158]: Are those metric scales?

Commented [Janka Hau159]: Check for correlation?

Commented [Janka Hau160]: Outliers were removed

Commented [Janka Hau161]: Here or earlier?

Commented [Janka Hau162]: Also 4 cluster solution sine k-means said 4 cluster solution is better

Commented [Janka Hau163]: Results on stability here or in results?

cluster analysis, the with PCS groups in cluster 1 was compared to the with PCS group in cluster 2, and similarly for the without PCS groups. A t-test was used for these comparisons. Effect size and cohens d were also compared (need to check why)

The clusters were compared in several expects with each other. In demographical variables (sex, age, and years of education), in the used variables for clusteranalysis. But also in their other cognitive variables (PVT, TMT, n-back, MoCa). Also results in the scores from questionnaires were compared. Not only were the two groups compared between each other, but also within comparasion took place. WithPCS and withoutPCS within one cluster were compared. Also withPCS and withoutPCS were compared between clusters (that means, withPCS in Cluster 1 was compared to withPCS in Cluster 2 to clarify). All comparisons were tested by t-test. T-test robust to….. Data is not normal distributed. That was tested by… cat function was used.

The two clusters where compared

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

EEG Recording and Analysis

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

Preprocessing

Commented [Janka Hau164]: Why t-test? And why is that robust? Why am I allowed to use that one?

Commented [Janka Hau165]: The analysis of this study was focused on the condition eyes open only.
All code described in the following sections can be found in this public GitHub repository: https://github.com/LGodbersen/Masters-thesis.

Commented [Janka Hau166]: EEG signals were collected using the 128-channel actiCap System (Brain Products GmbH, Munich, Germany) with electrodes positioned in an equidistant layout, with a sampling rate of 500 Hz and amplitude resolution of 0.1 µV.

Commented [Janka Hau167]: As alternative

Commented [Janka Hau168]: Here or earlier? Where should I mention how many Versuchsleiter!?

Commented [Janka Hau169]: Or just: EOG activity was recorded using two dedicated EOG electrodes, placed below each eye.

Commented [Janka Hau170]: Matlab is widely used by the EEG community and enabed us to use well-established Matlab-based EEG toolboxes that provide robust functions for computing functional, connectivity measures (Avila et al., 2023) - they followed a pragmatic approach towards preprocessing and adopted a simple, established, and automatic workflow in EEGLAB proposed by Pernet et al. And originally developed for ERP data. Adapted this pipeline to resting-state data and detail the seven preprocessing steps below.

Commented [Janka Hau171]: Loading the data
1. Line noise removal
2. High pass filtering and bad channel rejection
3. Re-referencing
4. Independent Component Analysis and automatic IC rejection
5. Interpolation of removed channels
6. Bad time segment removal
7. Data segmentation into epochs

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

The participants' EEG data were organized in BIDS (Brain Imaging Data Structure) format (Gorgolewski et al., 2016; Pernet et al., 2019). BIDS is a community standard that ensures homogeneity in the organization and description of raw neurocognitive/brain-derived/neuroscientific data, enabling efficient data sharing, minimizing errors, and supporting completely automated analysis workflows (Gorgolewski et al., 2016; Pernet et al., 2019; Truong, Robbins, Delmore & Makeig, 2023). The resting state EEG data, organized according to this standard, were identified and imported into MATLAB using the FieldTrip Toolbox. A trial defining function was built to select the data from the eyes-open condition for subsequent processing. This resulted in approximately 300 s per participant.

Filtering and Resampling

A finite impulse response (FIR) windowed-sinc (firws) filter, designed with a hamming windowed sinc function and implemented in the FieldTrip toolbox, was used for both high-pass and low-pass filtering of the continuous data. For high-pass filtering, a cut-off frequency of 0.1 Hz was applied to eliminate very low frequencies (drift) (Keil et al., 2013). This cut-off was based on the findings of Delorme (2023) and Winkler, Debener, Müller and Tangermann (2015), where filtering at 0.1 Hz or higher significantly improved data quality compared to no filtering. Filters above 0.1 were not used due to (I will come up with something).

Prior to applying low-pass filtering, the data was downsampled from 1000 Hz to 250 Hz, to reduce computational load while preserving sufficient temporal resolution for subsequent analysis. A cut-off frequency of 45 Hz was then used to eliminate high-frequency noise and mitigate potential 50 Hz line noise (Delorme, 2023). Finally, the data underwent re-referencing using the Common Average Reference (CAR) technique to remove the influence of the reference and improve signal quality (Ludwig et al., 2009). As the name implies, an average of the recordings from all electrode sites was computed and used as the reference (Ludwig et al., 2009; Offner, 1950). The function reref() was used (to perform this step). The data was converted into the EEGLAB data structure for further processing.

Commented [Janka Hau172]: Not only preprocessing

Commented [Janka Hau173]: Analyses are performed using Matlab 2020a (The Mathworks, Inc.3) on Windows or Mac OSx with the Statistical and Machine Learning Toolbox installed, along with EEGLAB4 (v2020.0) and its BIDS tool5 (v3.5) and LIMO EEG6 (v3) plugins—both of them available through the EEGLAB plugin manager.

Pernet et al. 2021

Commented [Janka Hau174]: EEGLAB (Delorme and Makeig, 2004) is the most commonly used platform for EEG data analysis (Hanke and Halchenko, 2011; Martínez-Cancino et al., 2020) and all steps proposed can also be reproduced from the user interface

Commented [Janka Hau175]: How to cite that correctly?

Commented [Janka Hau176]: Relevant?

Commented [Janka Hau177]: EEG (70 channel Easycap2) and ECG data were extracted from the binary MEG.fif files that combined MEG, EEG, ECG channels, event markers were time corrected (−34 ms) and electrode positions re-oriented to fit the head coordinate system. Out of the 19 participants, participant 1 was removed because ...

Commented [Janka Hau178]: Important for empty dataset

Commented [Janka Hau179]: What describes EEG and MRI data best together?

Commented [Janka Hau180]: Where to find?

Commented [Janka Hau181]: Correct like that?

Commented [Janka Hau182]: EEG data were high-pass filtered using a finite impulse response (FIR) filter designed ...

Commented [Janka Hau183]: Some authors argue against high-pass filtering (or restrict the applicable high-p ...

Commented [Janka Hau184]: .The FIR filter was chosen for its stability and linear phase characteristics. ...

Commented [Janka Hau185]: Subsequently, high-pass filtering was administered. Since filters above 0.1 Hz can le ...

Commented [Janka Hau186]: Since filters above 0.1 Hz can lead to ...

Commented [Janka Hau187]: Do I need literature?

Commented [Janka Hau188]: I think Lara changed that. Before more. Why not 0.1? Need to check voice messages

Commented [Janka Hau189]: Avila et al., 2023

Commented [Janka Hau190]: After artifact removal, the **CAR** technique was applied again to re-reference the data, ...

Commented [Janka Hau191]: True?

Commented [Janka Hau192]: Data is re-referenced to the average reference with the function pop_reref(). Avila ...

Due to empty dataset from one participant, the participant was excluded, leaving the dataset with 69 participants (something like that. But where should I write that?)

Artifact removal

After the initial filtering and resampling, the preprocessing pipeline continued with detecting and removing artifacts. First, large artifacts - including the removal of flat-line channels, noisy channels, and short-time bursts of noise - were removed from the data using the EEGLAB pop_clean_rawdata() function with specific parameters. Channels with flat lines for more than 5 seconds were removed (FlatlineCriterion = 5), based on the default recommendation (for this parameter) by Pernet et al. (2021). This ensured the exclusion of “dead” or disconnected channels, thereby improving data quality. Channels were further excluded if their signal could not be predicted from a randomly selected subset of the remaining channels for at least 85% of the recording time (ChannelCriterion = 0.85), to remove those that were highly dissimilar from the rest of the channels (Gil Ávila et al., 2023; Pernet et al., 2021). The euclidean distance metric was used to calculate the similarity between channels. Data segments with abnormally high amplitude bursts, exceeding 100 SD compared to neighboring segments, were eliminated (BurstCriterion = 100), as such extreme bursts are considered unlikely to reflect brain signals (Chang et al., 2018). The default BurstCriterion is set to 20, but it may be adjusted if the default setting results in rejecting too many data segments. Some people recommend setting the threshold to 100 (EEGLAB, "Automated Pipeline Tutorial", 2024), which aligns with the optimal cut-off range of 10 to 100 suggested by Chang et al. (2018). Therefore, a mild threshold of 100 was chosen here, as it still effectively removes large-amplitude artifacts while retaining valuable data (Chang et al., 2018). Time windows where more than 40% of the channels were marked as noisy were removed (WindowCriterion = 0.4), to ensure the quality of the remaining data. A more lenient threshold of 0.4 was chosen over the default of 0.25 to retain more data (even if it is potentially noisier). How many “bad” (excessively noisy) channels were detected or removed in this process?

Again the data is re-referenced to the average reference (CAR), this time using the EEGLAB function pop_reref() (Gil Ávila et al., 2023).

Secondly, Independent Component Analysis (ICA) (Bell and Sejnowski, 1995; Hyvärinen, 2013, Jung et al., 2000; Lee et al., 1999; Palmer et al., 2008) was performed on the data, to

Commented [Janka Hau193]: One participant with empty dataset (KA14HH)

Commented [Janka Hau194]: „No „bad“ (excessively noisy) channels were detected or removed in this process“ after running pop_clean_rawdata EEGLAB plug-in (Truong, Robbins, Delmore & Makeig,)

Commented [Janka Hau195]: One participant with empty dataset (KA14HH)

Commented [Janka Hau196]: Data was cleaned

Commented [Janka Hau197]: Delete?

Commented [Janka Hau198]: Langer Strich, wie funktioniert das?

Commented [Janka Hau199]: But they suggested 0.8 which is the default

Commented [Janka Hau200]: The Burst Criterion was set to 100, meaning that artifact-bursts that had a higher than 100 SD
amplitude compared to neighbouring 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.

Commented [Janka Hau201]: Seems weird but that‘s how it is written in tutorial

Commented [Janka Hau202]: Maybe just delete people?

Commented [Janka Hau203]: Criterion for removing time windows that were not repaired completely

Commented [Janka Hau204]: Or bad

detect and reject further artifacts, such as eye or muscle movements (Makeig et al., 1995). ICA was performed with the "runica" algorithm and function pop_runica() with the extended InfoMax method. The runica algorithm was employed with the extended InfoMax method. using the pop_runica function implemented in EEGLAB. To avoid rank deficiency, the number of components was set to one less than the total number of channels (Kim, Luo, Chu, Cannard, Hoffman & Miyakoshi, 2023). This approach decomposes the EEG signal into independent components, potentially separating artifacts from neural activity. Due to the non-deterministic nature of the ICA algorithm, its results vary across repetitions. That is, every repetition of the ICA algorithm leads to small differences in the reconstructed time series after removing artifactual components (Gil Ávila et al., 2023). The resulting ICA weights, which represent the transformation matrix for this decomposition, were saved in a separate file.

Automatic component rejection was implemented using ICALabel (Pion-Tonachini, Kreutz-Delgado & Makeig, 2019), as automatic artifact rejection is preferred over the manual one to ensure standardization (Miljevic et al., 2022). Artifactual components are automatically classified by the ICLabel classifier (Pion-Tonachini et al., 2019). Thresholds were set at probabilities of 0.8 (80%) for muscle-related components (Pernet et al., 2021) and 0.5 (50%) for eye-related components. Components exceeding these thresholds were flagged and automatically removed using the EEGLAB function pop_subcomp(). By default, only components whose probability of being "muscle" is higher than 80% were subtracted from the data (Pernet et al., 2021). The two EOG channels (31 and 32) were removed from the dataset. The cleaned dataset was then checked for consistency using eeg_checkset().

Thirdly and finally, an additional artifacts removal step was implemented to address any remaining problematic channels. This process involved a statistical approach to identify outlier channels based on their signal characteristics. The standard deviation and mean were calculated for each channel across all time points. Then, overall mean values for these standard deviations and means were computed across all channels. Thresholds were established at 2.5 standard deviations above and below the overall mean, creating an acceptable range for channel activity. Channels with standard deviations falling outside this range were identified as outliers. These outlier channels were then removed from the dataset using the function EEGLAB function pop_select(), further refining the EEG data

Commented [Janka Hau205]: stolen

Commented [Janka Hau206]: In recent years, several EEG data preprocessing pipelines have been developed and published
by different laboratories. To our knowledge, there has been no systematic review of these, nor is it quite clear what measures should best be used for fair comparison. It is best that EEG
researchers acquaint themselves with the problems involved in adequate data preprocessing and
test for themselves the particular pipeline they use or construct for this purpose. Because there
is no agreed-upon standard (K. A. Robbins et al., 2020), we hesitate to promote a particular
approach (see https://osf.io/8brgv/ for an example of an automated pipeline). We prefer to involve
ICA decomposition in this process as it is shown to perform well in identifying and separating out
several classes of non-brain source signals typically mixed in the scalp data (eye movements,
scalp muscle activities), as well as identifying major spatially localizable effective brain sources
that represent much of the brain's (largely cortical) contribution to the scalp data.

T… et al.

Commented [Janka Hau207]: Truong, Robbins, Delmore & Makeig, 2023

Commented [Janka Hau208]: This was supported by applying ICLabel (Pion-Tonachini et al., 2019), a neural network classifier
trained on a large body of expert-labeled IC data, to automatically classify components as
representing brain sources or as any of several classes of non-brain sources (see discussion
below). Applying ICLabel before removing line noise correctly identified two strong line noise ICs
but also caused ICLabel to classify effective brain sources still containing substantial noise noise
as most likely representing line noise rather than brain source activity. After running zapline-plus
on the scalp data and then applying the AMICA weights to the cleaned data to obtain the IC time …

Commented [Janka Hau209]: Truong, Robbins, Delmore & Makeig, 2023

Commented [Janka Hau210]: How many good channels were left in both groups?

Commented [Janka Hau211]: Detecting and excluding bad channels is important (Delorme, 2023). After the ICA, the data
were checked again to reject more possible bad channels or epochs. For each participant, all …

Commented [Janka Hau212]: Detecting and excluding bad channels is very important (Delorme, 2023).

Commented [Janka Hau213]: 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 cor- …

quality. This step ensures that channels with unusually high or low variability, which might represent persistent artifacts or malfunctioning electrodes, are excluded from subsequent analyses.

Interpolate bad channels

Channels removed in the previous step were interpolated using the EEGLAB function pop_interp() with the default spherical splines method (Perrin, Pernier, Bertrand & Echallier, 1989), ensuring a consistent number of channels across participants (Gil Ávila et al., 2023). Interpolated channels were inserted into the original channel order. On average …. % of the channels in each group were interpolated.

Epoch length and number

Lastly, the continuous data are segmented into epochs with the function eeg_regepochs() implemented in the EEGLAB toolbox. By default, data are segmented into 2-second epochs (Gil Ávila et al., 2023), however longer epochs might be desirable for … to increase frequency (Gil Ávila et al., 2023).EEG data for each participant were segmented into into 5-second nonoverlapping epochs. This function will then output the new epoch EEG as a dataset on EEGLAB (Bonello, Garg, Garg & Audu, 2018).

For the restingstate 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 the delta and beta power, the data was cut into 5 s epochs.

Power Analysis

Statistical Analysis

T-test for two group comparasing. For four groups different test.

Results

Cluster Analysis

Which two clusters? Which four clusters? How are they different from each other? T-Werte what is interesting to tell? Table? Stabilty of cluster, validity,…

Clinical data(?)

Might be interesting to compare the reported groups vs “my” groups

EEG Power

Delta (frontal ROI)

Beta (central ROI)

Correlations with clinical data(?)

Commented [Janka Hau214]: ?

Commented [Janka Hau215]: 7. Data segmentation into epochs. Lastly, the continuous data are segmented into epochs with the function pop_epoch(). By default, data are segmented into 2-second epochs with a 50% overlap. Although longer epochs might be desirable for the Alpha Peak Frequency estimation to increase frequency resolution, short epochs favor the reliability of functional connectivity measures40,41 . Thus, we propose 2-second epochs to establish a balance between frequency resolution, stationarity of the signal, and reliability of the later extracted features. Fifty percent overlap was chosen to provide a smooth estimation of the power spectra and mitigate the loss of signal due to tapering42 . Epochs containing a discontinuity (e.g., because a segment containing an artifact was discarded) are rejected automatically. Data segmentation was adapted from Pernet et al.14 …

Commented [Janka Hau216]: For the restingstate delta power longer segments are preferred, which is why in the prepro- …

Commented [Janka Hau217]: ‘Epoching’ of EEG data refers to extracting sections (epochs) of the data of equal duration time …

Commented [Janka Hau218]: If I want to do the whole thing in steps

Commented [Janka Hau219]: Not in zotero yet

Commented [Janka Hau220]: Maybe . Freeman 2004

Commented [Janka Hau221]: Power spectrum. Power spectra are computed with the FieldTrip function ft_freqanalysis between 1 and …

Commented [Janka Hau222]: Donoghue et al. (2020) summarize that evaluating a change in absolute power could potentially …

Commented [Janka Hau223]: The differences between the groups for the hypotheses concerning both power and connectivity …

Commented [Janka Hau224]: Might be part of the results from cluster Analysis. To compare

Commented [Janka Hau225]: For the mean delta and beta power, the assumptions were also investigated. Normality assumption …

Commented [Janka Hau226]: The with PCS group exhibited a slightly lower average relative delta power in the frontal …

Commented [Janka Hau227]: Figure 2. Results of power analysis in the A delta (0.6 - 4 Hz) and B beta (14 - 30 Hz) …

Commented [Janka Hau228]: The with PCS group exhibited higher average relative beta power in the central ROI (M = …

Commented [Janka Hau229]: The frontal delta power correlated significantly with the HADS-D, ρ(44) = .31, p = .042, …

Sex differences

Results

- First compare Cluster 1 and Cluster 2
- Second compare within Cluster 1 and within Cluster 2
- Third, compare with and with & without and without
- Also compare the two groups, that are “false”
- Summarize

Cluster analysis

Cluster analysis (2 cluster solution)

Cluster 1 vs Cluster 2

The cluster analysis identified two distinct groups with varying characteristics across cognitive performance and demographic factors. Cluster 1 comprised 41 participants, while Cluster 2 included 29 participants. Regarding Post-COVID Syndrome status, Cluster 1 contained 33 individuals with Post-COVID Syndrome and 8 without, whereas Cluster 2 had 10 with Post-COVID Syndrome and 19 without. The gender distribution showed 27 females and 14 males in Cluster 1, compared to 14 females and 15 males in Cluster 2. No statistically significant differences were observed between clusters for age (M=50.59, SD=14.8 for Cluster 1; M=47.86, SD=12.1 for Cluster 2; p=0.4006) or education level (M=14.91, SD=2.8 for Cluster 1; M=15.83, SD=3.38 for Cluster 2; p=0.2377).

In terms of cognitive performance, significant differences were observed between Cluster 1 and Cluster 2 across several tests. For the Psychomotor Vigilance Test (PVT), Cluster 1 showed a significantly higher mean score (M=0.3571, SD=0.07) compared to Cluster 2 (M=0.2898, SD=0.02), p=5.836e-07. Regarding the Trail Making Test (TMT), Cluster 1 exhibited significantly higher mean completion times compared to Cluster 2 for both TMT-A (M=29.97s, SD=7.99 vs. M=19.49s, SD=4.02, p=9.302e-10) and TMT-B (M=62.76s, SD=25.2 vs. M=42.96s, SD=10.46, p=3.277e-05). For the N-back tasks, which were not used in the cluster analysis, Cluster 1 also had significantly higher mean scores for both 1-back (M=11.32, SD=5.21 vs. M=5.83, SD=3.93, p=3.964e-06) and 2-back (M=15.66, SD=3.0 vs. M=10.45, SD=3.95, p=2.347e-07). For TMT_diff, which represents the difference between TMT-B and

Commented [Janka Hau230]: Descriptively, especially in the beta band, there seem to be sex differences, see Figure B2 in Appendix B. Especially for the connectivity but also slightly 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.

Commented [JH231]: Is that maybe smart?

Commented [JH232]: Definitely need tables here (how to creat them?)

TMT-A scores, Cluster 1 showed a significantly higher mean difference (M=32.79, SD=22.06) compared to Cluster 2 (M=23.47, SD=9.5), p=0.01924. The Montreal Cognitive Assessment (MoCA) results indicated that Cluster 1 had more individuals with abnormal scores (9) compared to Cluster 2 (2), though no p-value was provided for this comparison.

Commented [JH233]: Should I?

The analysis of questionnaire results showed no statistically significant differences between clusters for FACIT (p=0.169), HADS-A (p=0.1213), HADS-D (p=0.2414), or PSQI scores (p=0.129).

or:

The analysis of questionnaire results revealed no statistically significant differences between clusters for several measures. The Functional Assessment of Chronic Illness Therapy (FACIT) scores showed no significant difference between Cluster 1 (M=33.15, SD=12.43) and Cluster 2 (M=37.17, SD=11.42), p=0.169. Similarly, the Hospital Anxiety and Depression Scale (HADS) scores for anxiety (HADS-A) did not differ significantly between Cluster 1 (M=6.69, SD=3.75) and Cluster 2 (M=5.17, SD=3.70), p=0.1213, nor did the depression scores (HADS-D) for Cluster 1 (M=5.69, SD=4.59) and Cluster 2 (M=4.39, SD=4.31), p=0.2414. The Pittsburgh Sleep Quality Index (PSQI) scores also showed no significant difference between Cluster 1 (M=7.85, SD=4.27) and Cluster 2 (M=6.24, SD=3.67), p=0.129.

Within cluster 1

In Cluster 1, the mean age for the withPCS group was 50.9 years (SD=13.6), while the withoutPCS group had a mean age of 49.1 years (SD=19.9), with no significant difference in age (p=0.8129). Education levels also showed no significant differences, with the withPCS group averaging 14.98 years (SD=2.61) compared to 14.6 years (SD=3.7) in the withoutPCS group (p=0.801).

No significant differences were found between withPCS and withoutPCS groups in cognitive variables within Cluster 1. The Psychomotor Vigilance Test (PVT) scores were similar, with the withPCS group scoring a mean of 0.362 (SD=0.0746) and the withoutPCS group scoring a mean of 0.338 (SD=0.0486), resulting in no significant difference (p=0.2822). In N-back 1, there was a trend towards significance (p=0.0875), where the withPCS group had a mean score of 11.9 (SD=5.31) compared to 8.75 (SD=4.13) for the withoutPCS group.

In terms of questionnaire results, FACIT scores indicated a trend towards significance (p=0.1024), with the withPCS group scoring lower (M=31.4, SD=12.1) compared to the withoutPCS group (M=40, SD=12.1). HADS-A scores showed no significant difference, as the withPCS group scored a mean of 6.78 (SD=3.57) versus 5.88 (SD=4.61) for the withoutPCS group (p=0.6165). Similarly, HADS-D scores were not significantly different, with means of 6.06 (SD=4.57) for the withPCS group and 4.00 (SD=4.65) for the withoutPCS group (p=0.3153). The PSQI scores also did not show significant differences, as the withPCS group had a mean score of 8.23 (SD=4.44) compared to 6.43 (SD=3.46) for the withoutPCS group (p=0.2735).

Within cluster 2

In Cluster 2, the mean age for the withPCS group was 51.5 years (SD=10.4), while the withoutPCS group had a mean age of 46 years (SD=12.8), showing no significant difference in age (p=0.2194). Education levels also showed no significant differences, with the withPCS group averaging 15.3 years (SD=3.54) compared to 16.11 years (SD=3.35) in the withoutPCS group (p=0.5606).

Within Cluster 2, significant differences were observed between withPCS and withoutPCS groups in cognitive variables and questionnaire scores. In N-back 1, the withPCS group performed significantly better, scoring a mean of 9 (SD=3.53) compared to the withoutPCS group's mean of 4.16 (SD=3.04; p=0.002).

In terms of questionnaire results, FACIT scores indicated that the withPCS group scored significantly lower on average (M=27.7, SD=11.1) compared to the withoutPCS group (M=42.2, SD=8.08; p=0.0026). HADS-A scores were significantly higher in the withPCS group (M=8, SD=3.27) compared to the withoutPCS group (M=3.68, SD=3.04; p=0.0029). The PSQI scores also showed significant differences, as the withPCS group scored higher on average (M=8.9, SD=3.45) than the withoutPCS group (M=4.47, SD=2.64; p=0.0033). A trend towards significance was observed for HADS-D scores as well, with means of 6.3 (SD=3.34) for the withPCS group and 3.33 (SD=4.51) for the withoutPCS group (p=0.0593).

withPCS cluster 1 vs withPCS cluster 2

In comparing the withPCS groups between Cluster 1 and Cluster 2, the mean age for the withPCS group in Cluster 1 was 50.9 years (SD=13.6), while in Cluster 2, it was slightly higher at 51.5 years (SD=10.4), with no significant difference in age (p=0.8911). Education levels

also showed no significant differences, with the Cluster 1 withPCS group averaging 14.98 years (SD=2.61) compared to 15.3 years (SD=3.54) in Cluster 2 (p=0.7984).

When examining cognitive variables, significant differences were noted in several areas. The Psychomotor Vigilance Test (PVT) scores were significantly higher in Cluster 1 (M=0.362, SD=0.0746) compared to Cluster 2 (M=0.293, SD=0.0204), with a p-value of 2.456e-05. In N-back 1, the Cluster 1 withPCS group had a mean score of 11.9 (SD=5.31), while the Cluster 2 group scored a mean of 9.0 (SD=3.53), approaching significance with a p-value of 0.05439. The N-back 2 scores also showed a significant difference, with Cluster 1 scoring a mean of 15.6 (SD=3.03) compared to Cluster 2's mean of 11.2 (SD=3.94; p=0.006317).

For the Trail Making Test, TMT-A scores were significantly higher in Cluster 1 (M=30.4, SD=7.93) than in Cluster 2 (M=20.4, SD=2.94; p=4.635e-07). TMT-B scores also indicated significant differences, with Cluster 1 scoring a mean of 63.7 (SD=25.7) compared to Cluster 2's mean of 42.7 (SD=9.72; p=0.0004043). The TMT_diff scores showed that the withPCS group in Cluster 1 had a higher mean difference (M=33.3, SD=22.6) compared to the Cluster 2 group (M=22.4, SD=8.43; p=0.02646).

In terms of questionnaire results, the FACIT scores for the withPCS group in Cluster 1 had a mean of 31.4 (SD=12.1), while those in Cluster 2 scored lower on average at M=27.7 (SD=11.1), but this difference was not statistically significant (p=0.3759). HADS-A scores showed no significant difference between clusters, with means of 6.78 (SD=3.57) for Cluster 1 and higher at M=8.00 (SD=3.27) for Cluster 2 (p=0.3287). HADS-D scores were similar as well, with means of 6.06 (SD=4.57) for Cluster 1 and slightly higher at M=6.3 (SD=3.34) for Cluster 2, resulting in no significant difference (p=0.8599). PSQI scores did not show significant differences either, with the withPCS group in Cluster 1 scoring a mean of 8.23 (SD=4.44) compared to a higher score of M=8.9 (SD=3.45) in Cluster 2 (p=0.6363).

withoutPCS cluster 1 vs withoutPCS cluster 2

When comparing the withoutPCS groups between Clusters 1 and 2, the mean age for the withoutPCS group in Cluster 1 was 49.1 years (SD=19.9), while in Cluster 2, it was lower at an

average of 46 years (SD=12.8), but this difference was not statistically significant (p=0.6863). Education levels also showed no significant differences; the withoutPCS group in Cluster 1 averaged 14.6 years (SD=3.7) compared to the average of 16.11 years (SD=3.35) in Cluster 2 (p=0.3485).

In terms of cognitive performance among withoutPCS groups, PVT scores were similar between clusters: M=0.338 (SD=0.0486) for Cluster 1 and M=0.288 (SD=0.0249) for Cluster 2, resulting in no significant difference (p=0.5959). N-back performance indicated that the withoutPCS group from Cluster 1 had a mean score of M=8.75 (SD=4.13) while those from Cluster 2 scored significantly lower at M=4.16 (SD=3.04; p=0.002). For N-back 2, there was no significant difference between groups; the withoutPCS group from Cluster 1 had a mean score of M=15.8 (SD=3..06) compared to M=10..1(SD =4..01) for those from Cluster 2 (p = 0..4678).

For TMT results within withoutPCS groups, TMT-A scores showed no significant differences: M =28..2(SD =8..53) for Cluster 1 and M =19..0(SD =4..50) for Cluster 2(p = 0..3495). Similarly, TMT-B scores were not significantly different between groups: M =58..7(SD =24..4) for Cluster 1 and M =43..1(SD =11..1)(p = 0..9324). The TMT_diff scores also did not reveal any significant differences between clusters: M =30..6(SD =21..1) for Cluster 1 and M =24..0(SD =10..2)(p = 0..6431).

Regarding questionnaire results within withoutPCS groups, FACIT scores indicated no significant differences: M =40(SD =12..1) for Cluster 1 and M =42..2(SD =8..08)(p = 0..6546). HADS-A scores were similar as well: M =5..88(SD =4..61) for Cluster 1 and M =3..68(SD =3..04)(p = 0..2458). HADS-D scores showed no significant differences either: M =4..00(SD =4..65) for Cluster 1 compared to M =3..33(SD =4..51)(p = 0..752). PSQI scores did not show any significant differences between clusters: M =6..43(SD =3..46) for Cluster 1 and M =4..47(SD =2..64)(p = 0..2145).

withoutPCS cluster1 vs withPCS cluster2

When comparing the withoutPCS group from Cluster 1 with the withPCS group from Cluster 2, the mean age for the withoutPCS group in Cluster 1 was 49.1 years (SD=19.9), while the

Commented [JH234]: „Falsch zugeordnete“ p-values? Important? Might be

withPCS group in Cluster 2 had a mean age of 51.5 years (SD=10.4). This difference in age did not reach statistical significance (p=0.6863).

Commented [JH235]: This is wrong

In terms of education, the withoutPCS group in Cluster 1 averaged 14.6 years (SD=3.7), whereas the withPCS group in Cluster 2 had a higher average of 15.3 years (SD=3.54). Again, this difference was not statistically significant (p=0.3485).

Examining cognitive variables, the Psychomotor Vigilance Test (PVT) scores showed that the withoutPCS group in Cluster 1 had a mean score of 0.338 (SD=0.0486), while the withPCS group in Cluster 2 scored significantly lower at a mean of 0.293 (SD=0.0204). The N-back 1 scores revealed a more substantial difference, with the withoutPCS group scoring a mean of 4.16 (SD=3.04) compared to the withPCS group's mean score of 9.0 (SD=3.53). For N-back 2, the withoutPCS group had a mean score of 10.1 (SD=4.01), while the withPCS group scored higher at a mean of 11.2 (SD=3.94).

For the Trail Making Test, TMT-A scores indicated that the withoutPCS group from Cluster 1 had a mean of 19.0 (SD=4.50), while the withPCS group from Cluster 2 scored significantly higher at a mean of 20.4 (SD=2.94). TMT-B scores also showed that the withoutPCS group had a mean score of 43.1 (SD=11.1) compared to the withPCS group's mean score of 42.7 (SD=9.72). The TMT_diff scores for the withoutPCS group were lower, with a mean of 24.0 (SD=10.2) compared to the withPCS group's mean difference of 22.4 (SD=8.43).

In terms of questionnaire results, the FACIT scores for the withoutPCS group in Cluster 1 had a mean of 40 (SD=12.1), while those in Cluster 2 scored lower on average at M=27.7 (SD=11.1). HADS-A scores showed that the withoutPCS group scored a mean of 5.88 (SD=4.61) compared to the withPCS group's higher average score of M=8.00 (SD=3.27). HADS-D scores were similar, with means of M=4.00 (SD=4.65) for the withoutPCS group and M=6.3 (SD=3.34) for the withPCS group.

Finally, PSQI scores indicated that the withoutPCS group in Cluster 1 scored a mean of 6.43 (SD=3.46), while those in Cluster 2 had higher scores on average at M=8.9 (SD=3.45).

Overall, these comparisons highlight differences between the withoutPCS group from Cluster 1 and the withPCS group from Cluster 2 across cognitive performance measures and questionnaire results, suggesting varying levels of cognitive and psychological impact between these groups despite similar demographic characteristics such as age and education level.

Overall, these comparisons indicate that while there are notable differences between the withPCS groups across cognitive performance measures and some questionnaire results when comparing Clusters 1 and 2, the withoutPCS groups exhibited minimal differences across both cognitive variables and questionnaire measures between clusters.

Summary of findings

The comparisons across different clusters and groups revealed several key findings regarding cognitive performance and questionnaire results.

In Cluster 1, individuals with Post-COVID Syndrome (withPCS) showed no significant differences in cognitive variables compared to those without PCS (withoutPCS). However, trends towards significance were noted in N-back 1 and FACIT scores, suggesting that the withPCS group may have performed slightly worse. In terms of age and education, no significant differences were found between the two groups.

In Cluster 2, more pronounced differences emerged between withPCS and withoutPCS groups. The withPCS group demonstrated significantly better performance in N-back 1 and higher scores on HADS-A and PSQI compared to the withoutPCS group. Additionally, the withPCS group had lower FACIT scores, indicating a potential decline in quality of life.

When comparing the withPCS group from Cluster 1 to the withPCS group from Cluster 2, significant differences were observed in cognitive performance, particularly in PVT and N-back tasks, with Cluster 1 performing better. Questionnaire results also indicated that the Cluster 1 group had higher FACIT scores compared to the Cluster 2 group.

Finally, when comparing the withoutPCS group from Cluster 1 with the withPCS group from Cluster 2, notable differences were found across cognitive measures and questionnaire results. The withoutPCS group generally performed better on cognitive tasks like PVT and N-back, while the withPCS group scored lower on FACIT and higher on HADS-A.

Overall, these findings highlight the varying impacts of Post-COVID Syndrome on cognitive functioning and psychological well-being across different clusters and groups.

Or:

In summary, the comparisons across the various groups revealed several key findings regarding cognitive performance and psychological well-being.

In Cluster 1, individuals with Post-COVID Syndrome (withPCS) did not exhibit significant differences in cognitive variables compared to those without PCS (withoutPCS), although trends suggested slightly worse performance in N-back tasks and lower FACIT scores for the withPCS group. In Cluster 2, more pronounced differences emerged, with the withPCS group demonstrating significantly better performance in N-back tasks and higher scores on HADS-A and PSQI compared to the withoutPCS group, alongside lower FACIT scores.

When comparing the withPCS group from Cluster 1 to that from Cluster 2, significant differences were noted in cognitive performance, particularly in PVT and N-back tasks, with Cluster 1 performing better overall. Additionally, the Cluster 1 group had higher FACIT scores than those in Cluster 2.

Finally, a comparison of the withoutPCS group from Cluster 1 with the withPCS group from Cluster 2 highlighted notable differences across cognitive measures and questionnaire results. The withoutPCS group generally performed better on cognitive tasks like PVT and N-back, while the withPCS group scored lower on FACIT and higher on HADS-A.

These findings collectively underscore the varying impacts of Post-COVID Syndrome on cognitive functioning and psychological health across different clusters and groups.

(Overall, these comparisons indicate that while Cluster 1 showed minimal differences between withPCS and withoutPCS groups across various measures, Cluster 2 exhibited more pronounced disparities in cognitive performance and questionnaire results between these groups.)

Cluster analysis (4 cluster solution)

Discussion

Clusters

Cluster 1 always says the same, the other one that gets split up

Delta power hypothesis

Beta power hypothesis

The current study examined the ….

TMT is a valid test (Sánchez-Cubillo et al., 2009).

(Kane, Conway, Miura & Colflesh, 2007) N-back tasks are continous-recognition measures, that present stimulus sequences.

Do people with long covid fullfill criteria for MCI? Many people with MCI evolving into dementia. How is that with people who experience cognitive impairment after COVID? Do they also have bigger chance to get dementia?

Commented [Janka Hau236]: Our result of no difference in delta power at frontal ROI does not support either the GABAhypothesis 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). Kopa´nska et al. (2022) did not find any significant differences in delta power either. Their control were the 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. 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. These findings would indicate that having pronounced frontal delta power coincides with more depressive tendencies, more fatigue and less cognitive functioning. This is in direct contrast to Ortelli et al. (2023), who found their score of the perceived cognitive difficulties scale to be negatively correlated with the delta source power, meaning less cognitive difficulties at higher delta power. It is also in contrast with Cecchetti et al. (2022), who found the frontal assessment battery (FAB) to be positively correlated with delta power (left and right centrol-temporal). Here, a higher FAB score indicates better cognitive functioning. Both with the power results and the correlations, the following aspect can be discussed. …

Commented [Janka Hau237]: 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, the frontal and occipital regions appeared to differ between the groups, but the permutation test did not show significance. The 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 µV2. Using an arbitrary …

Commented [Janka Hau238]: However, caution must be taken when trying to generalize the present results to clinical populations since patients may be using compensatory strategies to complete the test (Jefferson et al., 2006 ; Spikman et al., 2001).

Might be good for discussion

Commented [Janka Hau239]: They see the n-back task bit critically