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Exploring easily accessible neurophysiological biomarkers for predicting Alzheimer's disease progression: a systematic review

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Abstract

Alzheimer disease (AD) remains a significant global health concern. The progression from preclinical stages to overt dementia has become a crucial point of interest for researchers. This paper reviews the potential of neurophysiological biomarkers in predicting AD progression, based on a systematic literature search following PRISMA guidelines, including 55 studies. EEG-based techniques have been predominantly employed, whereas TMS studies are less common. Among the investigated neurophysiological measures, spectral power measurements and event-related potentials-based measures, including P300 and N200 latencies, have emerged as the most consistent and reliable biomarkers for predicting the likelihood of conversion to AD. In addition, TMS-based indices of cortical excitability and synaptic plasticity have also shown potential in assessing the risk of conversion to AD. However, concerns persist regarding the methodological discrepancies among studies, the accuracy of these neurophysiological measures in comparison to established AD biomarkers, and their immediate clinical applicability. Further research is needed to validate the predictive capabilities of EEG and TMS measures. Advancements in this area could lead to cost-effective, reliable biomarkers, enhancing diagnostic processes and deepening our understanding of AD pathophysiology.

Keywords Biomarkers, Neurophysiology, Alzheimer disease, Transcranial magnetic stimulation, Electroencephalography, Event-related potentials

Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by a progressive decline in cognitive and behavioral functions severe enough to interfere with activities of daily living [1]. AD is the most common cause of dementia, with prevalence increasing with age, reaching approximately 30% in individuals older than 85 years and leading to more than 50 million affected individuals worldwide [2, 3]. Growing evidence supports the notion that AD neurodegeneration may progress along a continuum starting often from a phase characterized by subjective cognitive decline (SCD), a self-reported experience of cognitive impairment or mental confusion compared

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to a previously normal cognitive status, unrelated to an acute event, with a normal cognitive performance on standardized clinical tests [4, 5]. Not all individuals with SCD will experience a progressive worsening of cognitive functions, as demonstrated by a recent meta-analysis showing that the annual conversion rate from SCD to MCI is approximately 6.6% [6]. The risk of conversion appears to be higher in individuals who, despite manifesting normal cognition by conventional measures, display markers of AD pathology, such as elevated levels of brain amyloid detected through positron emission tomography, abnormally decreased levels of cerebrospinal fluid (CSF) amyloid beta-protein, and increased levels of total and hyperphosphorylated tau. This condition may represent a preclinical phase of AD [7–10]. Patients with a preclinical AD may thus subsequently progress into a prodromal phase, characterized by the emergence of objective cognitive impairments detectable through standardized clinical assessments, leading to a diagnosis of "mild cognitive impairment" (MCI), and eventually advancing to dementia [4, 6, 11]. Evidence from cross-sectional and longitudinal studies indicates that MCI patients show an annual conversion rate of 5–17% to AD [12]. Despite the significant epidemiological impact of AD, there are currently no effective treatments available to prevent or modify the natural course of the disease. Nevertheless, of the 121 agents currently in the AD clinical trial pipeline, 83% target the underlying biology of AD with the intent of disease modification and to prevent the transition from SCD to AD [13, 14]. Consequently, identifying reliable biomarkers for the early detection and monitoring of disease progression is critically important. Indeed, when dementia is clinically diagnosed, it may be too late for a disease-modifying treatment to be effective since the neurodegenerative cascade has advanced beyond the point of reversibility. Detecting preclinical AD would allow for early intervention to slow or even prevent the progression of the disease. In addition, a reliable prognostic biomarker can be used as inclusion criteria or surrogate endpoint in clinical trials. Several neuroimaging and CSF biomarkers providing prognostic information for AD have been identified [15–21]. Unfortunately, these tests are expensive, invasive, and are not available in all neurological centers. Conversely, neurophysiological biomarkers sourced from techniques like electroencephalography (EEG) and transcranial magnetic stimulation (TMS) offer the advantages of providing real-time information on neural function at specific cortical circuits levels, are low-cost and non-invasive, and thus are valuable for tracking disease progression and treatment response over time [22–24]. To date, a comprehensive synthesis regarding the utility of neurophysiological indices in predicting conversion across AD continuum is lacking in the literature. Most reviews conducted so far have focused on identifying neurophysiological markers for early diagnosis, without examining the aspects related to the risk of conversion between different stages of the disease [25, 26]. In addition, while recent reviews and meta-analyses have focused specifically on certain EEG measures [25, 27], the potential utility of other neurophysiological indices, such as event-related potentials (ERPs), TMS and emerging techniques like TMS-EEG in predicting the progression along the AD continuum remains unclear. Assessing the current evidence on the predictive value of various clinically applicable neurophysiological indices could help identify factors that favor one technique over another, and highlight the most promising indices for testing a combined use in evaluating the risk of conversion from SCD to AD. This review aims to fill this gap by offering an integrated perspective on the utility of various neurophysiological measures as biomarkers for AD conversion across its continuum.

Methods

Search strategy

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram (https://www.bmj.com/content/339/bmj.b2700).

The PRISMA flow diagram is presented in Fig. 1.

A literature search in PubMed and SCOPUS was performed in January 2024 using the following search string: ((transcranial magnetic stimulation [Title/Abstract]) OR TMS [Title/Abstract]) AND Alzheimer's disease [Title/Abstract], ((EEG [Title/Abstract]) OR electroencephalography [Title/Abstract]) AND Alzheimer's disease [Title/Abstract], ((ERP [Title/Abstract]) OR event related potentials [Title/Abstract]) AND Alzheimer's disease [Title/Abstract]; ((transcranial magnetic stimulation [Title/Abstract]) OR TMS [Title/Abstract]) AND mild cognitive impairment [Title/Abstract] OR MCI [Title/Abstract], ((EEG [Title/Abstract]) OR electroencephalography [Title/Abstract]) AND mild cognitive impairment [Title/Abstract] OR MCI [Title/Abstract], ((ERP [Title/Abstract]) OR event related potentials [Title/Abstract]) AND mild cognitive impairment [Title/Abstract] OR MCI [Title/Abstract]; ((transcranial magnetic stimulation [Title/Abstract]) OR TMS [Title/Abstract]) AND subjective cognitive impairment [Title/Abstract] OR subjective cognitive decline [Title/Abstract], ((EEG [Title/Abstract]) OR electroencephalography [Title/Abstract]) AND subjective cognitive impairment [Title/Abstract] OR subjective cognitive decline [Title/Abstract], ((ERP [Title/Abstract]) OR event related potentials [Title/Abstract]) AND subjective cognitive impairment [Title/Abstract] OR subjective cognitive decline [Title/Abstract]. The search was limited to human participants and publications in English. All articles published before January

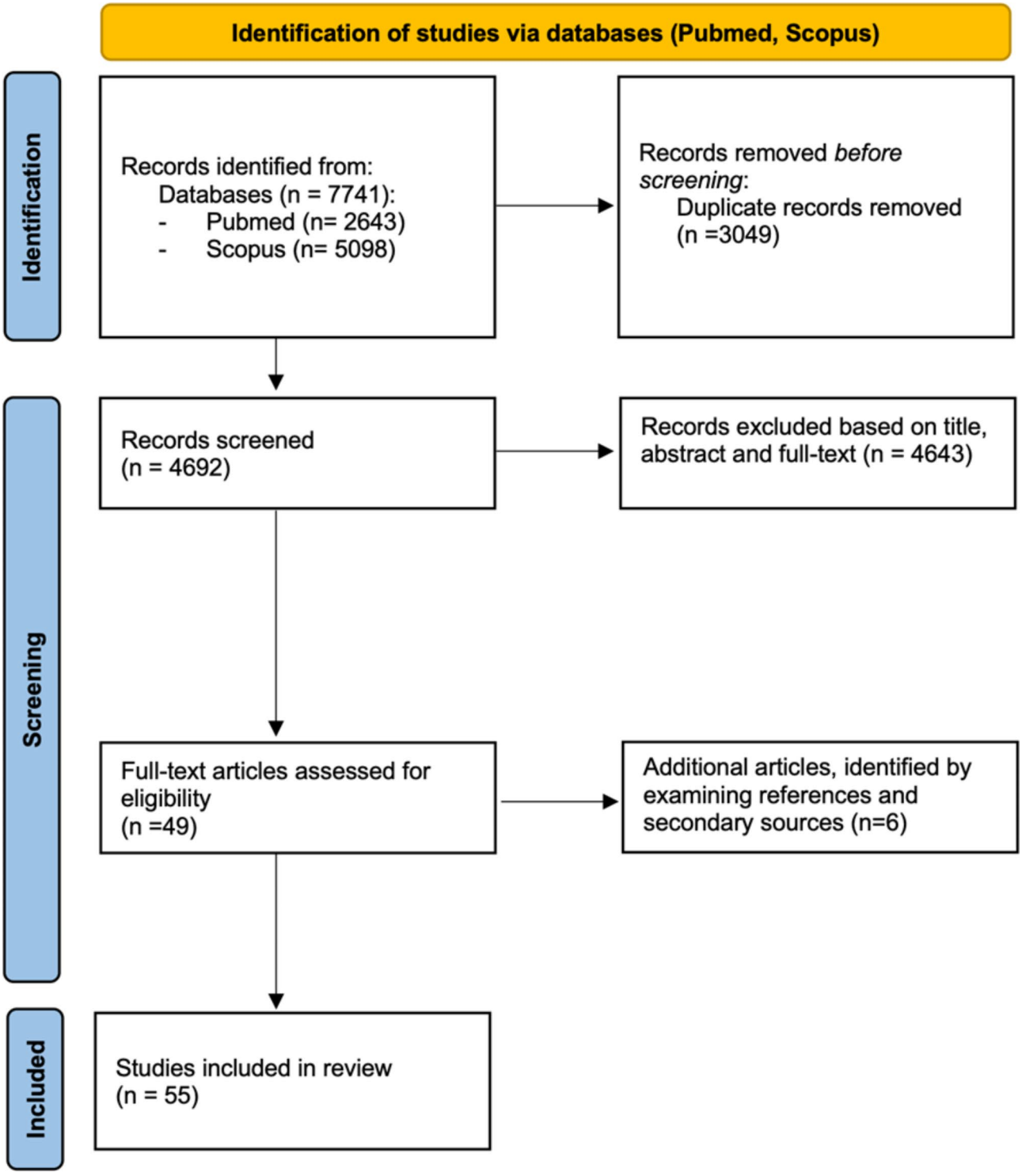

Fig. 1 PRISMA diagram for systematic literature reviews

2024 were included. All search results were aggregated in Excel for Windows; duplicates were discarded, so unique references were retained at first.

Study selection

Records were screened according to title and abstracts by two independent reviewers (MC and CC). Relevant articles and studies in which eligibility could not be determined based on title or abstract were selected for full-text review. Disagreement between the reviewers was resolved through debate, and the resulting decisions were unanimous.

Studies were eligible for inclusion only if: (I) participants with AD were diagnosed by formal criteria [28, 29]; (II) MCI participants were diagnosed according to the Petersen criteria, including only the amnestic types (aMCI) [30]. Alternatively, MCI participants were included it they had been demonstrated to have AD-type pathology by an increased amyloid and tau deposition using CSF or neuroimaging techniques according to NIA-AA criteria [31]. The adoption of these criteria to select MCI participants in this review was based on the notion that both the amnestic subtype of MCI and MCI with positive AD biomarkers have a higher likelihood of being underpinned by AD pathology [31–33]. (III) Subjects with SCD were diagnosed according to criteria by Jessen et al., 2014 [11]. No restriction was made by reason of participant's age or disease duration. Since our main aim was to identify neurophysiological biomarkers that are directly applicable in clinical settings to predict disease progression along the AD continuum, we have focused our review on studies that identified EEG and TMS-based measures. We did not include studies that utilized magnetoencephalography, as although this technique has seen increasing application in AD research in recent years, it remains technically more demanding and less cost-efficient, making it challenging to implement in clinical practice. As the aim was to produce a comprehensive review to detect any evidence of the utility of a putative neurophysiological biomarker, no study quality threshold was set. For this reason, we included both longitudinal and cross-sectional studies, the latter evaluating the association between putative biomarkers and disease progression measures at a single point across groups of patients with different stages of the AD continuum. Among the measures of disease progression that we have considered, there are well-known CSF (Aβ 1–42, phospho-tau 181; total-tau) [15, 16, 34, 35], neuroimaging biomarkers (hippocampal volumetry, cortical thinning, amyloid and tau PET) [15, 16, 35, 36] and clinical indices, including reliable global measures of cognition (e.g. Mini-mental State Examination (MMSE), Cambridge Cognitive Examination, Montreal Cognitive Assessment (MoCA)) [37, 38]. Finally, we checked the reference list of included articles, and the references cited within these sources to supplement our database searches, ensuring a comprehensive capture of relevant literature.

Results

The search produced 7,741 articles, of which 2,643 were from PubMed and 5,098 were from Scopus. 3,049 duplicate articles were removed. After the title, abstracts and full-text screening had been completed, 4,643 articles were removed. Finally, 49 articles were identified as meeting the inclusion criteria. Subsequently, our comprehensive search strategy, which included examining the references of these articles and their secondary sources, led to the identification of six more studies, culminating in a total of 55 relevant articles. 35 out of 55 studies employed a longitudinal design, whereas a cross-sectional approach was used in the remaining studies.

Electroencephalography

All EEG studies, along with details on the methodological approach and metrics used to evaluate biomarkers performance are summarized in Table 1. EEG recording offers a noninvasive tool for identifying possible AD biomarkers by providing high temporal resolution measures of neuronal oscillatory activity [23, 39, 40]. The technique allows for investigating brain dynamics at rest or during a task, thereby highlighting inherent and task-related neuronal patterns. Comprehensive analysis of the EEG signals incorporates frequency and power analysis, as well as changes in power relative to a particular event or task, known as Event-Related Synchronization (ERS) / Desynchronization (ERD) [41, 42]. Furthermore, EEG can be used to assess brain functional connectivity, identifying synchronized neuronal activity across different electrodes [43, 44]. Lastly, EEG recording also allows the analysis of global measures of brain activity known as microstates - stable, brief periods of global patterns of scalp potential topographies [45, 46].

EEG spectral power measures

Resting state EEG Converging evidence coming from longitudinal studies has shown that progressive MCI patients are characterized by an increase in power within the delta [47, 48] and theta [47–51] frequency bands. Similarly, patients with mild AD are characterized by a widespread increase in delta sources compared to healthy elderly subjects, a change that is sensitive to the progression of the disease [52]. Also, an increase of theta power was reported in aMCI compared to SCD and non-amnestic MCI, whereas an increase of anterior delta sources has been reported in amnestic MCI and SCD compared to healthy controls (HCs) [53]. Three of these studies reported significant differences in theta activity only for posterior regions [49, 51, 53]. One study reported a more

Table 1 EEG studies focusing on biomarkers of conversion across the AD spectrum

First author and year	Participants	Study design	Methods	Main results	Sensitivity/Specificity
Jovicich et al., 2019	144 aMCI (81 Aβ42/P-tau ratio positive, 63Aβ42/P-tau ratio Negative)	Longitudinal (24 months)	rsEEG (Spectral analysis (LORETA) aoERPs rsfMRI CSF biomarkers EEG channels:19 Montage system: 10–20 Reference: Free reference (earlobes or cephalic)	CSF-marker positive MCI: ↓ Parietal, occipital, temporal and limbic source activity of the low frequency alpha band ↑ widespread delta and theta source activity ↑ limbic source activity of theta rhythms over time	n.a.
Gouw et al., 2017	205 nondemented, amyloid positive subjects (63 SCD, 142 MCI)	Longitudinal (median period of 2.2 years)	CSF biomarkers rsEEG (Spectral analysis) EEG channels:21 Montage system: 10–20 Reference: average reference including all electrodes	*Markers of clinical progression* MCI: ↑ delta and theta power in parietal/occipital regions ↓ alpha power and peak frequency in parietal/occipital regions SCD: ↑ delta and theta power in all regions ↓ relative alpha power and peak frequency in frontal regions	n.a.
Huang et al., 2000	38 mild AD; 24 HS; 31 MCI	Longitudinal (average interval of 25.5 months; range 12–48)	rsEEG Spectral analysis (FFT; GFP) EEG channels:20 Montage system:10–20 Reference: mastoids	*Progressive MCI vs. Stable MCI* ↓ amplitude of alpha GFP More anterior localization of theta, alpha and beta2 activity	*Progressive MCI vs. Stable MCI* Absolute power: Alpha(T4-T6) SE 86% / SP 53% Relative power: Theta(F3-C3), Alpha (C4-P4) SE 79% / SP 94%
Poil et al., 2013	86 MCI	Longitudinal (2 years)	rsEEG (spatial, temporal and spectral biomarkers) EEG channels: 21 Montage system:10–20 Reference: common average of all electrodes except Fp1and Fp2	A diagnostic index, including the integration of several EEG biomarkers (amplitude correlations with Cz in Beta, bandwidth of subject-specific beta frequency, peak width of dominant beta peak, range of amplitude values in beta, ratio between theta and alpha power, and alpha relative power), may predict the progression to AD with higher SE and SP than EEG alone.	*Progressive MCI vs. Stable MCI* Peak width of the dominant beta frequency: SE 64% / SP 62% Set of 6 biomarkers: SE 88% / SP 82%
Musaeus et al., 2018a	138 HS, 117 MCI, 117 AD	Cross-sectional	rsEEG (spectral analysis) CSF biomarkers EEG channels: 19 Montage system: 10–20 Reference: average reference including all electrodes	↑ relative power in theta band in the temporal regions in MCI ↑↑ relative power in theta band in the temporal regions in AD ↓ alpha power in the full band in MCI than in HS Relative theta power in temporo-parietal regions was negatively correlated with neuropsychological measures (MMSE, learning, recall, recognition and the total CERAD score) No significant correlations between relative power in the theta band and CSF biomarkers	n.a

Table 1 (continued)

First author and year	Participants	Study design	Methods	Main results	Sensitivity/Specificity
Rossini et al., 2006	69 MCI	Longitudinal (almost 14 months)	rsEEG Spectral analysis (FFT) Source Location (LORETA) EEG coherence EEG channels:19 Montage system: 10–20 Reference: free reference	*Progressive MCI vs. Stable MCI* ↑ fronto-parietal midline coherence, ↑ delta (temporal), theta (parietal, occipital and temporal), and alpha1 (central, parietal, occipital, temporal, limbic) sources at baseline	n.a.
Gaubert et al., 2021	304 HS (A+/A-, N+/N-, AD decliners/AD non decliners)	Longitudinal (5 years)	rsEEG (Spectral analysis and connectivity analysis) ApoE genotype 18 F-florbetapir PET FDG-PET 3T MRI EEG channels: 224-16-4 Montage system: 10–20/10–10/5–5 Reference: Vertex, Re-referenced to common average offline	The best classifier for the prediction of neurodegeneration was logistic regression with 4 channels EEG with five items preselected followed by the logistic regression with 16 channels EEG with all items pre-selected. The best classifier for the prediction of decline to prodromal AD was logistic regression with the following combination of groups of features: demographical, neuropsychological data, APOE4 genotype and hippocampal volumetry, enabling a median Area under curve of 0.70, a 67% balanced accuracy, 50% sensitivity, 83% specificity, 14% PPV and 97% NPV	n.a.
Babiloni et al., 2006	155 MCI, 193 mild AD, and 126 HS	Cross-sectional	rsEEG Spectral analysis (FFT) Source Location (LORETA) EEG channels: 19 Montage system: 10–20 Reference: Re-referenced to common average offline	Occipital Delta and alpha1 source in parietal, occipital, temporal, and 'limbic' areas are ↑ in MCI and AD	n.a.
Babiloni et al., 2010	79 HS; 53 SCD; 51 non-amnestic MCI; 92 aMCI	Longitudinal (2–3 years)	rsEEG Spectral analysis (FFT) Source Location (LORETA) EEG channels: 19 Montage system: 10–20 Reference: free reference	MCI compared to HS: ↑ frontal delta source amplitude SCD compared to HS: ↓ parietal and occipital theta sources amplitude	n.a.
Babiloni et al., 2011	100 aMCI	Longitudinal (1year)	rsEEG Spectral analysis (FFT) Source Location (LORETA) EEG channels:19 Montage system: 10–20 Reference: free reference	*Stable MCI vs. Progressive MCI* ↑ posterior cortical sources amplitude of alpha1 rhythms	n.a.

Table 1 (continued)

First author and year	Participants	Study design	Methods	Main results	Sensitivity/Specificity
Luckhaus et al., 2008	88 MCI; 42 AD	Longitudinal (1 year)	rsEEG Spectral analysis (FFT) EEG channels: 32 Montage system: 10–20 Reference: average of the F3-F4 electrodes	*Progressive MCI and AD vs. Stable MCI* ↓ alpha power over posterior leads	n.a.
Jelic et al., 2000	27 MCI, 15 AD, 16 HS	Longitudinal (21 months)	rsEEG Spectral analysis (FFT) EEG channels:20 Montage system: 10–20 Reference: not reported	*Progressive MCI vs. Stable MCI* ↑ theta relative power at temporo-occipital derivations. ↓ beta relative power at temporo-occipital derivations.	n.a.
Babiloni et al., 2009b	33 mild AD, 52 aMCI, 47 HS	Cross-sectional	rsEEG Spectral coherence (total coherence) EEG channels: 19 Montage system: 10–20 Reference: cephalic reference	↑ total coherence of delta rhythms in the AD continuum (HS < MCI < AD) ↓ alpha1 total coherence in AD than MCI and HS	n.a
Babiloni et al., 2009a	35 AD, 88 aMCI, 60 HS	Cross-sectional	rsEEG Spectral analysis (FFT) Source Location (LORETA) MRI (hippocampal volume) EEG channels:19 Montage system: 10–20 Reference: Re-referenced to common average offline	Power of occipital, parietal and temporal alpha1 sources was positively correlated with the normalized hippocampal volume	n.a.
Babiloni et al., 2013	57 HS, 102 aMCI, 108 AD	Cross-sectional	rsEEG Spectral analysis (FFT) Source Location (LORETA) MRI EEG channels: 19 Montage system: 10–20 Reference: Mastoid, Re-referenced to common average offline	↓ global alpha1 sources amplitude in MCI than HCs ↑ global delta sources amplitude in AD > MCI > HS In the MCI and AD group cortical grey matter volume negatively correlated with amplitude of delta source and positively correlated with amplitude of alpha1 sources	n.a.
Babiloni et al., 2013	88 mild AD; 35 HS	Longitudinal (1 year)	rsEEG Source Location (LORETA) EEG channels:19 Montage system: 10–20 Reference: Re-referenced to common average offline	MCI vs. HS ↓ amplitude in alpha sources AD vs. MCI and HS ↑ amplitude in delta sources ↓ amplitude of alpha 1 sources	n.a.
Babiloni et al., 2014	54 MCI, 45 HS, 50 AD	Longitudinal (1 year)	rsEEG Source Location (LORETA) EEG channels: 19 Montage system: 10–20 Reference: Re-referenced to common average offline	↓ power of parietal, occipital and temporal low frequency alpha source in MCI < AD at baseline ↓ power of parietal, occipital and temporal low frequency alpha source in MCI and AD after 1-year follow up	n.a.

Table 1 (continued)

First author and year	Participants	Study design	Methods	Main results	Sensitivity/Specificity
Goodman et al., 2018	33 AD, 34 MCI, 31 HS	Cross-sectional	EEG (ERS during N-back working memory task) EEG channels:64 Montage system: 10–20 Reference: electrode posterior to Cz, Re-referenced to the average mastoid electrode	↓ theta-gamma coupling in MCI < AD compared to HS during the 2-back condition.	n.a.
Babiloni et al., 2015	45 HS, 100 aMCI, 90 AD	Cross-sectional	rsEEG Spectral analysis (FFT) Source Location (LORETA) MRI (Gray matter density) EEG channels: 19 Montage system: 10–20 Reference: cephalic, Re-referenced to common average offline	Amplitude of occipital alpha1 sources was positively correlated with occipital GMD and with MMSE score across all groups Amplitude of occipital alpha sources distinguish HS and AD subjects	n.a
Hsiao et al., 2014	21 AD, 21 MCI	Cross-sectional	rsEEG Spectral analysis (FFT) Functional connectivity analysis EEG channels: 19 Montage system: 10–20 Reference: the average of the two linked mastoid electrodes	Differences in cortico-cortical connection within the DMN between AD and MCI ↓ imaginary coherence in the delta and theta bands between the precuneus, posterior cingulate cortex and anterior cingulate cortex in AD ↑ imaginary coherence in the delta, theta and beta2 bands between the medial temporal lobe and medial frontal cortex and posterior cingulate cortex in MCI Correlation between MMSE score and imaginary coherence values	n.a.
Smailovic et al., 2018	210 SCD, 230 aMCI, 197 AD	Cross-sectional	rsEEG (GFP and GFS) CSF biomarkers EEG channels: not declared Montage system:10–20 Reference: free reference	Negative correlation between: -CSF Aβ42 values and theta and delta GFP -p- and t-tau CSF levels and alpha and beta GFP Positive correlation between: Aβ42, p- and t-tau CSF levels and alpha and beta GFS	n.a.
Lian et al., 2021	46 MCI, 43 AD, 43 HS	Cross-sectional	Microstate analysis EEG channels: 64 Montage system:10–20 Reference: between Cz and CPz, Re-referenced to common average offline	Differences in microstate duration, occurrence and coverage across HS, MCI and AD Transition probability from A to B (asymmetrical classes) was negatively correlated with MMSE score.	n.a.
Musaeus et al., 2019a	17 AD, 27 MCI, 38 HS	Longitudinal (3 years)	rsEEG Quantitative coherence Imaginary part of coherence EEG channels: 19 Montage system: 10–20 Reference: Re-referenced to common average offline	*Progressive MCI* ↑ of delta and theta CoH across fronto-temporal regions ↓delta imaginary part of coherence for frontal-frontal, temporal-frontal, and parietal-frontal connections Negative correlation between theta coherence and Addenbrooke's Cognitive Examination	n.a.

Table 1 (continued)

First author and year	Participants	Study design	Methods	Main results	Sensitivity/Specificity
Musaeus et al., 2019b	17 AD, 27 MCI, 38 HS	Longitudinal (3 years)	Microstate analysis CSF analysis EEG channels: 19 Montage system: 10–20 Reference: Free reference	↑ occurrence and coverage for microstate A in MCI and AD than HS No significant differences between progressive MCI and stable MCI for duration, occurrence and coverage (the largest difference was found for microstate D)	n.a
Musaeus et al., 2018b	17 AD, 27 MCI, 38 HS	Longitudinal (3 years)	RsEEG (qEEG coherence and iCoH) CSF biomarkers EEG channels: 19 Montage system: 10–20 Reference: Re-referenced to common average offline	↓ baseline relative power in the parietal electrodes in the beta1 band in progressive MCI Negative correlation between parietal beta1band relative power and Aβ42	n.a.
Missonnier et al., 2006	24 MCI	Longitudinal (1 year)	EEG during N-back working memory task (Synchronization analysis) EEG channels: 20 Montage system:10–20 Reference: linked earlobes	↓ theta ERS power over all electrode's sites in progressive MCI than stable MCI	*Progressive MCI vs. Stable MCI* Theta ERS: SE 87% / SP 60%
Deiber et al., 2015	45 MCI, 97 Older controls (OCs)	Longitudinal (18 months)	EEG during attention and working memory task (Event-related spectral power, ERPs, Intertrial coherence) EEG channels: 30 Montage system: not declared Reference: linked earlobes	↓ P3 amplitude in MCI than OCs ↓ alpha ERD in stable OCs than deteriorated OCs and MCI (no differences between deteriorated OCs and MCI) ↓ beta ERD in stable OCs and MCI than deteriorated OCs ↓ beta ITC in deteriorated OCs than stable OCs.	n.a.
Prieto del Val et al., 2016	34 aMCI, 26 HS	Longitudinal (2 years)	EEG during memory encoding/retrieval task (spectral analysis) MRI (3D-T1 MPRAGE) EEG channels: 59 Montage system: 10–20 Reference: linked mastoids	↑ alpha ERD during memory recognition in stable aMCI than progressive aMCI Alpha ERD during encoding in posterior cingulate cortex combined with amygdala volume have a higher predictive value for AD conversion than the two items considered alone	*Progressive MCI and AD vs. Stable MCI* Amygdala volume: SE 75% / SP 79% Alpha ERD in posterior cingulate cortex: SE 58% / SP 93% Alpha ERD in left cuneus: SE 75% / SP 72% Alpha ERD in posterior cingulate cortex and amygdala volume: SE 77% / SP 82%

Table 1 (continued)

First author and year	Participants	Study design	Methods	Main results	Sensitivity/Specificity
Mazaheri et al., 2018	25 aMCI, 11 HS	Longitudinal (3 years)	EEG during a word comprehension task EEG channels: 19–32 electrodes Montage system: 10–20 Reference: Re-referenced offline to linked mastoids	↓ theta power in parietal regions during lexical processing of the word Positive correlation between lexical theta activity and Boston naming test ↓ central theta activity and late frontal theta suppression during meaning processing	*Progressive MCI vs. Stable MCI and HS* theta power during lexical retrieval at electrode Pz for the Congruent words: SE 60% / SP 81% theta power during lexical retrieval at electrode Pz for the Incongruent words: SE 60% / SP 76% theta power during semantic processing at Cz for Congruent words: SE 73% / SP 86%) theta power during semantic for incongruent words: SE 80% / SP 95%
Dubois et al., 2018	318 SCD	Longitudinal (30 months)	rsEEG EEG during a cognitive task (memory recall of words) EEG channels: 256 electrodes Montage system: Whole head Geodesic 300 EEG system Reference: not reported	↓ of α:θ ratio due to an increase in α oscillations over time in prefrontal areas in participants who were positive for amyloid β deposition at baseline.	n.a.
Tóth et al., 2014	9 aMCI; 11 HS	Longitudinal (1 year)	rsEEG Phase lag index EEG channels:33 electrodes Montage system:10–20 Reference: The tip of the nose	↓ delta and theta phase lag index within frontal and between frontal and temporal and parietal areas in MCI compared to HS	n.a.

aMCI, amnesticMCI; MCI, mild cognitive impairment; rsEEG, resting state electroencephalography; aoERPs, auditory oddball event related potentials; rsfMRI, resting state functional magnetic resonance imaging; ADAS-Cog13, Azheimer's disease assessment scale – Cognitive subscale; SCD, subjective cognitive decline; CSF, cerebrospinal fluid; HS, healthy subjects; GFP, global field power; FFT, fast fourier transformation; AD, Alzheimer disease; MMSE, mini-mental state examination; CERAD, consortium to establish a registry for Alzheimer's disease; A, amyloid beta peptide; N, neurodegeneration; ApoE, Apoliprotein E; 18 F-florbetapir PET, 18 F positron emission tomography with florbetapir; FDG-PET, 18 F-fluorodeoxyglucose positron emission tomography; 3T MRI, 3Tesla magnetic resonance imaging; GMD, gray matter density; GFP, global field power; GFS, global field synchronization; CoH, coherence; iCoH, imaginary part of coherence; ERP, event-related potentials; ERD, event-related desynchronization; ERS, event-related synchronization, n.a. not available, SE: sensibility, SP: specificity

anterior localization of theta activity in progressive MCI [50], while another reported a widespread localization of delta and theta activity [47]. It is important to note that this evidence stems from studies employing a methodology that allows for comparison across different studies (see Table 1). Findings from a cross-sectional study have demonstrated that power within the theta frequency band is negatively correlated with neuropsychological measures but is not associated with CSF biomarkers [54].

Five studies found lower alpha relative power [48, 50, 55], absolute power [56], or power of reconstructed sources [50, 52] in people with progressive compared to stable MCI [48, 50, 55, 56] as well as in early AD patients when compared to healthy elderly subjects [52]. EEGs were recorded with reference to the linked mastoids in one study [50], using a common average reference in three studies [48, 52, 55], and with the averaged signals from electrodes F3 and F4 as the reference in one study [56] (see Table 1). Notably, three of these studies found these differences significant only at posterior electrodes [48, 50, 56]. Conversely, two smaller longitudinal studies reported no significant differences in alpha power by comparing MCI patients and AD patients [49, 57]. The EEG methodology, however, differed between these studies (See Table 1). A large 30-months longitudinal study involving 318 participants with SCD and stratified by brain β-amyloid deposition on 18 F-florbetapir PET (positive or negative) at baseline, found significant changes in cortical oscillatory activity in amyloid-positive patients. This was indicated by a decrease in theta/alpha ratio, primarily driven by a substantial increase in alpha oscillations over time in prefrontal areas [58].

Five studies investigated low (8–10.5 Hz) and high (10.5–13 Hz) alpha bands separately in MCI and AD patients [47, 51, 53, 59, 60]. Rossini and colleagues [51] reported increased lower alpha power in posterior sources in patients with progressive MCI, a finding not replicated in subsequent studies by Jovicich et al. [47] and Babiloni et al. [53, 59, 60]. Jovicich et al. [47] and Babiloni et al. [59, 60] found that prodromal AD patients showed decreased lower alpha power in posterior sources. This decrease was reported in amnestic MCI and AD patients compared to HCs [53]. All these studies employed standardized low-resolution brain electromagnetic tomography (sLORETA) software for the cortical sources analysis of the EEG rhythms [47, 51, 53, 59, 60] (see Table 1). Cross-sectional studies suggest that lower alpha power in posterior sources could be linked to AD pathology, as it positively correlates with cortical gray matter [61, 62] and normalized hippocampal volume measures [63], as well as with MMSE scores [62, 64]. In conclusion, the shift in the predominant posterior rhythm towards an increased relative theta and delta frequencies at the expense of alpha could serve as promising biomarkers for progression along the AD continuum.

Three longitudinal studies investigated activity in the beta-frequency range across the AD continuum [52, 55, 57]. A common average reference was employed in these studies (Table 1). Musaeus et al. [57] reported reduced low (13–17.99 Hz) beta power in the parietal regions in those MCI patients who later manifest progression to AD. The Authors also found that low beta power in these patients negatively correlated to CSF Aβ values and positively correlated with Addenbrooke´s Cognitive Examination scores [57]. In a one-year longitudinal study involving a cohort of 88 early-stage AD patients and 35 healthy elderly subjects, Babiloni et al. reported a progressive decrease in posterior low beta power during the follow-up period [52]. Finally, Poil and colleagues [55] used a logistic regression analysis to demonstrate that combining several EEG biomarkers into a diagnostic index could predict individuals who are likely to progress to AD with a sensitivity of 88% and specificity of 82%. The most effective set of biomarkers consisted of the amplitude of beta at Cz electrode placement, bandwidth of the subject-specific beta frequency, peak width of the dominant beta peak, range of amplitude values in beta (13–30 Hz), the ratio between theta and alpha power and alpha relative power.

The ability of EEG metrics, along with hippocampal volumetry, apoE4 genotype and neuropsychological measures in predicting amyloid status, neurodegeneration status and the likelihood of progression to AD, was also tested in a 5-year longitudinal study on a cohort of 304 SCD patients, by using a machine learning approach [65]. The ten EEG metrics that were evaluated in the study included power spectral density (in delta, alpha, theta, beta and gamma frequency), median spectral frequency, spectral entropy, algorithm complexity and weighted symbolic mutual information, a metric of functional connectivity, in theta and alpha bands. AD pathology was determined based on a combination of non-invasive measures, specifically the 18 F-florbetapir positron emission tomography (PET) scan and 18 F-FDG PET scan. Patients were classified based on the presence or absence of amyloid deposition as determined by the 18 F-florbetapir PET scan and on neurodegeneration status (neurodegenerative positive or neurodegenerative negative) as determined by the 18 F-FDG PET scan. Clinical progression to prodromal AD during the 5-year follow-up was defined using the IWG criteria [66]. The study demonstrated that, while brain amyloidosis and decline to AD were most strongly predicted by a combination of demographic, neuropsychological data, apoE4 and hippocampal volumetry, EEG was the best feature for predicting AD-specific neurodegeneration. In particular, a widespread increase of median spectral frequency and an

increase in power spectral density in gamma frequencies in the fronto-central regions were the most predictive EEG features of neurodegeneration. Another important finding of the study is that the reduction of the number of channels from a high-density EEG (224 channels) to a low-density EEG (16-channel and 4-channel EEG) did not alter predictive performance [65].

In a cross-sectional study involving 197 AD patients, 230 MCI patients and 210 SCD, Smailovic et al., aimed to assess potential correlations between CSF biomarkers, including amyloid β42, total tau and phospho tau protein levels, and global field power (GFP), a quantitative EEG metric representing the overall electric field power over the entire scalp at any given instant [67]. A negative correlation was found between CSF Aβ42 and delta and theta GFP, as well as between phospho and total tau CSF levels and alpha and beta GFP. This finding suggests that GFP might serve as a potential biomarkers of disease progression across the AD spectrum.

Task-related EEG spectral perturbations Several studies explored whether changes in EEG power measures during cognitive information processing can predict the progression across the AD continuum. The methods across these studies varied considerably in terms of EEG recording protocols, tasks employed, and outcome measures, making difficult to draw definitive conclusions (See also Table 1).

Missonnier and colleagues [68] in a 1-year longitudinal study on 24 MCI patients investigated whether theta ERS that occurs in response to an N-back working memory task predicts conversion to AD. The study demonstrated that at baseline, the 13 patients later identified as having progressive MCI showed reduced theta ERS during the N-back task compared to those with stable MCI. Importantly, the two groups did not differ in terms of reaction time or performance in N-back. This suggests that theta ERS, as a neurophysiological marker, might not solely rely on working memory performance. These findings highlight the potential of theta ERS as a marker capable of detecting subtle neural deficits more effectively than traditional clinical behavioral measures, potentially improving the accuracy of predicting MCI progression to AD.

Deiber and colleagues [69] recorded EEG during a simple attentional and a 2-back working memory task in a cohort of 97 elderly HCs and 45 age-matched MCI patients. The study demonstrated that HCs who developed subtle cognitive decline and MCI after 18 months showed increased alpha ERD over parietal electrodes compared to stable HCs. Alpha ERD, however, did not distinguish between deteriorated HCs and MCI. Conversely, the beta ERD over lateral parietal electrodes was reduced in stable HCs and MCI patients compared to deteriorated HCs. The observed increased alpha ERD in deteriorated HCs and MCI might reflect the necessity for enhanced attentional resources for task realization at the initial stage of cognitive decline. In addition, the study also examined whether the evaluation of inter-trial coherence (ITC) - a measure of how consistent the oscillatory phase is across trials - during the attention and working memory task could predict cognitive decline. A reduction in beta ITC over the parieto-occipital regions has been found in HCs who later manifested cognitive decline compared to those who remained stable. Additionally, there was a strong tendency for a smaller beta ITC over the same regions in MCI patients compared to the stable HCs. Unfortunately, due to the low number of MCI patients who progressed to AD, the study could not assess the potential for these EEG biomarkers as predictors of progression to MCI.

Mazaheri and colleagues [70] in a 3-year longitudinal study evaluated the ability of time-frequency representations of power in response to a word comprehension task to predict dementia conversion in a cohort of 25 aMCI and 11 HCs. MCI patients who progressed to dementia showed a significant reduction in theta power on posterior parietal regions at the first presentation of the target word. This change corresponds to the access to lexico-syntactic properties of the word, suggesting potential linguistic processing deficits. This early lexical theta activity was positively correlated with the Boston Naming test, a neuropsychological measure sensitive to compromised lexical retrieval abilities and aphasia. MCI patients converting to AD also exhibited a unique oscillatory pattern for meaning processing, including diminished central theta activity, late frontal beta suppression linked with word congruency, and increased beta suppression associated with semantic congruence. Taken together, these findings suggest that the breakdown of the brain network subserving language comprehension, as indicated by EEG oscillatory changes, might predict conversion from MCI to AD.

Finally, a two-year longitudinal study involving a cohort of 26 HCs and 34 participants with aMCI found that the aMCI patients who developed dementia at the end of the study exhibited a reduction in alpha ERD over the posterior cingulate cortex during memory encoding and retrieval at baseline evaluation [71]. This phenomenon has been hypothesized to reflect early synaptic changes in this particularly vulnerable region [71].

Functional connectivity measures

Resting state regional electrode intercorrelations In our review, we included four studies aimed to assess the potential of regional connectivity, evaluated by using resting-state EEG coherence (COH), phase lag index or imaginary part of coherence (iCOH) [51, 72–74] as a potential

biomarker of progression across the AD continuum. The methodology for EEG recordings as well as the outcome measures employed in these studies were quite heterogeneous, making a direct comparison not feasible (See Table 1).

In a 14 months longitudinal study, Rossini et al. [51] reported higher resting state fronto-parietal COH across several frequency bands, including low alpha, delta and theta, in MCI who progressed to AD compared to stable MCI.

To investigate reliable functional connectivity biomarkers that can capture the cognitive decline in MCI patients, Toth and colleagues conducted a one-year longitudinal study involving a cohort of 9 MCI and 11 HCs. The rsEEG phase lag index in five frequency bands was calculated at baseline and at the end of the study. The authors observed that aMCI patients exhibited a decreased delta and theta phase lag index within frontal and between frontal and temporal and parietal areas compared to HCs at baseline and at the 1-year follow up [72]. These neurophysiological findings were more pronounced at the end of follow-up period. However, due to the brief longitudinal design of the study, which lasted only one year, the authors could not determine whether these findings are useful for predicting the conversion from MCI to AD.

In a 3-year longitudinal study on a cohort of 17 patients with AD, 27 patients with MCI, and 38 older HCs, Musaeus and colleagues [74] found that progressive MCI had an increased delta and theta COH across fronto-temporal regions, and a decreased delta imaginary part of coherency for frontal-frontal, temporal-frontal, and parietal-frontal connections. A negative correlation between theta coherence and Addenbrooke's Cognitive Examination was also reported.

Finally, Hsiao and colleagues, in a cross-sectional study, examined the rsEEG functional connectivity within the default mode network in 21 mild AD and 21 MCI patients [73]. The study demonstrated a reduced delta and theta iCOH between the precuneus, posterior cingulate cortex and anterior cingulate cortex in AD patients. On the other hand, AD patients exhibited an enhanced delta, theta and beta2 iCOH between the medial temporal lobe, medial frontal cortex and posterior cingulate cortex. Neuropsychological performance, as assessed by MMSE, was negatively correlated with the delta iCOH values between the right medial temporal lobe and right medial frontal cortex, as well as with the theta iCOH values between the right medial temporal lobe and right posterior cingulate cortex. Conversely, a positive correlation was observed between MMSE scores and alpha2 iCOH between the left medial temporal lobe and anterior cingulate cortex.

Task-related changes in regional electrode intercorrelations The theta-gamma coupling (TGC) measures local neural communication and integration that underlies working memory and consists of the modulation of high-frequency gamma oscillations by low-frequency theta oscillations [75]. A recent cross-sectional study investigated frontal TGC in a cohort of 31 HCs, 33 AD and 34 MCI patients [76]. EEG was recorded using a 64-channel system with electrodes placed according to the 10–20 montage, referenced to an electrode positioned posterior to the Cz electrode. The study found the lowest TGC values during the working memory task in AD patients followed by MCI and HCs. TGC was identified as the strongest predictor of working memory performance in AD and MCI patients in a linear regression analysis, suggesting its reliability as a working memory measure. However, no data on TGC predictive value concerning conversion across the AD spectrum exists.

Resting-state global connectivity Two cross-sectional studies evaluated resting state global connectivity measures across the entire scalp across different stages of the AD continuum. Babiloni et al., examined global functional coupling of the EEG rhythms by employing COH for all combinations of electrode pairs in a cross-sectional multicenter study on a cohort of 33 mild AD, 52 aMCI and 47 HCs [77]. EEG data were recorded from 19 electrodes positioned according to the international 10–20 system, using a common average reference. Total delta COH was higher in the AD than the MCI group, and likewise, it was also higher in the MCI than in the healthy control group. A negative correlation between total delta COH and measures of global cognition, such as MMSE, across the three groups of patients was reported. On the other hand, in a large cohort of 197 AD patients, 230 MCI patients and 210 SCD, Smailovic et al., evaluated possible correlations between CSF biomarkers of neurodegeneration and global field synchronization (GFS), a reference-free measure of synchronization across all EEG electrodes that explores the global interactions of brain areas during different cognitive tasks or states [67]. A positive correlation was found between Aβ42, p- and t-tau CSF levels, and GFS in the alpha and beta ranges.

Global measures of spatial and temporal properties of resting-state networks A recently introduced method for investigating spontaneous brain activity's global temporal and spatial properties relies on the concept of EEG microstates [45, 46]. These are defined as dynamically varying, organized global patterns of scalp potential topographies recorded via multichannel EEG arrays. The application of microstate analysis in cognitive neuroscience is grounded in the principle that individual brain functions are not localized but involve parallel process-

ing across distributed networks. Previous studies have defined four reproducible and common microstates, representing fundamental 'building blocks' of different cognitive functions: A for attention, B for language processing, C for visual processing, and D for introspective thoughts. Changes in their sequence can signify cognitive or neuropsychiatric conditions.

In a 3-year longitudinal study on a cohort consisting of 17 patients with AD, 27 patients with MCI, and 38 older HCs, Musaeus and colleagues [78] did not observe significant differences in terms of microstate duration, occurrence, or coverage between progressive and stable MCI. Patients with MCI and AD had significantly higher occurrence and coverage for microstate A than HCs. However, no significant correlations were found between coverage and occurrence of microstates A and CSF biomarkers or neuropsychological measures.

Conversely, in a cohort of 43 HCs, 46 MCI and 43 AD patients, Lian and colleagues [79] demonstrated a significant increase in duration and occurrence for microstate A in AD patients versus MCI or HCs. Also, coverage for microstate C decreased significantly in AD compared to MCI. Notably, no significant parameter differences between HCs and MCI were found. It is also important to note the presence of a negative correlation between the transition probability from A to B and MMSE scores. In both studies, EEG signals were re-referenced to the average reference during data preprocessing (See Table 1).

Event-related potentials

All ERPs studies, along with details on the methodological approach and metrics used to evaluate biomarkers performance are summarized in Table 2.

ERPs are small-voltage electrical potentials derived from EEG signals and generated by the brain in response to specific events or stimuli, that are related to the encoding of specific internal or external events and thus provide information about a broad range of cognitive and affective processes [80–82]. The nomenclature for ERPs is usually based on the direction of their voltage deflection (P for positive, N for negative) and the approximate timing (e.g., P300 component peaks around 300ms) or order of the peak (N1 for first negative-going peak), though others are abbreviations of their names (such as the MMN for the, or mismatch negativity) [82]. Several experimental paradigms were used in the field of dementia research.

Auditory oddball paradigm and P300 evaluation

The auditory oddball paradigm is an experimental procedure used in ERP studies involving the presentation of two types of auditory stimuli: infrequent "target" stimuli, to which participants are asked to respond, and frequent "standard" stimuli that serve as the background [83]. Two longitudinal studies have assessed the usefulness of P300 in predicting conversion across different stages of the AD spectrum [84, 85]. There is consistent evidence that evaluating the latency of P300 may be useful as a marker of prodromal AD. Bennys and colleagues [84] studied a cohort of 71 MCI patients and 31 HCs followed for 1 year and found that P300 latency values differentiated between patients who converted to AD, patients who developed MCI and HCs. Notably, an increase in P300 latency was identified in patients with progressive MCI, setting them apart from those with stable MCI and the HCs. Also, the P300 latency showed a sensitivity and specificity of 80% and 90%, respectively, in differentiating progressive MCI versus stable MCI. Interestingly, the P300 latency was inversely correlated with MMSE and positively correlated with executive and attention impairment [84]. Papaliagkas and colleagues [85] concurrently examined P300 characteristics and CSF beta-amyloid (1–42) values in a cohort of 53 MCI patients over a follow-up period of one year. They found that those MCI patients who converted to AD had lower beta-amyloid (1–42) values and prolonged P300 latencies compared to those with stable MCI, although the differences in the P300 latency did not reach statistical significance. The small number of MCI patients who converted to AD in the study might have influenced statistical significance [85]. The utility of P300 latency in differentiating between AD, MCI and HCs has been corroborated in several cross-sectional studies. These studies simultaneously evaluated groups at different stages of the AD spectrum [86–88]. Furthermore, two of these investigations reported a negative correlation between MMSE scores and P300 latencies [86, 88]. While P300 latency changes across various stages of the AD spectrum, it remains uncertain whether modifications in P300 amplitude might also contribute to distinguishing these conditions. Findings coming from longitudinal and cross-sectional studies provided conflicting results, with some studies reporting a reduction as cognitive impairment progresses [85, 86, 88], whereas others reporting no changes [87, 89]. However, it is worth noting that minor differences were observed even in these latter studies, though they did not reach statistical significance. This could be attributed to the limited sample size [87, 89]. The identified studies did not perform a comparison in terms of diagnostic accuracy in predicting the conversion to AD between ERP-based measures and behavioral measures.

Auditory oddball paradigm and N200 evaluation

Two longitudinal studies have evaluated the role of N200 as a neurophysiological biomarker of conversion from MCI to AD [90, 91]. The same group performed both studies on a cohort of MCI patients, followed for 1 year [90, 91]. Results coming from these studies suggested

Table 2 ERPs studies focusing on biomarkers of conversion across the AD spectrum

Author and year	Participants	Study design	Method	Main results	Sensitivity/Specificity
Yamasaki et al., 2016	15 aMCI who converted to AD; 15 HS (older); 15 HS (younger)	Longitudinal (24 months)	VEP with different visual stimuli (Chromatic stimulus, achromatic stimulus, face stimuli, word stimuli, optic flow motion stimulus)	VEP latencies for higher ventral (faces) and dorsal (word, optic flow) stimuli were prolonged in aMCI. VEPs to higher-dorsal stimuli exhibited the strongest correlation with neuropsychological scores.	n.a.
Olichney et al., 2002	14 aMCI; 14 HS	Longitudinal (annual follow-up clinical assessment – mean follow up period was 2 years)	Word repetition ERP paradigm EEG channels:19 Montage system: 10–20 Reference: left mastoid online (re-referenced to an average of both mastoids offline)	Latency of N400 was slower in MCI. Reduced effect of word repetition on the LPC in MCI Correlation between LPC repetition effect amplitude and verbal memory abilities.	n.a.
Papaliagkas et al., 2010	53 MCI	Longitudinal (11 months)	Lumbar puncture (beta amyloid 1–42 levels) Auditory oddball paradigm (P300) EEG channels: 2 (Cz, Pz) Montage system: 10–20 Reference: linked earlobes	↑ Latencies and ↓ amplitude of the P300 in progressive MCI than stable MCI	*Progressive MCI vs. Stable MCI* CSF-beta amyloid 1–42 levels (cut off value; >472 pg/ml): SE 100% / SP 77,1% P300 amplitude (cutoff value 15 µV): SE 100% / SP 48.9% P300 latency (cutoff value 455 ms): SE 60% / SP 75% Combined CSF-beta amyloid 1–42 levels + P300 amplitude: SE 100% / SP 89% Combined CSF-beta amyloid 1–42 levels + P300 latency: SE 80% / SP 98%
Papaliagkas et al., 2011	22 aMCI; 30 HS	Longitudinal (23 months)	Auditory event-related potentials EEG channels:2(Cz, Pz) Montage system: 10–20 Reference: linked earlobes	N200 latency correlated with baseline MMSE in MCI N200 amplitude decreased and P300 latency increased with time in MCI. N200 latency ↑ in MCI compared to HS during follow up N2/P3 inter peak index differences between the baseline and the end point were ↓ in stable-MCI compared than AD-converted group	n.a.
Bennys et al., 2011	71 MCI; 31 HS	Longitudinal (1 years)	Cognitive ERPs during auditory oddball paradigm EEG channels:4 median derivations (Fz-Cz-Pz-Oz) Montage system: 10–20 Reference: linked earlobes	↓ P3b amplitude, ↑P3b latencies and ↑ N2 latencies in patients with progressive MCI compared with stable MCI P3b latencies in the frontal and parietal areas were negatively correlated with attention (direct span, reverse span) and executive functions (TMT-A, TMT-B, verbal fluency) N2 amplitude in the parietal area correlated with executive functions (TMT-A, verbal fluency) and attention (direct span, reverse span)	*Progressive MCI vs. Stable MCI* P3b amplitude (cut-off point 8.26 µV): SE 83% / SP 72% N2 amplitude (cut-off point 4.46 µV): SE 80% / SP 62% P3b latency (cut-off point 318 ms): SE 80% / SP 90%

Table 2 (continued)

Author and year	Participants	Study design	Method	Main results	Sensitivity/Specificity
Missonnier et al., 2005	24 MCI	Longitudinal (1 year)	ERP waveform subtraction analysis between the n-back and control tasks EEG channels:20 Montage system: 10–20 Reference: linked earlobes	Absent positive-negative working memory component in progressive MCI compared to stable MCI	n.a.
Olichney et al., 2008	32 aMCI	Longitudinal (3 years)	ERP paradigm (semantically congruous and incongruous target) EEG channels:19–32 Montage system: 10–20 Reference: re-referenced off-line to linked mastoids	↓/Abnormal N400 or P600 word repetition effects in converter group compared to non-converter group (87-88% likelihood of dementia within 3 years)	*Progressive MCI vs. Stable MCI* Abnormal N400 or P600: SE 81–94%, SP 79–86%, PPV 87–88%
Papaliagkas et al., 2009a	51 MCI; 14 HS	Longitudinal (11 months)	CSF cytochrome C levels Auditory ERPs EEG channels:2(Cz, Pz) Montage system: 10–20 Reference: linked earlobes	↑ levels of cytochrome C in MCI compared to HS AD converters had ↑ N200 latency and cytochrome C levels N200 amplitude correlated with CSF cytochrome c levels	*Progressive MCI vs. Stable MCI* N200 Latency (cutoff value 287 ms): SE 100%, SP 91%
Papaliagkas et al., 2009b	53 MCI	Longitudinal (11 months)	CSF beta-amyloid (1–42) levels Auditory ERPs EEG channels:2(Cz, Pz) Montage system: 10–20 Reference: linked earlobes	↑ N200 latencies and ↓ beta-amyloid (1–42) levels in progressive MCI compared to stable MCI Negative correlation between N200 latency and beta-amyloid (1–42) levels	*Progressive MCI vs. Stable MCI* CSF-beta amyloid 1–42 levels (cut off value; >472 pg/ml): SE 100% / SP 77,1% N200 latency (cut off value: 287 msec): SE 100%, SP 91% Combined: SE 100%, SP 100%
Papadaniil et al., 2016	21 AD; 21 MCI; 21 HS	Cross-sectional	Two-tone oddball paradigm EEG channels:256 Montage system: 256 HCGSN adult 1.0 Reference: Free reference	=MMN and P300 amplitude in MCI, AD and HS ↑ latency MMN and P300 in MCI ↑ latency MMN and P300 in AD P300 generators shift to temporal lobe in AD. For the MMN, higher brain activation is localized in inferior frontal and superior temporal gyrus in HS, whereas it is localized in parietal sites in AD	n.a.

Table 2 (continued)

Author and year	Participants	Study design	Method	Main results	Sensitivity/Specificity
Bennys et al., 2007	30 AD; 20 MCI; 10 HS	Cross sectional	ERPs (auditory oddball paradigm) Neuropsychological evaluation (MMSE, Mattis dementia rating scale, TMT, Stroop test, FAB, Grober-Buschke scale) EEG channels:4 Montage system: 10–20 Reference: linked earlobes	P3 latencies at parietal and frontal site differentiate the 3 groups N2 latencies in frontal regions discriminated MCI from HS Inversion of the normal amplitude gradient of P3 in MCI, with a peak in the frontal regions Negative correlation between MMSE and N2 and P3 latencies in frontal and parietal regions Positive correlation between N2 and P3 latencies and executive and attention functions	n.a.
Tsolaki et al., 2017	21 MCI; 21 AD; 21 HS	Cross-sectional	256-channel EEG Two-tone oddball experiment EEG channels:256 Montage system: 256 HCGSN adult 1.0 Reference: Free reference	= Auditory N2a in MCI and HS, whereas a unilateral left temporo-parietal distribution appeared in the AD ↑ P300 latencies in MCI, mostly in frontal areas ↑↑ P300 latencies in AD from frontal to occipital areas ↓ P300 amplitude as cognitive impairment progresses P300 latency negatively correlated with MMSE in AD and MCI	n.a.

aMCI, amnesticMCI; MCI, mild cognitive impairment; AD, Alzheimer disease; HS, healthy subjects; VEP, visual evoked potentials; LPC, late positive component; ERP, event-related potentials; MMSE, mini-mental state examination; TMT-A, trial making test-A; TMT-B, trial making test-B; CSF, cerebrospinal fluid; FAB, frontal assessment battery; EEG, electroencephalography, n.a. not available; SE, sensibility; SP, specificity; PPV, positive predictive value

that, at baseline evaluation, the N200 latency is longer in MCI who developed AD than in MCI who remained stable at the end of follow-up [90, 91]. Moreover, in one study a negative correlation between CSF beta-amyloid (1–42) levels and N200 latency was reported [91]. Based on these findings, the N200 latency may be an independent, single, neurophysiological predictor of MCI progression to AD. In both studies, it was not assessed whether N200 latency offers better discrimination compared to behavioral measures in predicting progression to AD.

Auditory oddball paradigm and evaluation of N2/P3 interpeak index

Papaliagkas and colleagues designed a 2-year longitudinal study on 22 MCI patients to determine if there were changes in the latencies and amplitudes of the N200 and P300 components [89]. Results of the study showed a progressive and significant increase of P300 latencies and a reduction of N200 amplitude in MCI patients during the follow-up. The authors failed to observe any correlation between P300 features and neuropsychological test, whereas a negative correlation between N200 latency and baseline MMSE score was reported. Given that the amplitude of P300 and N200 latency remained constant, the authors proposed using the N2/P3 interpeak index as a marker of conversion between MCI and AD. This neurophysiological index, which is calculated by dividing the sum of N200 and P300 amplitudes by the difference in P300 and N200 latencies, essentially represents the voltage gradient in the latency window between N200 and P300. Notably, the changes in this index over time were significantly smaller in the stable MCI group compared to the AD converter group [89].

Semantic incongruity paradigm and N400 component

In this widely used paradigm, a participant reads various sentences presented one word at a time on a computer screen; most sentences are semantically appropriate or expected, but some have an incongruous or unexpected final word. The ERP response to semantic incongruity is called N400 component, as it displays a negative voltage of around 400 ms after the word is presented. Two longitudinal studies used this paradigm to find a neurophysiological biomarker to predict the conversion to AD. First, Olichney et al. [92] in a cohort of 14 MCI patients and 14 HCs, found that the latency of the N400 was higher in MCI than HCs. Moreover, unlike HCs who typically exhibit a substantial late positivity known as P600 in response to new congruous words, a response that diminishes with repetition, MCI patients display an abnormal or reduced repetition effect, with a more centrally distributed and earlier response at around 500 ms. Notably, the late positive component repetition effect

was significantly reduced in MCI patients who converted to AD compared to those who did not. Finally, a positive correlation between P600 amplitude and several measures of verbal memory abilities, including the California verbal learning test and dementia rating scale, has been observed [92]. The same group of researchers designed another prospective study to evaluate if semantic incongruity paradigms may be useful for differentiating MCI to AD converters and non-converters [93]. In a cohort of 32 aMCI followed for three years, an abnormal reduction of N400 or P600 word repetition effects were observed only in the converters group. Results of the study suggested that MCI patients who display abnormalities in these two ERP components had an 87 to 88% likelihood of developing dementia within 3 years, in contrast to those presented spared responses that only had an 11 to 27% likelihood [93].

Visual evoked potentials

A longitudinal study evaluated the usefulness of visual evoked potentials (VEPs) optimized to separately activate lower and higher levels of the ventral and dorsal streams as biomarkers for early detection of aMCI [94]. In an elegant experimental design, Yamasaki and colleagues compared VEP evoked by chromatic, achromatic, face, word, and optic flow motion stimuli in 15 aMCI who later converted to AD, 15 older HCs and 15 younger HCs. All subjects in the study performed well in VEP tasks, correctly identifying every stimulus that was presented. The study showed that VEP latencies for higher ventral (face stimuli) and dorsal (optic flow motion) stimuli were significantly prolonged in aMCI, whereas they were not affected in older HCs. In addition, the amplitude of VEPs for higher-level dorsal stimuli positively correlated with neuropsychological scores, as assessed by the Wechsler Memory Scale-Revised, whereas the latency values showed a contrasting, inverse correlation with the same scores. Finally, the parameters of VEPs associated with higher level dorsal stream activity also exhibited the highest accuracy in discriminating aMCI patients from older HCs. Collectively, these findings suggest that VEPs associated with higher-level dorsal stream activity could serve as a sensitive biomarker for the early detection of aMCI.

ERPs during working memory tasks

A 1-year longitudinal study on 24 MCI patients was performed to test the usefulness of the positive-negative working memory component (PNwm) as a biomarker of conversion to AD [95]. The PNwn is an ERP observed during the successful execution of spatial and verbal working memory tests. It is detected over parietal electrodes and occurs from 140 to 280 ms after the onset of a new visual stimulus. The study employed a control task and two additional n-back tasks of varying complexity, revealing that the PNwm was absent under demanding conditions at baseline evaluation in the 13 MCI patients who later progressed to AD. By considering behavioral data, it is important to underline that during the n-back testing, reaction times increased as the task became more difficult, but this increase was similar in both progressive and stable MCI patients. The PNwn density, which was expressed as the area in μV^2 within specific temporal limits and then normalized through logarithmic transformation, showed no correlation with n-back performances or clinical outcome, suggesting that the PNwm may represent an independent predictor for the progression of MCI. Based on these findings and previous neuroradiological evidence, it has been hypothesized that impairment of neural generators within the parietal cortex may be a critical factor in converting MCI to AD. However, while another 18-month longitudinal study found PNwn alterations in MCI compared to stable HCs, it failed to find significant differences between those HCs who developed subtle cognitive impairment at the end of the study and those remaining cognitively stable [69].

Transcranial magnetic stimulation

All TMS studies, along with details on the methodological approach and metrics used to evaluate biomarkers performance are summarized in Table 3.

Single-pulse TMS studies

Single-pulse TMS (spTMS) technique is designed to assess the integrity of the brain circuitries and the relative degree of corticospinal excitability [96–98]. Among possible spTMS parameters, independent groups mainly used resting motor threshold (rMT) and stimulus intensity needed to evoke motor-evoked potentials (MEP) of 1mV (SI1mV) to evaluate AD progression [97, 99–102].

Resting motor threshold (rMT) The rMT is defined as the lowest stimulus intensity, expressed as a percentage of maximal stimulator output, required to induce a minimal MEP (peak to peak amplitude of at least 50 microvolts in at least 5 of 10 trials) in a relaxed muscle [97, 99–101]. It depends on the excitability of several neural elements, mainly including the cortico-cortical axons' excitatory synaptic contacts with the corticospinal neurons and spinal cord structures [97].

In a 4-year longitudinal study on a cohort of 40 aMCI and 20 HCs, rMT value was significantly lower in patients than in HCs at baseline evaluation and correlated with time of conversion to AD, suggesting that motor cortical hyperexcitability might be regarded as potential neurophysiological marker of conversion from amnestic MCI to AD [103]. In line with this result, in a cross-sectional study on two independent samples of 151

Table 3 TMS studies focusing on biomarkers of conversion across the AD spectrum

Author and year	Participants	Study design	Method	Main results	Sensitivity/ Specificity
Trebbastoni et al., 2016	40 aMCI; 20 HS	Longitudinal (48 months)	rMT ; rTMS (X/I – MEP ratio)	↓ rMT and X/I – MEP ratio in MCI	n.a.
Ferreri et al., 2021	17 aMCI; 15 HS	Longitudinal (6 years)	TMS (M1 stimulation) 100 TMS trials (intertrial interval 6–8 s) Intensity of stimulation:120% rMT EEG channels: 32 Montage system: 10–10 Reference: linked mastoids	↓ GMFP amplitude at 45–50 ms post-TMS in aMCI than controls at C3 ↓ broadband ITC (alpha, beta and gamma) in aMCI close to the stimulation site	*Progressive MCI vs. Stable MCI* sDA: 100/100%, gamma ITC: 86/83%
Motta et al., 2018	60 AD; 30 HS	Longitudinal (18 months)	Clinical assessment and MMSE at 6,12 and 18 months; rMT, SICI, ICF, SAI; iTBS protocol	= SICI and ICF ↓ iTBS induced plasticity in AD ↓ SAI in AD ↓ rMT in AD Negative correlation between LTP plasticity and both CSF t-tau and p-tau levels No association between LTP plasticity and CSF Aβ1–42 level Positive correlation between LTP plasticity and verbal memory performances	n.a.
Olazaran et al., 2010	11 MCI that converted to AD; 12 HS	Longitudinal (21 months)	SICI; ICF	↓2ms-SICI in patients = ICF	n.a.
Di Lorenzo et al., 2020	21 MCI; 24 Prodromal AD (PROAD); 28 AD	Longitudinal (3 years)	Clinical assessment and MMSE at 6, 12, 18, 24, 30 and 36 months; SICI, ICF, SAI; cTBS, iTBS; CSF biomarkers (T-tau/Aβ1–42 ratio; P-tau181/ Aβ1–42 ratio)	↓ rMT in PROAD and AD ↓ iTBS induced plasticity in MCI ↓↓ iTBS induced plasticity in PROAD and AD = SICI, SAI, ICF LTP-like cortical plasticity (iTBS-induced) is associated with disease progression	n.a.
Julkunen et al., 2011	5 AD; 5 MCI; 4 HS	Cross-sectional	50 TMS pulses at 110% rMT on M1; Clinical dementia rating scale; MMSE EEG channels: 60 Reference: re-referenced to common average	Positive correlation between P30 amplitude and cognitive decline (MMSE, CDRS)	n.a.
Zadey et al., 2021	Two independent samples (22AD, 129 AD); 26 HS	Cross-sectional	ADAS-Cog; rMT	Positive correlation between rMT and ADAS-Cog scores	n.a.
Terranova et al., 2013	10 AD; 14 HS	Cross-sectional	SAI (ISI was set at 25 ms); 5 Hz-PAS (600 pulses; ISI 25 ms)	↓ SAI in AD ↓ PAS induced-cortical plasticity in AD PAS changes did not correlate with any cognitive parameter	n.a.
Meder et al., 2021	15 AD; 15 aMCI; 23 HS	Cross-sectional	rMT; SI1mv	↓ SI1mv in aMCI compared to HS No differences between AD and HS No relation between neuropsychological (MMSE, CDRS) or CSF data (Aβ1–42 level) and TMS measures	n.a.
Lahr et al., 2016	24 MCI; 24 HS	Cross-sectional	PAS (180 pulses; ISI 25 msec)	=PAS induced-cortical plasticity in MCI and HS No correlation between PAS effect and hippocampal volume, MoCA or verbal learning memory test	n.a.

Table 3 (continued)

Author and year	Participants	Study design	Method	Main results	Sensitivity/ Specificity
Kumar et al., 2017	32 AD; 18 HS	Cross-sectional	TMS (DLPFC stimulation) PAS (100 pulses, ISI 25 msec) n-back (1- and 2-back condition) EEG channels:64 Montage system: 10–20 Reference: re-referenced to common average	Impaired DLPFC plasticity in AD patients. Patients with AD had impaired performances on the 1-back condition compared with controls. Positive correlation between plasticity of DLPFC and working memory performance on the 1-back and 2-back across both groups.	n.a.
Joseph et al., 2021	24 AD; 11 HS	Cross-sectional	64 channel EEG; TMS (DLPFC stimulation) 100 TMS trials (0.1 Hz) Intensity of stimulation: SI1mV EEG channels:64 Montage system: 10–20 Reference: electrode posterior to Cz	The DLPFC-cortical evoked activity was higher in AD patients as compared with HS. No difference between two groups in individual P30, N45 or P60 amplitudes. DLPFC cortical evoked activity was negatively associated with MoCA total scores and SOC problem solved and positively associated with EXIT total scores	n.a.

aMCI, amnesticMCI; MCI, mild cognitive impairment; HS, healthy subjects; rMT, resting motor threshold; rTMS, repetitive TMS; MEP, motor evoked potentials; EEG, electroencephalography ; TMS, transcranial magnetic stimulation; M1, primary motor cortex; GMFP, global mean field power; ITC, intertrial coherence; AD, Alzheimer disease; MMSE, mini-mental state examination; SICI, short interval intracortical inhibition; ICF, intracortical facilitation; SAI, short-latency afferent inhibition; iTBS, intermittent theta burst stimulation ; LTP, long-term potentiation ; cTBS, continuous theta burst stimulation; CSF, cerebrospinal fluid; CDRS, clinical dementia rating scale ; ADAS-Cog, Azheimer's disease assessment scale-cognitive subscale; PAS, paired associative stimulation; SI1mV, stimulus intensity needed to evoke MEP of 1 mV; DLPFC, dorsolateral prefrontal cortex; MoCA, Montreal Cognitive Assessment; SOC, Stockings of Cambridge; EXIT, Executive Interview, n.a., not available, SE, sensitivity, SP, specificity; sDA, stability of the dipolar activity

AD participants, a negative correlation between rMT values and total scores on the Alzheimer's Disease Assessment Scale - Cognitive Subscale (ADAS-Cog), a reliable measure of cognition, has been reported. Indeed, higher motor cortical excitability, expressed as lower rMT was associated with greater global cognitive dysfunction, expressed as higher ADAS-Cog score in AD [104]. According to these findings, in a longitudinal study, Motta et al., found that rMT values at baseline were reduced in newly diagnosed AD compared to HCs. The correlation between rMT values and CSF biomarkers or neuropsychological scores was not explored. However, using a ROC curve analysis, the area under the curve for rMT was found to be below the generally accepted threshold for good diagnostic accuracy, suggesting that this spTMS-based measure may not be a reliable diagnostic marker for AD [105]. A cross-sectional study found no correlation between rMT values and CSF Aβ1–42 levels and neuropsychological scores, including MMSE and clinical dementia rating scale [106].

The observation that decreased rMT values were associated with conversion from aMCI to AD [103] and greater global cognitive dysfunction in AD patients [104] suggests that motor cortical hyperexcitability could be related to the neurodegenerative changes underlying AD. In conclusion, some evidence suggests that the rMT may be used as a potential neurophysiological marker of AD progression.

Stimulus intensity needed to evoke motor-evoked potentials of 1mV (SI1mv) By gradually increasing the intensity of the stimulation in a relaxed muscle, it is also possible to estimate the SI1mV, another frequently used measure of the integrity of the corticospinal tract [102, 107, 108].

In a longitudinal study, Meder and colleagues compared the SI1mV and paired associative stimulation (PAS)-induced plasticity in a cohort of 15 AD, 15 aMCI and 23 HCs. SI1mv was significantly lower in aMCI compared to HCs and AD, while no difference was observed between AD and HCs. None of the neurophysiological measures correlated significantly with demographic data, clinical scores, or CSF beta-amyloid (1–42) levels [106]. The time of the study was too short (almost 2 weeks) to verify the validity of any measures as a possible progression biomarker. However, by performing a test-retest reliability analysis the authors found that the SI1mV might be a reliable TMS measure for testing motor cortical excitability in longitudinal studies [106].

The observation that SI1mv values were normal in AD and did not correlate with clinical severity or pathological biohumoral markers suggests that SI1mv may reflect a compensatory mechanism in aMCI patients. Thus, it may

have limited utility in predicting progression from preclinical to clinically evident AD.

Paired pulse TMS studies

Several paired-pulse TMS (ppTMS) paradigms have been designed to investigate inhibitory or excitatory intracortical circuits and inter-cortical connections and consist of a conditioning stimulus followed by a test stimulus delivered with a variable inter-stimulus interval (ISI) [97, 109]. Depending on the intensity and ISI used, several paradigms reflecting the activity of different neurotransmitter circuits can be performed using the MEP amplitude as an outcome measure [97, 109].

Short-interval intracortical inhibition (SICI) SICI protocol can be used to measure GABA-A-mediated inhibitory mechanisms by applying two magnetic pulses with a short ISI to the motor cortex [97, 110]. In an 18-month longitudinal study on a cohort of 60 newly diagnosed AD and 30 HCs, Motta et al., [105] evaluated the effectiveness of SICI as a TMS-based biomarker of cognitive decline or potential diagnostic biomarker. The authors failed to find any difference in SICI and ICF between AD and HCs groups. The potential correlation between SICI and the CSF biomarker profile and cognitive domain dysfunction, as evaluated through neuropsychological tests, has not been investigated.

In a recent 3-year longitudinal study on a cohort of 21 MCI, 21 prodromal AD and 24 AD with manifest dementia, stratified according to CSF biomarkers profiles, similar results were obtained for SICI [111]. On the opposite hand, in a 2-year longitudinal study on a cohort composed of 12 patients with MCI who converted to AD and 12 HCs, SICI was found to be reduced in AD patients at the MCI clinical stage compared to HCs at the baseline evaluation, even if statistical significance was only observed for 2-ms SICI, for the presence of a high-individual variability [112]. However, this measure was normalized by donepezil in the follow-up evaluation. It is important to note that the observed normalization of SICI by pharmacological treatment may be considered as a correlate of the symptomatic improvement induced by the drug, indicating that this neurophysiological measure may not be a reliable marker of disease progression in MCI patients [112].

Intracortical facilitation (ICF) Delivering a subthreshold conditioning stimulus 10–25 ms before a test stimulus enhances motor cortical excitability in a paradigm known as ICF, a phenomenon that is believed to be mediated by glutamatergic transmission [97, 110]. Longitudinal studies failed to show that ICF measurement at baseline evaluation is useful in distinguishing between AD [105] or MCI patients [112] and HCs.

Short-latency afferent inhibition (SAI) SAI involves the delivery of a conditioning stimulus to the median nerve and a test stimulus to the motor cortex [113, 114]. The resulting inhibition of the MEP is thought to reflect sensorimotor integration mechanisms based on GABA and cholinergic circuits. Given the role of cholinergic transmission in AD pathology, the SAI is one of the most frequently evaluated parameters in studies on the AD continuum [105, 115–118].

Two studies reported that SAI is reduced in AD compared to HCs [105, 118]. Even if SAI can discriminate between AD and HCs, Motta and colleagues demonstrated, by using multivariable regression analysis, that it is not associated with clinical progression, as measured as delta MMSE score at 18 months with respect to baseline [105]. Moreover, contrasting with the above-cited studies, a recent 3-year longitudinal study that examined a cohort of AD, MCI and prodromal AD patients, stratified according to CSF biomarkers profiles, failed to observe any significant differences in response to SAI protocols among these groups [111]. The study's authors suggested that cholinergic impairment may not entirely depend on the underlying AD pathology, influenced by a general mechanism of aging [111].

Repetitive TMS studies

Repetitive TMS (rTMS) techniques have been used to induce short- and long-term plasticity changes in cortical excitability [97, 119–121]. Low frequency rTMS (LF rTMS), typically delivered at 1 Hz, is known to induce short-term inhibition of cortical excitability, while high frequency rTMS (HF rTMS), usually delivered at 5–20 Hz, is known to induce short-term facilitation. Other rTMS patterned protocols known as continuous theta burst stimulation (cTBS) and intermittent theta burst stimulation (iTBS) have been proposed to induce respectively long-term depression (LTD)-like and long-term potentiation (LTP)-like plasticity [122–125]. Finally, the PAS paradigm involves the repeated pairing of peripheral nerve stimulation with TMS to the motor cortex to induce long-term associate plasticity changes [102, 126, 127].

Repetitive transcranial magnetic stimulation (rTMS) Trebbastoni et al. [103] investigated the possibility of predicting the conversion from MCI to AD by measuring every 12 months for 4 years, the facilitatory effects of HF rTMS (5 Hz) delivered on the dominant motor area in 40 aMCI and 20 HCs. The authors found decreased short-term facilitation in aMCI patients than in HCs at baseline evaluation and the degree of the reduction inversely correlated with time of conversion to AD, suggesting that altered synaptic plasticity measure might

be regarded as a potential neurophysiological marker of conversion from aMCI to AD.

Intermittent theta burst stimulation (iTBS) In a 18-month longitudinal study on a cohort composed of 60 newly diagnosed AD and 30 HCs, Motta et al., [105] evaluated whether motor cortical plasticity changes as measured by iTBS are related to CSF biomarkers profile and to cognitive domain dysfunction, as evaluated by means of neuropsychological tests. Compared to HCs, AD patients showed a decrease of LTP-like cortical plasticity in the primary motor cortex, which inversely correlated with CSF t-tau and p-tau levels but not beta-amyloid (1–42) levels. Also, higher values of LTP were associated with higher long-term verbal memory performances. Finally, by performing a univariate linear regression analysis, the level of LTP-like plasticity was associated with the probability of rapid cognitive decline, showing a significant association with delta MMSE at 18-months with respect to baseline [105]. These findings have been replicated by a recent 3-year longitudinal study involving 73 patients, who were stratified into three groups based on their CSF biomarkers profiles and cognitive status [111]. Specifically, the groups included MCI patients, who had negative CSF biomarkers and no dementia, prodromal AD patients, who had positive CSF biomarkers indicative of AD pathology but no dementia and AD patients, who exhibited both positive CSF biomarkers and clinical dementia. The study revealed that MCI patients had a moderate impairment of iTBS-induced cortical plasticity, while AD and prodromal AD groups had a more severe loss of LTP-like cortical plasticity. Moreover, the study found that patients with prodromal AD and MCI who progressed to dementia had weaker LTP-like plasticity at their first evaluation, suggesting that this measure may represent a new biomarker to predict the clinical progression to manifest dementia. In one of these studies, iTBS was administered by delivering a 5 Hz stimulation for 2 s, repeated every 10, resulting in 600 pulses. However, the TMS intensity used in this study was not specified [105]. In the other study [111], the TMS intensity was clearly set at 120% rMT; however, details about the specific iTBS paradigm used, including the timing and number of repetitions, have not been provided. As a result, it is not possible to determine if a consistent methodology was employed across all studies.

Paired associative stimulation (PAS) We found no longitudinal studies investigating the PAS paradigm-induced effects as conversion biomarkers across the AD continuum. Findings coming from cross-sectional studies investigating PAS in AD and MCI patients showed conflicting results. Terranova and colleagues found that the PAS paradigm fails to induce changes in MEP amplitude in AD, suggesting an impairment of LTP-like cortical associative plasticity [118]. On the other hand, Lahr and colleagues found no differences in the PAS effect between MCI and HCs [128], indicating that PAS-induced cortical plasticity might be preserved during the initial stages of AD but becomes dysfunctional as the disease progresses. However, the PAS effect was not correlated with ApoE genotype or markers of disease severity, including hippocampal volume, MoCA, or verbal learning memory test scores [128], casting doubt on the utility of PAS paradigm-based measures in predicting conversion to AD. The validity of PAS protocols in providing clinically useful markers in AD has also been challenged in a recent study on 23 HCs, 15 AD, and MCI patients that found no effect of PAS in any of the groups [106].

TMS-EEG studies

The concurrent use of TMS with simultaneous EEG offers the unique possibility to obtain real-time information on cortical reactivity, brain effective connectivity, and network integrity [129–132]. This TMS-EEG approach offers promising potential in developing biomarkers for predicting AD progression [24]. A recent six-year prospective TMS-EEG study investigated whether sensorimotor network excitability as measured by TMS-evoked potentials (TEPs) from M1 stimulation might predict AD progression in a cohort of 17 aMCI and 15 HCs [133]. Ferreri and colleagues reported that MCI patients showed reduced sensorimotor network excitability and disrupted alpha, beta and gamma synchronization compared to HCs, as revealed by the decreased TEP N45 amplitude and ITC, respectively. Interestingly, beta and gamma ITC reduction at the motor cortex level was prominent in MCI patients who later converted to AD compared to those who remained stable. Moreover, the stability of the dipolar activity, a parameter obtained from the global mean field power that measures the variations of the dipolar activity power over time, was able to discriminate progressive MCI from stable MCI patients, suggesting that it can be used as a potential disease progression surrogate. In a cross-sectional TMS-EEG study on a cohort of 5 AD, 5 MCI patients and 4 HCs [131], a positive correlation was observed between the P30 amplitude elicited from M1 stimulation and clinical measures of cognitive decline, including MMSE and Clinical dementia rating scale.

In recent years, two cross sectional studies evaluated cortical excitability and plasticity in the dorsolateral prefrontal cortex (DLPFC) of AD patients [134, 135]. In one study, Joseph et al., assessed potential differences in cortical evoked activity (CEA), by calculating a rectified area under the curve for the TEP and TEP peaks amplitudes across a cohort of 24 AD patients and 11 HCs. The authors found that DLPFC-CEA was higher in AD patients compared to HCs, with no differences

in individual TEP peaks, including P30, N45 and P60, reported between the two groups. Intriguingly, DLPFC-EA was significantly correlated with global cognition measures, including the MoCA total scores and executive function measures, such as the executive interview total scores and the CANTAB Stocking of Cambridge number of problems solved in minimum moves [134]. Furthermore, DLPFC plasticity, assessed through the PAS paradigm, was reported to be deficient in AD patients compared to HCs as detailed in a recent cross-sectional study by Kumar et al., involving a cohort of 32 patients with AD and 16 HCs. In this study a positive correlation between PAS-induced LTP and working memory performance, assessed using the n-back, was also found [135]. Beside these studies, preliminary studies suggest that TMS-EEG may provide neurophysiological biomarkers capable of revealing brain network dysfunction not observable in spontaneous brain oscillations [136, 137]. Future studies should evaluate the predictive potential of these novel TMS-EEG biomarkers for the progression along the AD continuum.

Discussion

Which are the most promising neurophysiological biomarkers of conversion across AD continuum?

To identify the most promising neurophysiological biomarkers of progression applicable in clinical settings across the AD continuum, we relied on evidence from longitudinal studies included in our review. The majority of these studies focused on EEG-based measures (30 studies), while only five examined TMS-based markers. This discrepancy might may partly stem from the broader availability and easier applicability of EEG-based techniques in clinical settings, combined with the more complex implementation and theoretical concerns surrounding the use of TMS as a direct biomarker. Additionally, significant challenges in integrating TMS into clinical practice include its reliability both within and across sessions, which may not be as consistent as that of EEG [138–141], along with ethical and safety concerns, particularly when applying TMS in populations with AD. Among the EEG studies, those investigating the predictive value of spectral power measurements [47–50, 56, 59, 60], demonstrated the highest consistency in terms of methodological approaches and results. The findings from these studies indicate that, as individuals progress from healthy aging or SCD to MCI and ultimately AD, there is a global and posterior reduction in resting-state alpha activity, accompanied by an increase in theta and delta frequency power [47, 48, 56, 59, 60]. Although the exact mechanisms generating alpha rhythm remain an open question, posterior alpha oscillations are thought to reflect thalamo-cortical and cortico-cortical interactions [142–144]. The pathophysiological underpinnings of changes observed in patients presenting with AD pathology have been linked to the modulation of posterior alpha rhythm by the acetylcholine neurotransmitter system, which is dysregulated in AD, contributing to the disease's pathophysiology [145, 146].

Moving from EEG to ERPs-based parameters, the latency of P300 and N200, has emerged as a reliable marker in differentiating individuals who will progress along the AD continuum from those who will remain stable. Longitudinal studies [84, 85, 90, 91] have consistently demonstrated that prolonged latencies in these waves may help identify MCI patients at higher risk of converting to AD. ERP measures provide valuable insights into the cognitive trajectories of individuals across the AD continuum. Specifically, the P300 wave, a parieto-central positivity associated with the conscious detection of a task-relevant stimulus, is believed to reflect cognitive processes such as decision-making, attention allocation, and memory storage [147–149]. Conversely, the N200 wave, primarily elicited in frontal-central regions, is linked to cognitive control, novelty detection, and sequential matching, with the midcingulate cortex identified as a potential neural generator [150, 151]. Importantly, these cognitive domains, indexed by P300 and N200, closely align with the early functions impaired during AD progression [152–155]. Finally, considering evidence coming from longitudinal studies evaluating TMS-based parameters, we found that rMT and measures of iTBS or rTMS-induced cortical plasticity show promise as neurophysiological markers for predicting AD progression risk [103, 105, 111]. A direct relationship has been observed between reductions in rMT and the timing of AD conversion [103]. Similarly, during the MCI stage, deficient iTBS or rTMS-induced cortical plasticity has been linked to an elevated risk of conversion to AD [111]. These findings suggest that impairments in motor cortex excitability and synaptic plasticity emerge early in the AD continuum, even when cognitive functions are still relatively intact. While the precise pathophysiological mechanisms behind motor cortex hyperexcitability in AD remain uncertain, hypotheses include increased excitability of intracortical excitatory circuits and impaired intracortical inhibitory circuits, leading to motor cortex disinhibition [156–159]. Disruption of cortical LTP mechanisms may stem from early tau- and Aβ-mediated synaptic dysfunction at the level of dendritic spines, as shown in AD animal models [160, 161]. Interestingly, electrophysiological investigations employing whole-cell patch clamp techniques suggested that these synaptic changes may precede amyloid plaque formation and cognitive decline, highlighting their role in early AD pathology [158, 159, 162].

How do neurophysiological biomarkers perform in terms of sensitivity and specificity?

An ideal biomarker of conversion across the AD continuum must demonstrate both high sensitivity, meaning it should accurately identify the proportion of true progressing patients, and high specificity, ensuring it can correctly exclude individuals who remain cognitively stable. This balance is essential for reliably predicting disease progression while minimizing false positives that could lead to unnecessary interventions or inclusion in clinical trials. Evidence coming from these studies indicate that the sensitivity and specificity of neurophysiological biomarkers vary based on the methods and parameters used. EEG-based measures, including ERPs and spectral power, show promise in differentiating progressive MCI from stable MCI and predicting AD conversion [50, 55, 84, 85, 90, 91, 93]. EEG-based spectral power changes, such as reduced occipital alpha and increased theta, show sensitivity ranging from 64 to 86% and specificity from 53 to 94%, effectively differentiating normal aging from AD [50, 55]. ERPs, including prolonged P300 and N200 latencies, exhibit sensitivity ranging between 60 and 100% and specificity from 75 to 91%, providing moderate diagnostic value in predicting MCI conversion [85, 90, 91]. Therefore, while several neurophysiological biomarkers show potential for predicting AD progression, their accuracy could be limited when used in isolation. Few studies have directly compared the predictive ability of neurophysiological and CSF-based biomarkers [85, 91]. In one study, CSF-beta amyloid 1–42 levels alone demonstrated a sensitivity of 100% and specificity of 77.1%, while P300 amplitude had a sensitivity of 100% but a lower specificity of 48.9%. When combined, the sensibility remained 100%, and the specificity improved to 88.9% [85]. Similarly, another study from the same group comparing progressive MCI and stable MCI found that while CSF-beta amyloid 1–42 alone achieved a sensitivity of 100% and specificity of 77.1%, the N200 latency alone showed superior performance with sensibility and specificity of 100% and 91%, respectively [91]. Combining these two markers yielded a perfect sensibility and specificity of 100%, demonstrating the added value of integrating neurophysiological and biomarker data for more accurate predictions of conversion across AD continuum [91]. Similar preliminary evidence came from the comparison between neuroimaging markers and EEG-based markers [71]. Although neuroimaging markers were more effective than neurophysiological markers in distinguishing individuals at risk of progression from stable subjects, the combination of the two types of markers resulted in an increase in specificity and sensitivity, and consequently improved diagnostic accuracy [71]. It is important to highlight that, even if neurophysiological biomarkers may prove useful for predicting conversion across different stages of the AD continuum, they are not specific to AD pathology [163–166], as they can also be altered in other conditions that pose challenges in the differential diagnosis with AD. Therefore, while they could be potential useful as markers of disease progression, they may have limited utility from a diagnostic perspective.

Relationship between neurophysiological biomarkers and established biological, neuroradiological and clinical measures of disease progression: evidence coming from cross-sectional studies

There is limited evidence from the longitudinal studies included in our review regarding the relationship between neurophysiological markers and established biomarkers of progression along the AD continuum, including neuroimaging, biohumoral and neuropsychological markers. However, findings from cross-sectional studies investigating EEG and ERPs-based measures align well with longitudinal observations supporting the potential utility of some neurophysiological markers in tracking progression across the AD continuum. Several cross sectional studies have demonstrated a significant correlation between posterior alpha power and established neuroradiological [61–63] and neuropsychological [62, 64] measures of AD progression. Similarly, two cross-sectional studies have clearly shown that the latency of P300 is negatively correlated with neuropsychological clinical scales [86, 88]. Notably, the latency of P300 is significantly modulated with the progression of cognitive impairment, being more prolonged in AD compared to MCI and in MCI compared to HCs [87]. Regarding the insights from cross-sectional studies that investigated TMS-based measures for assessing the risk of progression along the AD continuum, these are primarily linked to certain information that may be used for future construction of prospective study designs. Two cross sectional studies utilizing TMS-EEG provided proof of concept for the potential study of non-motor areas in deriving measures useful for defining the risk of progression along the AD continuum [134, 135]. It has been demonstrated that AD patients exhibit alteration in cortical excitability and synaptic PAS-induced plasticity in the DLPFC [134, 135]. Notably, an indication of the possible use of measures exploring these aspects at the level of this non-motor region as prognostic markers comes from the observation that such measures seem to correlate with global cognition measures. This approach could help overcome the commonly raised concern regarding the use of TMS measures targeting the primary motor cortex in a condition primarily affecting cognitive functions. However, these observations are preliminary and require further validation through longitudinal studies with large sample sizes.

Current gaps in the application of neurophysiological biomarkers across the AD continuum

The application of neurophysiological markers, such as EEG, ERPs or TMS parameters, for estimating the risk of conversion along the AD continuum faces several limitations that must be addressed before these techniques can be widely adopted in clinical and research settings. First, there is considerable variability in the methodological approaches used across different studies, including differences in EEG acquisition protocols, reference electrode choices, and data analysis techniques. This lack of methodological standardization represents a major challenge in establishing reliable biomarkers with clear clinical relevance across studies exploring EEG-based measures. Each of the above-cited factors can significantly affect the quality of the EEG signal, potentially altering parameters such as the amplitude and location of the EEG potentials under investigation. An example of this challenge is represented by measures based on the correlations between signals recorded from different electrodes, which may be used to infer a form of connectivity between brain regions. These electrode intercorrelations are indeed highly dependent on scalp location and, consequently, on the reference used. Second, inconsistency in the selection of outcome measures further complicate the development of robust neurophysiological markers. To date, studies have explored a range of neurophysiological parameters, but a clear consensus on which measures are most relevant for predicting AD progression has not yet been established. This is exemplified by studies focusing on interelectrode correlations, where multiple measures, including resting-state EEG COH, phase lag index or iCOH have been employed. Finally, there is a need for additional longitudinal validation studies, particularly involving large patient cohorts, to confirm the predictive value of neurophysiological markers. Although initial findings from smaller studies are promising, larger-scale investigations are crucial to assess the generalizability of the results and their applicability across diverse populations. Future longitudinal studies should aim to examine the comparison as well as correlations between neurophysiological markers and behavioral measures or established AD biomarkers, such as neurobiological or neuroradiological measures. Furthermore, future studies should also clarify if by examining indices that combine all these biomarkers could be valuable to assess if a multimodal approach enhances diagnostic precision. Lastly, while only a few studies have investigated neurophysiological alterations in SCD so far, it is noteworthy that neurophysiological measures could potentially capture functional alterations occurring before the onset of structural damage and clinical symptoms. Given this potential, the exploration of neurophysiological measure in SCD should be a focal point for future research.

Limitations

In conducting this systematic review, several methodological limitations must be acknowledged. Firstly, our search strategy, which was confined to Title/Abstract searches and did not include medical subject headings (MeSH) may have inadvertently excluded some relevant studies. However, this approach was employed to target the most directly relevant articles, assuming that critical keywords pertinent to our research objectives would be prominently featured in these sections. To further mitigate the risk of excluding pertinent articles, we expanded our search by using two comprehensive databases, such as PubMed and Scopus. Additionally, we checked the reference list of included articles and the references cited within these sources, further mitigating this risk. Secondly, the inclusion of cross-sectional studies presents another limitation, as these studies, by their nature, provide only a snapshot view at a single point in time. This characteristic significantly restricts our ability to draw robust conclusions about the utility of biomarkers in tracking the progression of AD. However, we specifically selected cross-sectional studies that evaluated the association between putative biomarkers and reliable neuroradiological and neurobiological progression measures, complementing the longitudinal data to form a more comprehensive understanding of the disease continuum. Finally, the inclusion of older studies that did not employ cerebrospinal fluid or imaging biomarkers to demonstrate underlying AD-pathology may represent another limitation. Nevertheless, the inclusion of these studies in our review is justified by the fact that the adoption of biomarkers for understanding underlying AD pathology is a relatively recent development and there is a limited number of longitudinal studies that have employed these criteria for inclusion.

Conclusions

In conclusion, our comprehensive review sheds light on the potential of easily accessible neurophysiological measures, such as spectral power analysis, P300/N200 latencies and indices of cortical excitability and synaptic plasticity, in predicting the likelihood of conversion to AD in SCD or MCI patients. While these markers show significant promise, it is crucial to emphasize that the current body of evidence is not sufficiently robust to warrant their immediate incorporation into standard clinical practice for AD prediction. A cautious, stepwise approach is necessary, allowing for additional research and validation studies to clarify their role in diagnosing and monitoring AD progression. As the search for reliable, accessible, and cost-effective AD biomarkers continues, the potential of EEG and TMS measures undoubtedly merits further investigation and exploration.

Abbreviations

AD	Alzheimer's disease
SCD	Subjective cognitive decline
MCI	Mild cognitive impairment
HCs	Healthy controls
EEG	Electroencephalography
CSF	Cerebrospinal fluid
TMS	Transcranial magnetic stimulation
aMCI	Amnestic mild cognitive impairment
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
NIA-AA	National Institute on Aging and Alzheimer's Association
PET	Positron emission tomography
Aβ 1–42	β-Amyloid Peptide (1–42)
MMSE	Mini-mental state examination
ERS	Event-Related Synchronization
ERD	Event-Related Desynchronization
18F-FDG PET	18 F-Fluorodeoxyglucose Positron Emission Tomography
IWG	International Working Group
GFP	Global field power
ITC	Inter-trial coherence
COH	Resting-state EEG coherence
iCOH	Resting-state EEG or imaginary part of coherence
TGC	Theta-gamma coupling
GFS	Global field synchronization
MMN	Mismatch negativity
VEPs	Visual evoked potentials
PNwm	Positive-negative working memory component
spTMS	Single-pulse TMS
rMT	Resting motor threshold
MEP	Motor-evoked potentials
SI1mV	Stimulus intensity needed to evoke motor-evoked potential MEP of 1mV
ADAS-Cog	Alzheimer's Disease Assessment Scale - Cognitive Subscale
ppTMS	Paired-pulse TMS
ISI	Inter-stimulus interval
SICI	Short-interval intracortical inhibition
ICF	Intracortical facilitation
SAI	Short-latency afferent inhibition
rTMS	Repetitive transcranial magnetic stimulation
LF rTMS	Low frequency repetitive transcranial magnetic stimulation
HF rTMS	High frequency repetitive transcranial magnetic stimulation
cTBS	Continuous theta burst stimulation
iTBS	Intermittent theta burst stimulation
LTD	Long-term depression
LTP	Long-term potentiation
PAS	Paired associative stimulation
TEPs	TMS-evoked potentials

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