

The combined use of electroencephalography and cerebrospinal fluid analysis in the diagnosis and prognosis of Alzheimer's disease: a scoping review

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Abstract

Alzheimer's disease (AD) is the most widespread neurodegenerative disease, affecting millions of people globally each year. Identifying reliable biomarkers for both the diagnosis and, more significantly, for the early detection of the disease is considered crucial for the future research. Recent studies have proposed that cerebrospinal fluid biomarkers (CSF), including amyloid-beta ($A\beta$), t-tau (total tau), phosphorylated (p-tau), and neurogranin can identify preclinical stages of AD. At the same time, electroencephalography (EEG), as a non-invasive diagnostic tool was found to correlate with these biomarkers. This scoping review systematically investigates the correlation between different EEG patterns and technologies with CSF biomarkers in the early stages of AD, such as mild cognitive impairment (MCI) and subjective cognitive decline (SCD), with emphasis on the disease's progression and diagnostic precision. Following PRISMA guidelines, studies published between 1998 and 2024 were identified using PubMed and ScienceDirect. The results consistently revealed that lower levels of $A\beta$ -42 were negatively correlated with decreased brain activity, whereas higher t-tau, p-tau and neurogranin levels were negatively correlated with increased brain activity. In addition, advanced EEG analyses such as microstates showed that disruptions in brain flexibility were also correlated with CSF both in MCI and AD. Despite some contradictory data, the combination of EEG and CSF biomarkers emerged as a more sensitive approach for early diagnosis and disease tracking across AD spectrum, providing promising insights for the prognosis and therapeutic interventions of the disease.

Keywords: Alzheimer's disease, electroencephalography, cerebrospinal fluid biomarkers, early diagnosis, mild cognitive impairment

JEL classifications: I10

Introduction

Alzheimer's disease (AD) is the most prevalent neurodegenerative disease worldwide, affecting more than 30 million people and impairing several cognitive processes (Rayathala et al., 2022). Since AD lacks a definitive medical treatment and its pathophysiological changes begin years before the first symptoms (Hsiao et al., 2013; Villemagne et al., 2013) it is crucial to identify and validate reliable biomarkers that reflect both preclinical and early clinical stages, contributing

to potential interventions (Smailovic et al., 2018). Recent advances in research and the increasing importance of biomarkers have shifted the understanding from a clinically symptom-based approach to a clinicopathophysiological perspective. (Aisen et al., 2017). In line with this, the 2011 NIA-AA guidelines identified preclinical stages of AD, including MCI and preclinical AD. The updated 2018 version formalized AD as a continuum, using the AT(N) biomarker classification, rather than relying solely on clinical symptoms. This approach acknowledges the disease as a continuous process, integrating amyloid-beta ($A\beta$), tau, and neurodegeneration across all stages to improve the diagnostic accuracy (Jack et al., 2018).

Cerebrospinal fluid (CSF) biomarkers, specifically amyloid-beta ($A\beta$ -42), tau protein (T-tau), and phosphorylated tau protein (P-tau) are essential for the staging and diagnosis of Alzheimer's disease (Blennow et al., 2004). These biomarkers are directly correlated with the AT(N) classification system, which classifies the disease according to the presence of amyloid plaques (A), tau pathology (T), and neurodegeneration (N).

The loss of neurons, the development of external senile plaques, and intracellular neurofibrillary tangles (NFT) are considered the main pathogenic features of AD (Selkoe et al., 2004). In the brain, $A\beta$ -42 tends to accumulate and form plaques due to its alternative cleavage of amyloid precursor protein (APP) (Lazo et al., 2009). Subjects with AD, as well as those with other dementias and neurologic disorders had lower amounts of $A\beta$ -42 levels in their CSF (Blennow et al., 2004). Tau protein is produced in the neuron and is in the axon, where it facilitates microtubule construction and stability (Grundke-Iqbal et al., 1986). Abnormal hyperphosphorylation of tau protein is a key factor in the formation of the neurofibrillary tangles (Hampel et al., 2010). Decreased levels of $A\beta$ -42 and increased levels of p-tau and t-tau have been observed in individuals with AD and MCI (Blennow et al., 2015; Hansson et al., 2006). However, CSF collection necessitates lumbar puncture, which is considered highly invasive procedure for patients.

Alternative diagnostic tools, such as electroencephalography (EEG), have gained attention, for the early detection and monitoring of AD over the last two decades (Jeong, 2004). EEG abnormalities in AD are primarily characterized by an increase in theta and delta activity (Coben et al., 1983; Coben et al., 1985; Musaeus et al., 2018) and decrease in beta and alpha activity (Kwak et al., 2006; Locatelli et al., 1998). Many studies have reported that EEG can potentially be used as a biomarker for dementia diagnosis, as it is inexpensive, non-invasive and simple to use (Adamis et al., 2005; Engedal et al., 2015; Jelic et al., 1998; Micanovic et al., 2013). EEG has also been shown to be sensitive in patients with MCI and capable of detecting the conversion from MCI to AD (Prichep et al., 1994).

In 1998 Jelic and his colleagues published the first study investigating how EEG slowing activity correlates with the CSF in patients with cognitive decline. Their findings revealed a positive correlation between higher levels of tau protein in the CSF and slower brain activity, specifically in the alpha/delta ratio. This pioneering study was crucial as it opened the door to explore the clinical applicability of combining EEG and CSF biomarkers. Inspired by that

subsequent studies have further explored how these diagnostic tools could work together to enhance our understanding of the pathophysiology of AD and maximizing early diagnostic accuracy and disease's progression (Ferreira et al., 2016; Kramberger et al., 2013; Smailovic et al., 2018;). Although these findings are promising, there is still a lack of a comprehensive overview of the connection between EEG and CSF in the Alzheimer's disease diagnosis. For this reason, this scoping review aims to systematically address this gap in the literature by providing valuable insights on how the combination of these two diagnostic tools can deepen our knowledge, particularly in terms of diagnostic precision and disease management.

Objectives

The specific objectives of this scoping review are to:

1. Identify and summarize the correlation between different EEG technologies and the CSF biomarker (A β -42, t-tau, p-tau, neurogranin and their ratios).
2. Examine how the correlation between EEG measurements and CSF biomarkers differs across AD, MCI, SCD and healthy individuals.
3. Assess the clinical applicability of these diagnostic tools for the early detection.
4. Evaluate whether these diagnostic tools can track disease progression.

Methods

Protocol and registration

The protocol for this scoping review was developed, following the guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for Scoping Reviews (PRISMA-ScR; Tricco et al., 2018) to examine the relationship between the EEG parameters and the CSF in the AD continuum and its progression. This scoping review is not available in any public database. However, the protocol and a more comprehensive version of the review can be provided, upon request.

Eligibility Criteria

The inclusion criteria for this review were: a) studies including patients diagnosed with Alzheimer's disease (AD), mild cognitive impairment (MCI), subjective cognitive decline (SCD), other types of dementia and healthy controls (HC), aimed at explore how different stages of the disease and different types of dementia influence the diagnostic process, using EEG and CSF; b) studies reporting classical EEG parameters and advanced techniques such as microstate analysis, to assess how different EEG measures could affect the diagnostic process; c) studies that include analysis of the classical proteins of the CSF such as A β -42/40, p-tau, t-tau, neurogranin and their ratios; d) only studies that directly address the relationship between EEG and CSF were been part of the review; e) both cross-sectional and longitudinal studies were taken into consideration in order to analyze the relation

of EEG and CSF across time; f) only English-journal articles were include in the review.

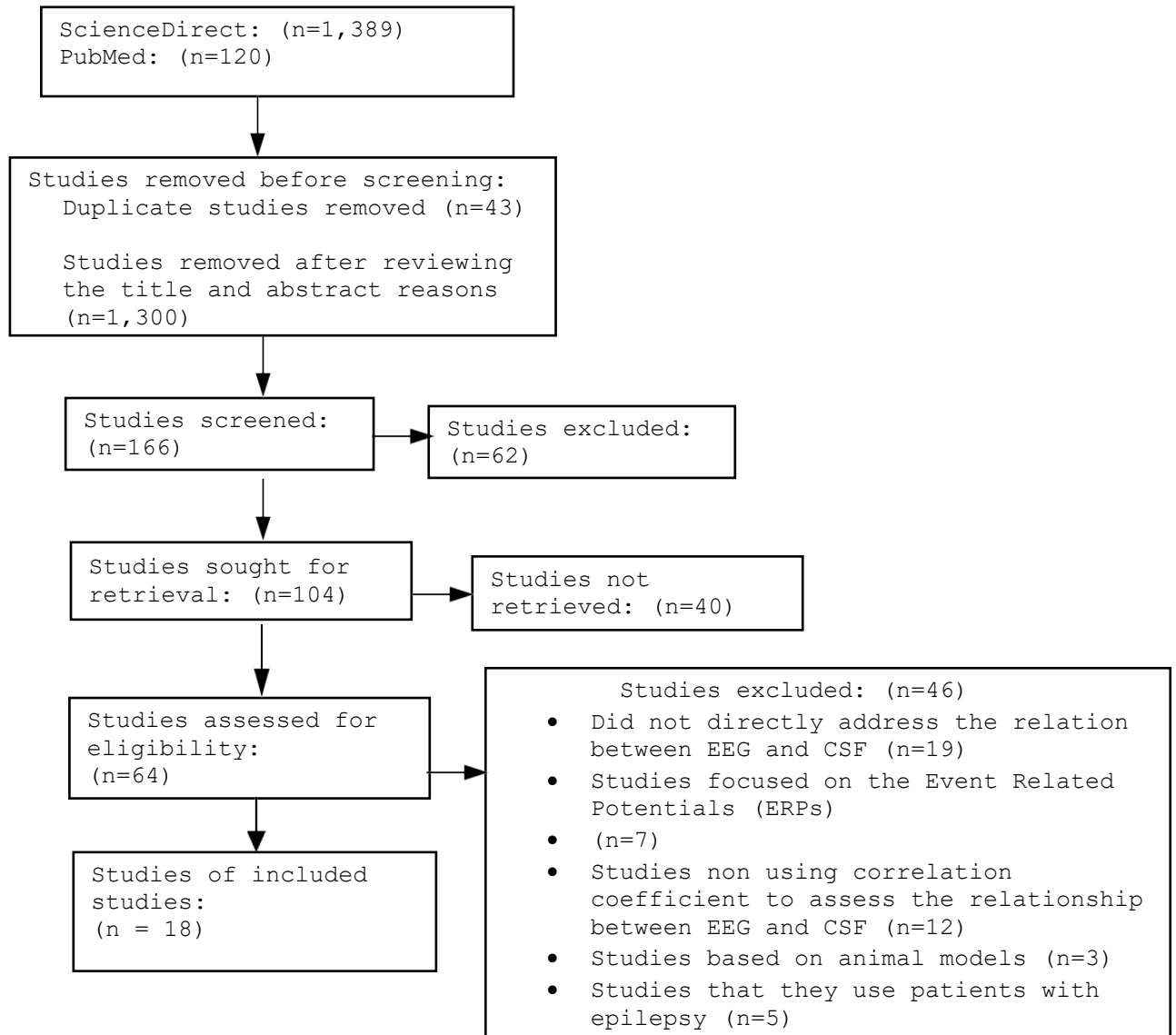
The exclusion criteria were: a) studies that focus on animal models, as the review aimed to assess the clinical applicability of EEG and CSF in human patients; b) studies that they report data about the EEG and CSF, but do not explicitly address the relationship between these two factors; c) studies that they were focusing on non-resting EEG such as the Event-Related Potentials (ERPs), were excluded as the review's purpose was to focus on clinical setting; d) studies involving patients with abnormalities in EEG due to epilepsy were not been a part of this review; e) studies that they do not provide correlation coefficient to address the relationship between EEG and CSF in AD diagnosis were excluded, since the purpose was to balance the validity and the reliability of the findings.

Information sources

A comprehensive search was conducted using PubMed and ScienceDirect in June of 2024, with a follow - up search in November 2024 to capture recent findings. The following search items were applied ("EEG OR electroencephalogram") AND "cerebrospinal fluid "AND ("biomarkers OR biomarker") AND "Alzheimer's disease AND "diagnosis. These keywords were chosen carefully to explore the relation between EEG and CSF in the AD diagnosis. As a result, a broader overview was achieved, covering studies from the first publication in 1998 until the most recent findings in 2024. Further details on the search strategy that was applied, including filters, is available in the figure 1.

Search and selection process

The search strategy was created and executed by the author, to minimize bias and ensure an objective approach. PubMed and ScienceDirect were chosen for their reliability and the precise search terms were carefully selected to align with reviews' objectives. The screening process began with titles and abstracts and was both efficient and rigorous, leading to the inclusion of 18 papers. Comprehensive details on the search strategy and the selection process are available in the figure 1.

Figure 1: Flowchart of the included studies in this review**Data charting process and data items**

Data from eligible studies were extracted capturing all the key information. To ensure that all the relevant data was systematically gathered, the charting form had several sections: a) study characteristics (author(s), journal, year of publication, title of the paper; b) sample characteristics (type of dementia), cognitive status (healthy cognitive individuals), demographic characteristics (age, sex, severity of cognitive impairment assessed with MMSE); c) EEG parameters (power analysis, frequency analysis, microstates analysis); d) CSF biomarker ($A\beta$ -42, $A\beta$ -40, p-tau, t-tau, neurogranin, different ratios); e) CSF collection (CSF via lumbar puncture (L3/L4, L4/L5) at, °C). As this current review was conducted by one author any doubts or disagreements were resolved by reviewing the discussion part of the study. A verification process took place after the extraction of the data. At this stage, a cross-checked with the original studies occurred

to maximize the accuracy of the relevant information in the chart form. Any inconsistencies or errors were resolved by the author by going back to specific sections of the studies to ensure transparency and consistency.

Critical appraisal of individual sources of evidence

For this scoping review, critical appraisal of individual sources of evidence was not performed. That was because the main goal was to map out and summarize the relationship between EEG technology and CSF biomarkers in the diagnosis of Alzheimer's disease, rather than assessing the quality of each study individually. Since scoping review is dedicated to capture and answer broader research questions by identifying literature gaps, the focus was on collecting relevant data among the studies rather than on potential bias or methodological integrity with them.

Synthesis of the results

The charted data were mapped to align with review's goal, focusing on the relationship between EEG and CSF for the diagnosis of AD. The studies grouped based on the stage of cognitive decline (SCD/MCI/AD), the difference between Alzheimer's disease and other types of dementia, the type of EEG measurements (frequency analysis/microstates), the CSF biomarkers and their respective ratios. As a result, this grouping approach allowed for the analysis and comparison of the extracted data, revealing how various cognitive stages correlated with specific EEG patterns and CSF profiles. For a more comprehensive and narrative perspective, see the table 1.

Table 1. Characteristic and results of the studies included in the review

Article citation	Sample	Male/ Female	Mean Age	Dementia severity (MMSE)	EEG features	A β -42	P-tau	T-tau
Smailovic et al., 2018	AD (n=197) MCI (n=230) SCD (n=210)	48.4% / 51.6%	58.9 $\pm$ 8.85	AD: 23.0 $\pm$ 4.3 MCI: 27.3 $\pm$ 2.1 SCD: 28.7 $\pm$ 1.7	GFP, GFS delta, theta, alpha, beta	(GFP)delta, theta AD: r=-0.329, -0.465 MCI: r=0.351*, -0.449* SCD: r=0.010, 0.095 (GFS)alpha, Beta MCI: r=0.022*, 0.010 AD: (alpha) r=0.045	-(GFP)alpha, beta MCI: r=-0.626*, -0.320* -(GFS)MCI: in alpha r=-0.023*, AD: in beta r=-0.305*, SCD: in beta r=-0.013*	(GFP)alpha, beta MCI: r=-0.337*, -0.162*, AD: in beta r=-0.198*, (GFS)in alpha MCI: r=-0.015*
Hata et al., 2017	Probable AD (=14)	42.86% / 57.14%	72.1 $\pm$ 7.6	17.3 $\pm$ 7.2	CSD LPS theta band	(CDS) in theta band r=-0.776*		(LPS) between the left frontal eye field and the right auditory area in the alpha2 r=-0.877 *
Lin et al., 2021	Early (n=30) and late onset AD (n=9) FTD (n=14) HC (n=24)	47.89% / 52.11%	70.9 $\pm$ 8.25	Early onset: 12 FTD: 19 HC: -	-Microstate analysis -Frequency spectral analysis	EOAD: microstate B r=-0.833* Transition from A to B microstate r=-0.714*	FTD: Visual EEG abnormalities with t-tau/A β -42 ratio r=0.756*	EOAD: Transition from A to C microstate r=-0.738*
Smailovic et al., 2019	AD (n=197) MCI (n=230) SCD (n=210) HC (n=308)	40.3% / 59.7%	66.3 $\pm$ 8.1	AD: 23.0 $\pm$ 4.3 MCI: 27.3 $\pm$ 2.1 SCD: 28.7 $\pm$ 1.7 HC: 29.3 $\pm$ 0.8	Microstate analysis (Eyes closed)	Weak correlation but *	Weak correlation	Weak correlation

Kramberger et al., 2014	AD (n=131) MCI (n=285) SCD (n=310) Mixed D. (n=29)	40.3% / 59.7%	67.1 ± 9.45	AD: 23.4 ± 3.9 MCI: 26.5 ± 3.1 SCD: 28.2 ± 2.3 Mixed D: 22.9 ± 4	BA, EA (EEG) abnormalities	High frequency (BA) with Aβ42/p-tau ratio r=0.01* Higher (EA) with Aβ-42 r=0.36 *		Low frequency (BA) r=-0.59* Higher (EA) positive correlation*
Musaeus et al., 2018	AD (n=117) MCI (n=117) HC (n=138)	41.9% / 58.1%	60.33 ± 7.79	AD: 23.52 ± 3.79 MCI: 27.11 ± 2.16 HC: 28.89 ± 1.35	Relative power (eyes closed)			Relative theta band in the left temporal electrodes r=0.24 but NS
Kouzuki et al., 2013	AD (early stages) (n=32)	43.75 / 56.25%	77.3 ± 9.2	26.2 ± 2.2 (>24 for the correlation results)	Alpha dipolarity (Dα, Dζ)	No significant correlation between Dα, Dζ and Aβ-42	(Da) and p-tau181 r=0.457* Ds and p-tau181 r=0.300 (Da) and p-tau181/Aβ-42 ratio r=-0.541* and for (Dζ) r=0.391*	
Ferreira et al., 2016	AD (n=135) MCI (n=124) SCD (n=64) DLB/PDD (n=15) Other D. (n=32) HC. (n=141)	45% / 55%	70.7 ± 10.63	AD: 23.4 ± 3.9 MCI: 27.1 ± 2.1 SCD: 28.6 ± 1.5 DLB/PDD: 28.6 ± 1.5 Other D: 23.5 ± 4.3 HC: 28.9 ± 1.3	-qEEG HC index, -qEEG DLB/PDD index	NS	abnormal qEEG HC index in AD showed greater global impairment and increased levels in CSF p-tau.	abnormal qEEG HC index in AD showed greater global impairment and increased levels in CSF T-tau and p-tau.

Musaeus et al., 2018	AD (n=15) MCI (progressive) (n=25) HC (n=37)	59.74% / 40.26%	69.07 ± 6.94	AD: 26.3 ± 3.2 MCI: 27.6 ± 1.5 HC: 29.1 ± 1.0	Relative power (eyes opened and closed)	r=-0.266* (Right temporal Beta2) r=0.261* (Right temporal Beta)		
Jiao et al., 2023	AD (n=330) MCI (n=189) VCI (n=57) FTD (n=47) DLB (n=21) HC (n=246)	40.45% / 59.55%	65.6 ± 9.15	AD: 11.63 ± 6.28 MCI: 22.70 ± 4.48 VCI: 13.51 ± 6.98 FTD: 12.20 ± 7.41 DLB: 12.76 ± 6.44 HC: 28.62 ± 1.09	Absolute and relative power -O2 (right occipital region) -O1 (left occipital region)	Absolute theta power of channel O2 r=-0.358* in MCI and AD relative theta power of channel O1 r= 0.373*	Absolute theta power of channel O2 r=0.442* in MCI and AD relative theta power of channel O1 r=-0.447*	
Jelic et al., 1998	AD (n=14) MCI (n=12) HC (n=14)	37.5% / 62.5%	60.9 ± 5.96	AD: 17 ± 4 MCI: 28 ± 1.7 HC: 29 ± 0.75	Global field power (GFP)			Alpha/delta ratio r=0.65* Alpha/theta ratio r=0.47 NS in MCI and HC
Yan et al., 2024	AD (n=56) HC (n=38)	58.33% / 41.67	61.2 ± 7.84	AD: 18.72 ± 6.36 HC: 28.46 ± 1.40	-Microstates, Global Field -Power (GFP) (eyes closed)	Duration of Microstate C r=-0.387* and for (Aβ-40) r=-0.362* Mean duration r= -0.401* Mean occurrence r=0.453*	NS	NS

Chino-Vilca et al., 2022	MCI	15 M 12 F	75.3 ± 5.77	M: 25.06 ± 3.65 F: 25.08 ± 2.93	Power analysis (32 channel)	M: theta power r=-0.801* F: NS	NS	M: theta cluster r=0.538* alpha power r=-0.832* F: beta power r=-0.798*
Sun et al., 2024	Positive in (Aβ42/Aβ40 ≤ 0.1) (n=47) Negative in (Aβ42/Aβ40 > 0.1) (n=35)		70.42 ± 8.92		Microstate analysis (eyes closed)	The frequency of occurrence in microstate negatively correlated with Aβ-42/Aβ-40 EEG energy, complexity, mutual information negatively correlated with Aβ-42/Aβ-40		
Babiloni et al., 2022	MCI with (n=8)/without epileptic activity (EEA) (n=34) HC (n=38)	26.25% / 47.5	68.7 ± 1.28	MCI with EEA: 25.7 ± 0.7 MCI without EEA: 25.3 ± 0.4 HC: 28.5 ± 0.2	-Standard resting EEG -EEG criteria for epileptic abnormalities	Decrease of Aβ-42 in MCI with EEA p=0.002*	NS	NS
Cecchetti et al., 2024	AD (n=64) EOAD (n=29) aMCI (n=48) naMCI (n=21) mdMCI (n=67) bvFTD (n=29) DLB (n=19)	47.5% / 52.5%	69.9 ± 6.7	AD: 19.00 ± 5.46 EOAD: 18.10 ± 5.33 aMCI: 26.0 ± 3.16	Individual alpha frequency (IAF)		p-tau/Aβ42 ratio: r=-0.13 with individual alpha frequency (IAF)	
Nielsen et al., 2019	AD (n=32) MCI (n=56) HC (n=41)	58.5% / 41.5%	67.5 ± 2.56	AD: 25 ± 0.866 MCI: 28 ± 0.866 HC: 29 ± 0.577	qEEG method, visual EEG assessments	qEEG Category r=-0.265*	qEEG Categories r=0.209*	qEEG Categories r=0.167

Note. AD, Alzheimer's Disease; MCI, Mild Cognitive Impairment; aMCI, Amnesic Mild Cognitive Impairment; mdMCI, Multiple Domains Mild Cognitive Impairment; SCD, Subjective Cognitive Decline; EOAD, Early onset Alzheimer's Disease; FTD, Frontotemporal Dementia; bvFTD, behavioral Variant of Frontotemporal Dementia; DLB, Dementia Lewy Bodies; PDD, Parkinson's Disease Dementia; Other D./Mixed D., Other Dementias/Mixed Dementias; VCI, Vascular Cognitive Impairment; GFP, Global Field Power; GFS, Global Field Synchronization; CSD, Current Source Density; LPS, Localized Power Spectrum; BA, Background Activity; EA, Episodic abnormalities; Da and D_s, mean and standard deviation of alpha dipolarity; qEEG index, Quantitative Electroencephalography index; NS, not statistically significant; * statistically significant.

-Only one study reports data for neurogranin from Smailovic et al. (2021). A negative correlation between GFP (Global Field Power) in theta band and neurogranin $r=-0.511^*$ for progressive MCI and a negative correlation between GFS (Global Field Synchronization) in theta band and neurogranin levels $r=-0.502^*$ for progressive MCI.

Results

EEG data and amyloid beta correlations

Many studies have examined the relationship between EEG activity and A β -42 levels in relation to Alzheimer's disease and its preclinical stages. In accordance with these studies, A β -42 levels of the CSF were correlated with different EEG features, including frequency bands, microstates and EEG abnormalities. A consistent finding across all the studies was that A β -42 levels were negatively correlated with various EEG characteristics, more prominently in AD patients, but also observable in MCI.

In the EEG frequency bands, the results from two studies complement each other, by indicating that lower levels of A β -42 negatively correlated with reduced brain activity of the brain. Specifically, in both AD and MCI Smailovic et al. (2018) found strong negative correlation between A β -42 levels and theta/delta activity, but only in MCI were these relationships statistically significant. This finding aligns with Chino-Vilca et al. (2022) who found that lower levels of A β -42 were associated with higher theta activity, specifically in male participants. In a comparable study Smailovic et al. (2021) also found a negative correlation between theta activity and neurogranin levels in progressing MCI patients. Even though neurogranin is a synaptic biomarker, this validated the idea that synaptic dysfunction represented both from A β -42 and neurogranin, may be a factor in theta power changes in MCI.

In addition to frequency bands several studies have investigated the relationship through microstates analysis. In the microstate analysis lower A β -42 levels were associated with increased occurrence of microstate C, suggesting impaired sensory and attention process (Smailovic et al., 2019). In the same line, longer durations of microstate C were linked to lower A β -42 levels, whereas more frequent occurrences were linked to increased levels of A β -42 (Yan et al., 2024). Similarly, Lin et al. (2019) highlighted that microstate B and

its transition from A to B had a negative correlation with A β -42 levels in AD patients, whereas in frontotemporal dementia patient's microstate D and A β -42 were negatively correlated, indicating disease-specific.

differences. This pattern was consistent also in results with MCI patients, where amyloid-beta accumulation disrupted microstates patterns and was linked to reduced signal complexity and connectivity (Sun et al., 2024).

Other EEG features such as abnormal EEG activity (EEA) and regional EEG have been studied in relation to A β -42 levels. Both AD and MCI who progress to Alzheimer's exhibited disrupted brain activity, characterized by EEG abnormalities that are negatively correlated with A β -42 levels (Babiloni et al., 2022; Nielsen et al., 2019). Regional EEG research confirms this link as well, with Hata et al. (2017) revealing negative correlation between A β -42 levels and current sink density (CSD) in the right temporal region of AD patients, potentially serving as early brain indicator of brain network disruption.

However, some studies found mixed and not statistically significant findings, regarding the relationship between EEG activity and A β -42 levels. Kramberger et al. (2013) reported negative association between episodic activity and A β -42 levels for AD, MCI, SCD, Mixed dementia patients. However, no significant differences were found between MCI and SCD, while a stronger correlation was observed in patients with mixed dementias. Additionally, not statistically significant difference between qEEG HC index and A β -42 were observed (Ferreira et al., 2016), even in the early stages of AD (Kouzuki et al., 2013).

EEG data and correlations with p-tau and t-tau protein levels

Consistently, t-tau and p-tau levels have been found to be negatively correlated with higher-frequency brain activity and positively correlated with lower-frequency brain activity. Global Field Power (GFP) in the beta and alpha bands were found to be negatively correlated with both t-tau and p-tau levels in MCI patients (Smailovic et al., 2019). Similarly, t-tau and EEG current sink density in the alpha-2 band were negatively associated in AD patients (Hata et al., 2017). One study also identified sex differences, reporting that t-tau levels were negatively associated with alpha band in male and beta band in women with MCI. In the same direction, slowing of dominant brain activity (BA) as well as the occurrence and amount of episodic slow activity in the EEG were positively correlated with increase t-tau levels, irrespectively of the clinical diagnosis (Kramberger et al., 2013). Abnormalities of qEEG HC index, power spectrum changes and signal complexity were also found to positively correlated with increased levels of t-tau and p-tau both in MCI and AD patients (Ferreira et al., 2016; Jiao et al., 2013; Nielsen et al., 2019). Only one study Jellic et al. (1998) reported a different direction of the relationship, finding that higher levels of t-tau were associated with less EEG slowing activity as Alzheimer's disease clinically manifest. Other studies have not found statistically significant correlation between EEG power, microstate analysis and p-tau and t-tau in both MCI and AD patients (Babiloni et al., 2022; Yan et al., 2024).

In microstate analysis tau pathology was negative correlated with the transition from microstate A to C in early onset AD patients (Lin et al., 2021), whereas Smailovic et al. (2019) reported positive

correlation between microstate B alterations and p-tau levels in AD patients, with weaker associations in MCI.

Correlations between EEG and CSF ratios

CSF ratios have been shown to correlate with EEG activity, providing possible diagnostic insights. For instance, a positive correlation was found between t-tau/A β -42 and visual abnormalities in FTD patients, as well as between A β -42/p-tau and alpha frequency in AD, MCI and SCD and mixed dementia patients irrespective of clinical diagnosis (Kramberger et al., 2014; Lin et al., 2021). In early AD Kouzuki et al., 2013 observed that specific patterns of alpha waves (mean and variability) were correlated with p-tau/A β -42. In fact, the p-tau/A β -42 ratio was more sensitive than tau levels and amyloid alone. However, a modest negative correlation observed by Cecchetti et al. 2024 between Individual Alpha Frequency (IAF) and p-tau/A β -42, indicating a small imbalance in brain frequency as tau levels increased. Similarly, Yan et al. 2024 failed to report a significant relationship according CSF ratios and EEG patterns.

Discussion

This scoping review aimed to clarify the relationship between different EEG patterns and CSF biomarkers in diagnosis and early detection of Alzheimer's disease. Studies consistently revealed that lower levels of A β -42 were associated with increased slow brain activity (delta/theta), while p-tau and t-tau levels were associated with decreased fast brain activity (alpha/beta) (Chino-Vilca et al., 2022; Hata et al., 2017; Jelic et al., 1998; Jiao et al., 2023; Smailovic et al., 2018). Similarly, advanced EEG technology like microstate analysis showed that these biomarkers affect the brain's ability to smoothly transit, indicating impaired neuronal flexibility in AD and even in the earliest stages (Lin et al., 2021; Smailovic et al., 2019; Yan et al., 2024). Also, combination of tau pathology and amyloid beta in ratio was more sensitive in relation to alpha EEG activity than A β -42 and p-tau alone (Kouzuki et al., 2013).

Higher beta activity was found to correlated with amyloid deposition in progressive MCI patients potentially reflecting the brain's compensatory mechanism to early disruption (Musaeus et al., 2018). In contrast, other studies recommended that theta activity is one of the first changes in the early stages, with increased levels of t-tau and neurogranin linked in the decline of theta power (Musaeus et al., 2018; Smailovic et al., 2021). However, the absence of statistically significant differences in AD pathology could be attributed to a plateau effect, where noticeable changes in theta band and its correlation with amyloid are expressed in early stages because of the amyloid saturation in the brain as the disease progress. Also, differences in study samples and variations in participants characteristics could influence the statistical significance of the correlation between EEG and CSF biomarkers.

In addition, the correlation between EEG and CSF biomarkers was also specified from men and women, providing further clinical validity to the findings. Sex differences were identified in the correlation between tau pathology and alpha band for men and beta band for women. Men were also found to be more vulnerable in the pre-dementia stage (MCI) compared to women (Chino-Vilca et al., 2022).

Although the relationship between EEG biomarkers and established biomarkers, such as, CSF could enhance our understanding in the Alzheimer's pathology, the combined use of EEG and CSF could be more valuable for the diagnosis and the early detection of the disease. Higher accuracy and reliability were achieved when EEG and CSF were combined to predict cognitive severity and conversion to AD (Jiao et al., 2023). Likewise, the addition of qEEG in the diagnostic process improved not only the detection of the disease in the pre-dementia stages but also enhanced the differential diagnosis (Ferreira et al., 2016). Moreover, EEG microstates have become useful non-invasive tools for potentially predicting A β levels of CSF (Yan et al., 2024), offering a promising way to assess amyloid burden, support early stages, contribute to treatment and monitor disease's progression (Sun et al., 2024).

A few limitations of the included studies should be mentioned. Firstly, the main limitation of this scoping review is that only two databases were used to identify the included studies and only English-language studies were considered. Additionally, many studies had small sample sizes, which can affect the generalizability of the findings. Moreover, the reporting of EEG parameters and variability in biomarker thresholds was inconsistent, potentially influencing the interpretation of the results. These issues reflect the necessity of standardizing protocols for EEG measurements and CSF analysis. Also, differences in the participants' characteristics such as sex, age and disease severity could affect the consistency and the statistical significance of the correlations between EEG and CSF. These variations highlight the need for larger and homogeneous cohorts that further validate this combined approach for early-stage AD diagnosis.

Further research should focus on identifying the most sensitive and valuable techniques for detecting Alzheimer's disease. By incorporating longitudinal studies to explore the relationship between EEG and CSF biomarkers within AD continuum, a better understanding of disease progression and precision over time may be achieved.

In conclusion, EEG offers valuable insights into the brain's synchronous activity, reflecting cognitive impairment across the AD continuum. By adopting a multidimensional approach, using various EEG methods and CSF biomarkers we could enhance our understanding of AD and benefits clinicians with powerful tools for early diagnosis before clinical symptoms become pronounced. Combining EEG and CSF biomarkers could improve the diagnostic accuracy in early-stage AD by providing a more comprehensive assessment of disease progression than individual markers alone. This integrated approach could also serve as a non-invasive first-line screening tool by utilizing EEG to detect neuronal changes, enabling to identify individuals at risk for AD prior to the need for CSF collection. Lastly, this combined approach can facilitate earlier detection, continuous monitoring of disease progression and support the development of personalized treatments.

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