Theoretical background

Cognitive impairment

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 refers 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.

SCD is the self-reported experience of worsening or more frequent confusion or memory loss. It is a form of cognitive impairment and one of the earliest noticeable symptoms of Alzheimer's disease and relared dementias.

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.

Daily function is largely preserved in MCI.

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Commented [JH2]: @article{jessen2014subjective, title={Subjective cognitive decline initiative (SCD-I) working group. A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease}, author={Jessen, Frank and Amariglio, Rebecca E and van Boxtel, Martin and Breteler, Monique and Ceccaldi, Mathieu and Ch{\'e}telat, Ga{\"e}l and Dubois, B and Dufouil, C and others}, journal={Alzheimers Dement}, volume={10}, number={6}, pages={844--852}, year={2014} }

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Commented [JH5]: @article{petersen2016mild, title={Mild cognitive impairment}, author={Petersen, Ronald C}, journal={CONTINUUM: lifelong Learning in Neurology}, volume={22}, number={2}, pages={404--418}, year={2016}, publisher={LWW} }

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).

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). 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 (1–2SD), 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).

In the ICD-10 the category mild cognitive disorder (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

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Commented [JH7]: 32. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005; 53(4): 695– 699. doi:10.1111/j.1532-5415.2005.53221.x. [DOI] [PubMed] [Google Scholar]
33. Kokmen E, Naessens JM, Offord KP. A short test of mental status: description and preliminary results. Mayo Clin Proc 1987; 62(4): 281– 288. doi:10.1016/S0025-6196(12)61905-3. [DOI] [PubMed] [Google Scholar]

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Commented [JH14]: 6 Petersen RC, Smith GE, Waring SC, Ivnik RJ, Kokmen E, Tangelos EG. Aging, memory, and mild cognitive impairment. *Int Psychogeriatr* 1997; 9 **(** Suppl. 1): 65–69. View
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7 Petersen RC, Stevens JC, Ganguli M, Tangalos EG. Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review). *Neurology* 2001; 56: 1133–1142. View
CASPubMedWeb of Science®Google Scholar

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Commented [JH16]: 66 Frisoni GB, Fratiglioni L, Fastbom J, Guo Z, Viitanen M, Winblad B. Mild cognitive impairment in the population and physical health: data on 1,435

Commented [JH17]: 38 Ritchie K, Artero S. Classification criteria for mild cognitive impairment. A population-based validation study. *Neurology* 2001; 56: 37–42.

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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).

Roberts & Knopman (2013): https://doi.org/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.[9–10] 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

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

Commented [JH20]: Christensen H, Henderson AS, Jorm AF, MacKinnon AJ, Scott R, Korten AE. ICD-10 mild cognitive disorder: epidemiological evidence on its validity. *Psychol Med* 1995; 25: 105–120.

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Graham, J.E. · Rockwood, K. · Beattie, B.L. ...
Prevalence and severity of cognitive impairment with and without dementia in an elderly population
Lancet. 1997; **349**:1793-1796
Full Text
Full Text (PDF)
Scopus (822)
PubMed
Google Scholar

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Unverzagt, F.W. · Gao, S. · Baiyewu, O. ...
Prevalence of cognitive impairment: data from the Indianapolis Study of Health and Aging
Neurology. 2001; **57**:1655-1662
Crossref
Scopus (280)
PubMed
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Commented [JH31]: Introduction restingstate!

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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).

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., 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

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Commented [JH34]: @article{neo2023resting, title={Resting-state EEG power differences in autism spectrum disorder: a systematic review and meta-analysis}, author={Neo, Wei Siong and Foti, Dan and Keehn, Brandon and Kelleher, Bridgette}, journal={Translational Psychiatry}, volume={13}, number={1}, pages={389}, year={2023}, publisher={Nature Publishing Group UK London} }

Commented [JH35]: Saby JN, Marshall PJ. The utility of EEG band power analysis in the study of infancy and early childhood. Dev Neuropsychol. 2012;37:253–73.

Commented [JH36]: EEG in AD and MCI

Commented [JH37]: 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.

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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 of 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.

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Commented [JH42]: EEG in cognitive impairment in AD

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Commented [JH44]: 88 Dement Geriatr Cogn Disord 2000;11:81–89 Claus/Ongerboer de Visser/Bour/Walstra/ Hijdra/Verbeeten/Van Royen/Kwa/ van Gool

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3 Soininen H, Partanen J, Laulumaa V, Paakkonen A, Helkala EL, Riekkinen PJ: Serial EEG in Alzheimer's disease: 3-year follow-up and clinical outcome. Electroencephalogr Clin Neurophysiol 1991;79:342–348.
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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

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type. J Neural Transm 1995;99:55–62.
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ease and healthy controls. Dementia 1994;5: ...

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cephalography power and coherence in Alz-
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ment. Dementia 1996;7:314–323

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blad B, Wahlund LO: Quantitative electroen-
cephalography power and coherence in Alz-
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campus: A review. Hippocampus 1992;2:93–
98.
52 Riekkinen PJ, Riekkinen M, Sirvio J, Mietti-
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Commented [JH53]: @article{duffy1995temporoparietal, title={Temporoparietal electrophysiological differences characterize patients with Alzheimer's disease: a split-half replication study}, author={Duffy, Frank H and MCAnulty, Gloria B and Albert, Marilyn S}, journal={Cerebral Cortex}, ...

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

The 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

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Commented [JH57]: @article{schreiter1994quantitative, title={Quantitative EEG analysis in early onset Alzheimer's disease: correlations with severity, clinical characteristics, visual EEG and CCT}, author={Schreiter-Gasser, Ursula and Gasser, Theo and Ziegler, Peter}, journal={Electroencephalography and clinical Neurophysiology}, volume={90}, number={4}, pages={267--272}, year={1994}, publisher={Elsevier} }

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 EEG 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 controls (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 increase 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 LOG artifact correction.

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

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 degenerative changes [26, 27]. The results of our study would

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Commented [JH60]: EEG in AD

Commented [JH61]: @article{elmstaahl1994quantitative, title={Quantitative EEG in elderly patients with Alzheimer's disease and healthy controls}, author={Elmst{\aa}hl, S{\"o}lve and Ros{\'e}n, Ingmar and Gullberg, Bo}, journal={Dementia and Geriatric Cognitive Disorders}, volume={5}, number={2}, pages={119--124}, year={1994}, publisher={S. Karger AG Basel, Switzerland} }

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produce delta waves in the EEG. Neurology
(Minncap) 1977;27:326-333

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 decline 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 pa-

Commented [JH66]: EEG in dementia

Commented [JH67]: @article{dierks1995correlation, title={Correlation between cognitive brain function and electrical brain activity in dementia of Alzheimer type}, author={Dierks, T and Fr{\"o}lich, L and Ihl, R and Maurer, K}, journal={Journal of Neural Transmission/General Section JNT}, volume={99}, pages={55--62}, year={1995}, publisher={Springer} }

Commented [JH68]: EEG in AD

Commented [JH69]: @article{kuskowski1993rate, title={Rate of cognitive decline in Alzheimer's disease is associated with EEG alpha power}, author={Kuskowski, Michael A and Mortimer, James A and Morley, Gerald K and Malone, Stephen M and Okaya, Amy J}, journal={Biological psychiatry}, volume={33}, number={8-9}, pages={659--662}, year={1993}, publisher={Elsevier} }

Commented [JH70]: Mini Mental State Examination

Commented [JH71]: EEG in AD

Commented [JH72]: @article{dringenberg2000alzheimer, title={Alzheimer's disease: more than a 'cholinergic disorder'—evidence that cholinergic--monoaminergic interactions contribute to EEG slowing and dementia}, author={Dringenberg, Hans C}, journal={Behavioural brain research}, volume={115}, number={2}, pages={235--249}, year={2000}, publisher={Elsevier} }

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tients, 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

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Commented [JH78]: EEG in MCI AD and normal old (Nold)

Commented [JH79]: @article{babiloni2006sources, title={Sources of cortical rhythms change as a function of cognitive impairment in pathological aging: a multicenter study}, author={Babiloni, Claudio and Binetti, Giuliano and Cassetta, Emanuele and Dal Forno, Gloria and Del Percio, Claudio and Ferreri, Florinda and Ferri, Raffaele and Frisoni, Giovanni and Hirata, Koichi and Lanuzza, Bartolo and others}, journal={Clinical neurophysiology}, volume={117}, number={2}, pages={252--268}, year={2006}, publisher={Elsevier} }

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 hippocampal 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.

Commented [JH80]: EEG in AD and cognitive impairment

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Commented [JH82]: @article{jeong2004eeg, title={EEG dynamics in patients with Alzheimer's disease}, author={Jeong, Jaeseung}, journal={Clinical neurophysiology}, volume={115}, number={7}, pages={1490--1505}, year={2004}, publisher={Elsevier} }

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 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

Commented [JH83]: EEG in MCI and AD
EEG introduction, why it’s great to use

Commented [JH84]: Good paper!

Commented [JH85]: @article{babiloni2016brain, title={Brain neural synchronization and functional coupling in Alzheimer's disease as revealed by resting state EEG rhythms}, author={Babiloni, Claudio and Lizio, Roberta and Marzano, Nicola and Capotosto, Paolo and Soricelli, Andrea and Triggiani, Antonio Ivano and Cordone, Susanna and Gesualdo, Loreto and Del Percio, Claudio}, journal={International Journal of Psychophysiology}, volume={103}, pages={88--102}, year={2016}, publisher={Elsevier} }

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 recorded from electrodes placed on the surface of the head. In 1929, Hans Berger reported a dominant 10-Hz oscillating voltage difference between two electrodes placed on the scalp in healthy subjects during a

wakeful eyes-closed relaxed state (the so-called alpha rhythm). Berger showed that the 10-Hz oscillations (10–50 microvolts) are reduced in amplitude when subjects open their eyes or perform a cognitive task. Nowadays, EEG is largely employed for basic scientific research and clinical applications since it is easy to use, non-invasive, cheap, and totally safe. As an important limitation, the EEG voltage measured depends on the position of the reference electrode. Furthermore, EEG is characterized by a low spatial resolution as compared to other measures of brain function such as functional magnetic resonance imaging (fMRI).

Indeed, different conductivities of head tissues (brain, meninges, skull, and scalp) attenuate and blur the spatial distribution of neural currents from brain to scalp electrodes. As a consequence, scalp EEG data present enhanced low-spatial components and negligible values of high-frequency brain oscillations (N40 Hz, gamma rhythms). To minimize these effects of head volume conduction, mathematical procedures have been developed to obtain reference-free measurements with attenuated head volume conductor effects, namely estimation of common average reference, source current density, and inverse EEG source solutions (Q12 Babiloni et al., 2009a, 2009b, 2009c).

Technical requirements make the EEG equipment a non-invasive and non-expensive device, with an overall present price of few tens of thousands of Euro needed for high-resolution EEG recording. EEG signals are derived from electric activity of neurons in the cerebral cortex. Specifically, these signals are mainly produced by post-synaptic ionic currents of synchronously active cortical pyramidal neurons reflecting the integrative information processing of signals coming from thalamus, brainstem, and other cortical modules. EEG signals are very large-scale measures of brain source activity, reflecting synaptic activity synchronized over macroscopic (centimeter) regional spatial scales (Nunez et al., 2001). Synchrony among neural populations in compact regions of the brain produces localized dipole current sources. Synchrony among neural populations distributed across the cortex results in regional or global networks consisting of many dipole sources. EEG signals have a high temporal resolution (b 1 ms) ideal to investigate 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 restingstate 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 intra-cortical (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, parietal, and occipital regions in MCI and AD subjects (Babiloni et al., 2009b).

Furthermore, the global delta and alpha power density was related to the total amount of atrophy of cortical gray matter in the amnesic MCI and in the AD subjects, as revealed by MRI voxel-to-voxel volumetry of lobar brain volume; the higher the total gray matter volume, the lower the global delta power density and the higher the global alpha power density (Babiloni et al., 2012).

The power density of the resting state eyes-closed EEG rhythms was repeatedly found to be correlated to cognitive status in MCI and AD subjects. It has been shown that the posterior alpha power density was positively correlated to the subjects' global cognitive status, as measured by ADAS-cog in the MCI or AD subjects; namely, the lower the alpha power density, the lower the cognitive status (Luckhaus et al., 2008). This relationship can be extended to the cognitive health condition. Furthermore, the posterior delta and alpha power density was correlated to the MMSE score in the Nold, MCI and AD subjects; namely, the lower the alpha power, the higher the delta power and the lower the cognitive status (Babiloni et al., 2006b).

It has been shown that in the MCI subjects, the markers of disease progression included an increase of the power density at theta and delta rhythms in the temporal and occipital lobes as well as the reduction of the beta power density in the temporal and occipital lobes (Jelic et al., 2000).

AD patients were characterized by an increase of theta and delta power density and by a reduction of the alpha and beta power density in the parieto-occipital lobes (Coben et al.,

1985). Furthermore, half of the AD patients showed an increase of the theta and delta power density in the temporal-occipital lobe (Soininen et al., 1989).

Power density of the resting state EEG rhythms does not capture one of the main features of the AD process, namely the impairment of functional or effective connectivity within long range brain networks underlying the cognitive dysfunction in prodromal and manifest AD patients. Indeed, the majority of the cognitive processes are highly distributed and dynamic processes, depending on the selective interplay among many neural populations distributed across several cortical and sub-cortical regions. In the same line, it is expected that temporally-coordinated brain networks underpinning cognitive functions do become more and more abnormal along the progression of AD neurodegeneration, so that AD can be viewed as a disconnection syndrome (Bokde et al., 2009). An ideal methodological approach is, therefore, the extraction of some functional indexes of the abnormalities of the functional brain connectivity across long term neural networks Q24 (Varela et al. 2001;Q25 Le Van Quyen et al. 2003; Börner et al. 2007).

Conclusion, the resting state EEG makers are promising to unveil abnormal functional connectivity and neuroplasticity of neurotransmission in the brain of AD patients.

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

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 children 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.

Commented [JH86]: Discussion (further research)

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Commented [JH89]: Read again to see if all is relevant for theoretical background

Commented [JH90]: @article{sun2024eeg, title={EEG signatures of cognitive decline after mild SARS-CoV-2 infection: an age-dependent study}, author={Sun, Yike and Sun, Jingnan and Chen, Xiaogang and Wang, Yijun and Gao, Xiaorong}, journal={BMC Medicine}, volume={22}, number={1}, pages={257}, year={2024}, publisher={Springer} }

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Zhou L, Zhang M, Wang J, Gao J. Sars-Cov-2: Underestimated damage to nervous system. Travel Med Infect Dis. ...

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Commented [JH95]: Sun Y, Chen X, Liu B, Liang L, Wang Y, Gao S, Gao X. Signal acquisition of brain-computer interfac ...

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Commented [JH97]: Del Brutto OH, Wu S, Mera RM, Costa AF, Recalde BY, Issa NP. Cognitive decline among individuals with history of mild symptomatic SARS-CoV-2 infection: a ...

Commented [JH98]: Antony AR, Haneef Z. Systematic review of EEG findings in 617 patients diagnosed with COVID-19. Seizure. 2020;83:234–41. ...

Commented [JH99]: Di Bella P, Attardi AG, Butera A, Mancini A, Calabrò N, Lo Re EG, et al. Semi-automatic analysis of specific electroencephalographic patterns durin ...

Commented [JH100]: Jedrzejczak WW, Gos E, Ganc M, Raj-Koziak D, Skarzynski PH, Skarzynski H. Effect of the ...

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].

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, life-style, 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.

Commented [JH101]: Organization WH. COVID-19 epidemiological update - 29 September 2023. 2023. Available from: https://www.who.int/publications/m/item/covid-19-epidemiological-update---29-september-2023.

Commented [JH102]: Yong SJ. Long COVID or post-COVID-19 syndrome: putative pathophysiology, risk factors, and treatments. Infect Dis. 2021;53(10):737–54.

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.

Allthough 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

Commented [JH103]: de Schotten MT, Foulon C, Nachev P. Brain disconnections link structural connectivity with function and behaviour. Nature Communications. 2020;11(1):5094.

Commented [JH104]: Klaassens BL, van Gerven JMA, van der Grond J, de Vos F, Möller C, Rombouts S. Diminished posterior precuneus connectivity with the default mode network differentiates normal aging from Alzheimer’s disease. Front Aging Neurosci. 2017;9:97.

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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 exhibited 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).

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.

Commented [JH108]: Ciarambino T, Para O, Giordano M. Immune system and COVID-19 by sex differences and age. Women's health (London, England). 2021;17:17455065211022262

Commented [JH109]: EEG in SCD

Commented [JH110]: @article{perez2024eeg, title={EEG Frequency Bands in Subjective Cognitive Decline: A Systematic Review of Resting State Studies}, author={Perez, Vanesa and Duque, Ar{\'a}nzazu and Hidalgo, Vanesa and Salvador, Alicia}, journal={Biological Psychology}, pages={108823}, year={2024}, publisher={Elsevier} }

Commented [JH111]: Very important for my thesis - Introduction

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 common 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).

Furthermore, 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). Third, 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.

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).

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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 electrical 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.

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).
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.

Commented [JH113]: EEG in MCI and AD

Commented [JH114]: @article{farina2020comparison, title={A comparison of resting state EEG and structural MRI for classifying Alzheimer's disease and mild cognitive impairment}, author={Farina, Francesca R and Emek-Sava{\c{s}}, DD and Rueda-Delgado, L and Boyle, Rory and Kiiski, Hanni and Yener, G{\"o}rsev and Whelan, Robert}, journal={Neuroimage}, volume={215}, pages={116795}, year={2020}, publisher={Elsevier} }

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.

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

Commented [JH115]: EEG in MCI and AD

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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 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.

Additionally, 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

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Commented [JH119]: EEG in MCI

Commented [JH120]: @article{caravaglios2023eeg, title={EEG resting-state functional networks in amnestic mild cognitive impairment}, author={Caravaglios, G and Muscoso, EG and Blandino, V and Di Maria, G and Gangitano, M and Graziano, F and Guajana, F and Piccoli, T}, journal={Clinical EEG and neuroscience}, volume={54}, number={1}, pages={36--50}, year={2023}, publisher={SAGE Publications Sage CA: Los Angeles, CA} }

Commented [JH121]: EEG in AD (early-onset AD)

Commented [JH122]: @article{ozbek2021resting, title={Resting-state EEG alpha/theta power ratio discriminates early-onset Alzheimer's disease from healthy controls}, author={{\"O}zbek, Ya{\u{g}}mur and Fide, Ezgi and Yener, G{\"o}rsev G}, journal={Clinical Neurophysiology}, volume={132}, number={9}, pages={2019--2031}, year={2021}, publisher={Elsevier} }

Commented [JH123]: EEG in MCI and AD

Commented [JH124]: @article{babiloni2011resting, title={Resting state cortical rhythms in mild cognitive impairment and Alzheimer's disease: electroencephalographic evidence}, author={Babiloni, Claudio and Vecchio, Fabrizio and Lizio, Roberta and Ferri, Raffaele and Rodriguez, Guido and Marzano, Nicola and Frisoni, Giovanni B and Rossini, Paolo M}, journal={Journal of Alzheimer's Disease}, volume={26}, number={s3}, pages={201--214}, year={2011}, publisher={IOS Press} }

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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 following 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].

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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 cerebrovascular 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].

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Commented [JH138]: EEG in cognitive impairment (MCI)

Commented [JH139]: @article{liu2024relationship, title={The relationship and pathways between resting-state EEG, physical function, and cognitive function in older adults}, author={Liu, Hairong and Wang, Jing and Xin, Xin and Wang, Peng and Jiang, Wanting and Meng, Tao}, journal={BMC geriatrics}, volume={24}, number={1}, pages={463}, year={2024}, publisher={Springer} }

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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].

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).

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Commented [JH160]: EEG in cognitive impairment (older adults)

Commented [JH161]: @article{finnigan2011resting, title={Resting EEG theta power correlates with cognitive performance in healthy older adults}, author={Finnigan, ...

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 dementia 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.

Commented [JH162]: EEG in AD (alpha)

Commented [JH163]: @article{lejko2020alpha, title={Alpha power and functional connectivity in cognitive decline: a systematic review and meta-analysis}, author={Lejko, Nena and Larabi, Daouia I and Herrmann, Christoph S and Aleman, Andre and {\'C}ur{\v{c}}i{\'c}-Blake, Branislava}, journal={Journal of Alzheimer's disease}, volume={78}, number={3}, pages={1047--1088}, year={2020}, publisher={IOS Press} }

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