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Resting-state functional and spectral alterations underlying cognitive decline in biomarker-confirmed Alzheimer's disease: A systematic review

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ABSTRACT

Alzheimer's disease (AD) is characterized by progressive cognitive decline associated with synaptic and large-scale network dysfunction. Resting-state alterations may provide functional correlates of AD pathology, but associations among intrinsic brain activity, biomarkers, and domain-specific cognition have not been systematically integrated across spectral and connectivity frameworks.

We systematically reviewed PubMed, Scopus, and Web of Science through May 2025 (PROSPERO CRD42024575913). Thirty studies ($N = 5898$) examining resting-state EEG, MEG, or fMRI, AD biomarkers, and cognition were synthesized following SWiM guidance.

Across studies, resting-state alterations showed converging associations with amyloid and tau measures from CSF, PET, and plasma. Five of six electrophysiological studies reported increased delta/theta activity and three of six reduced alpha/beta activity, supporting neural slowing. Greater low-frequency activity was generally associated with poorer global cognition and episodic memory, whereas reduced higher-frequency activity was linked to poorer attention and processing speed. Among 21 connectivity studies, 10 reported hyperconnectivity and 13 hypoconnectivity, with non-mutually exclusive categories. Hyperconnectivity, particularly within medial and anterior temporal circuits, was more frequent in earlier-stage groups and showed heterogeneous cognitive associations, including poorer and better-preserved performance. Broader hypoconnectivity across posterior default mode, medial temporal–posterior medial, and frontoparietal networks was more prominent in later-stage groups and more consistently associated with poorer global cognition, episodic memory, and executive function.

These findings support spectral slowing and stage-related network reorganization as functional correlates of cognitive impairment in biomarker-characterized AD. However, 25 of 30 studies were cross-sectional; therefore, these connectivity patterns should not be interpreted as a demonstrated within-person trajectory.

Abbreviations: AD, Alzheimer's disease; ADD, Alzheimer's disease dementia; ALFF, Amplitude of Low-Frequency Fluctuations; Aβ, Amyloid-beta; APOE, Apolipoprotein E; AT, Anterior temporal network; BOLD, Blood oxygen level-dependent; CSF, Cerebrospinal fluid; DAN, Dorsal attention network; DC, Degree centrality; DMN, Default mode network; EC, Eyes-closed; EEG, Electroencephalography; EO, Eyes-open; fALFF, Fractional amplitude of low-frequency fluctuations; FC, Functional connectivity; fMRI, Functional magnetic resonance imaging; FPN, Frontoparietal network; GFAP, Glial fibrillary acidic protein; HC, Healthy control; LN, Limbic network; MCI, Mild cognitive impairment; MEG, Magnetoencephalography; MMSE, Mini-Mental State Examination; MRI, Magnetic resonance imaging; MTL, Medial temporal lobe; NfL, Neurofilament light chain; pDMN, Posterior default mode network; PET, Positron emission tomography; PM, Posterior-medial network; POSI, Pathological Oscillatory Slowing Index; SBA-rr, Spontaneous brain activity at rest ratio; SCD, Subjective cognitive decline; SFC, Structure–function coupling; SMN, Sensorimotor network; SN, Salience Network; VAN, Ventral Attention Network; VN, Visual network.

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1. Background

One of the major causes of dementia in aging is Alzheimer's disease (AD). The earliest stages of AD are characterized by subtle alterations in neuronal function and large-scale brain network organization that may emerge years before the onset of overt cognitive symptoms (Selkoe and Hardy, 2016; Jack Jr et al., 2018). Contemporary biomarker frameworks conceptualize AD as a biological continuum in which pathological processes accumulate during a prolonged preclinical phase preceding clinical manifestations (Jack Jr et al., 2018; Sperling et al., 2011). Among these processes, the accumulation of amyloid-beta (Aβ) peptides and the subsequent formation of extracellular amyloid plaques are commonly observed early biological features and represent defining components of AD pathology (Selkoe and Hardy, 2016; Sperling et al., 2011). However, increasing evidence indicates that early vascular dysfunction, neuroinflammatory responses, and other pathophysiological mechanisms may also contribute to early network disruption and may precede or interact with amyloid pathology in some individuals (Iturria-Medina et al., 2016; Sweeney et al., 2018). Amyloid aggregation has been associated with synaptic dysfunction and neuroinflammatory responses that increase neuronal vulnerability (Heneka et al., 2015). As the disease progresses, hyperphosphorylated tau proteins accumulate intracellularly forming neurofibrillary tangles (NFTs), which disrupt the microtubule network necessary for axonal transport and ultimately lead to neuronal degeneration and cell death (Wang and Mandelkow, 2016). Together, amyloid plaques and tau pathology (widely recognized as central neuropathological hallmarks of AD) affect distributed brain networks supporting different cognitive domains (Seeley et al., 2009).

Over the past decades, neuroimaging techniques have played a central role in characterizing the structural, functional, and molecular alterations associated with AD. Structural magnetic resonance imaging (MRI) has revealed progressive patterns of cortical and hippocampal atrophy that track disease progression, while functional magnetic resonance imaging (fMRI) has identified BOLD-derived alterations in large-scale networks such as the Default Mode Network (DMN), which are thought to reflect early synaptic and network-level alterations (Dickerson and Sperling, 2009; Greicius et al., 2004; Mosconi, 2005). Metabolic and molecular imaging using positron emission tomography (PET) has further enabled the in vivo quantification of key pathological processes, including amyloid deposition, tau accumulation, and alterations in cerebral glucose metabolism (Villemagne et al., 2013; Palmqvist et al., 2017; Brier et al., 2012). These multimodal neuroimaging approaches have substantially advanced the understanding of associations between molecular pathology and network-level brain dysfunction in AD.

In parallel, electrophysiological methods such as electroencephalography (EEG) and magnetoencephalography (MEG) provide complementary insights into brain function by directly measuring neuronal activity with high temporal resolution (Babiloni et al., 2018; Jeong, 2004). Individuals with early-stage AD or mild cognitive impairment (MCI) frequently exhibit alterations in power spectral density and functional connectivity across several frequency bands. For example, Meghdadi et al. (Meghdadi et al., 2021) reported that patients with Alzheimer's disease dementia (ADD) showed significantly increased delta and theta oscillatory power and reduced alpha power compared with cognitively normal controls. Similarly, López et al. (López et al., 2014) demonstrated that individuals with amnestic MCI exhibited increased delta and theta power, along with decreased alpha and beta power, relative to cognitively normal individuals. Converging multimodal evidence suggests that electrophysiological alterations may reflect underlying molecular pathology. In particular, increased amyloid and phosphorylated tau deposition within regions of the Default Mode Network (DMN) has been associated with altered connectivity patterns in early AD (Palmqvist et al., 2017; Buckner et al., 2005). Franzmeier et al. (Franzmeier et al., 2019) demonstrated that brain regions with elevated tau burden exhibit altered functional connectivity, suggesting a relationship between tau accumulation and network dysfunction. Likewise, Putcha et al. (Putcha et al., 2022) reported that increased tau PET uptake was associated with reduced connectivity within the DMN, particularly in the early stages of AD.

From a cognitive perspective, a substantial body of neuropsychological research has characterized the pattern of cognitive dysfunction across the Alzheimer's disease continuum. Early impairments are most consistently observed in episodic memory, particularly in tasks involving delayed recall, associative binding, and the retention of newly learned information (deficits that may be detectable during preclinical or prodromal stages of the disease) (Grober et al., 2008; Albert et al., 2011). However, early cognitive manifestations are not restricted to episodic memory. Executive dysfunction may be particularly prominent in non-amnestic or dysexecutive presentations of AD (Townley et al., 2020), while deficits in attention and processing speed may emerge during MCI or co-occur with early memory impairment (Van Dam et al., 2013; Haworth et al., 2016). Spatial navigation and orientation are also increasingly recognized as sensitive early markers, reflecting dysfunction within medial temporal and parietal systems (Coughlan et al., 2018; Serino et al., 2025).

As pathology progresses, additional domains become compromised, including semantic memory, executive functioning, and visuospatial abilities, generating a multidomain pattern of impairment that broadly reflects the spread of underlying neuropathology (Salmon and Bondi, 2009). However, the relationship between neuropathology and cognitive phenotypes is often complex in older adults. Neuropathological studies indicate that mixed pathologies (most commonly the coexistence of AD pathology and cerebrovascular disease) are highly prevalent in individuals with dementia, frequently leading to overlapping neuropsychological profiles (Schneider et al., 2007; Kapasi et al., 2017). Although AD is typically associated with prominent deficits in episodic memory consolidation and language, vascular contributions may also influence executive and attentional processes, underscoring the need for caution when interpreting cognitive profiles in heterogeneous clinical populations (Salmon and Bondi, 2009; Schneider et al., 2007; Kapasi et al., 2017). Nevertheless, standardized neuropsychological assessments remain essential tools for detecting, staging, and monitoring disease progression, as declines in memory, naming, and problem-solving abilities reliably track clinical severity (Albert et al., 2011). Collectively, these findings highlight the progressive and multidomain nature of cognitive deterioration in AD and emphasize the importance of integrating cognitive markers with biological indicators to better capture disease trajectories.

Although the relationship between resting-state electrophysiology and cognitive performance has been widely investigated using different analytical approaches, recent systematic reviews have primarily focused on characterizing electrophysiological alterations across the AD spectrum or linking EEG features with molecular biomarkers. In contrast, fewer studies have examined how biomarker-confirmed AD pathology simultaneously relates to domain-specific cognitive outcomes and to resting-state neural alterations across multiple neuroimaging modalities. Therefore, the present study aimed to examine how resting-state neural alterations associated with AD biomarkers relate to domain-specific cognitive performance across the Alzheimer's disease continuum.

2. Methods

2.1. Literature search strategies

A comprehensive search strategy was employed to identify relevant studies examining how AD biomarkers relate to domain-specific cognitive performance across the disease continuum. The PICO (Participant, Intervention, Comparison, Outcome) framework was used to structure the search related to the research questions (Cooke et al., 2012). We systematically searched multiple electronic databases covering key

biomedical, psychological, and multidisciplinary research areas, including PubMed, Scopus, and Web of Science, using keywords and subject headings related to electrophysiology, cognitive performance, and AD. The search was conducted on 22nd May 2025. The keywords used in the literature search are presented in Table 1.

2.2. Inclusion and exclusion criteria

Studies were considered eligible if they examined biomarker-confirmed stages of the Alzheimer's disease continuum, employed resting-state functional neuroimaging techniques (including electrophysiological methods such as EEG/MEG and hemodynamic methods such as fMRI), and included at least one standardized measure of cognitive performance. Eligibility further required that participants were aged 50 years or older and that diagnoses of MCI due to AD or ADD were established according to standardized clinical criteria by qualified clinicians, with AD biomarker information used to support clinical characterization. Biomarker cutoffs followed those prespecified in the original studies and varied according to the assay, tracer, laboratory, or cohort. Studies were excluded if biomarker data (e.g., tau, amyloid…) were not reported or if neuroimaging resting-state measures associated with cognitive domains were not available.

2.3. Screening protocol

To avoid duplication, ensure the reliability of the process and follow a standard systematic review protocol, this review was registered in PROSPERO (publication code: CRD42024575913). The selected articles were imported into Rayyan (Ouzzani et al., 2016). The revision process, conducted by two reviewers (BC and SA), adhered to the PRISMA guidelines for systematic reviews (Page et al., 2021), ensuring methodological rigor. The reviewers paid attention to the exclusion and inclusion criteria, particularly in the measurement of biomarkers in the included sample. The article's titles and abstracts were initially screened, and full texts were obtained and subsequently reviewed for those manuscripts selected in the first stage. Disagreements were resolved in specific meetings to review each conflicting point (screening protocols and final selection are depicted in Fig. 2).

Table 1
Search terms. Lists the key concepts and search terms employed in PubMed, Scopus, and Web of Science (May 2025).

Key Concept	Search Terms Used
Alzheimer's disease	"Alzheimer's disease diagnosis*" OR "Alzheimer's Disease" OR "Continuum Alzheimer's Disease" OR "AD continuum" OR "early stages Alzheimer's Disease" OR "prodromal Alzheimer's Disease" OR "preclinical Alzheimer's Disease" OR "early diagnosis Alzheimer's Disease" OR "Alzheimer" OR "AD"
Cognitive performance	"cognition" OR "neuropsychology" OR "cognitive markers" OR "cognitive functioning" OR "cognitive domains" OR "brief cognitive screening" OR "screening test" OR "cognitive battery" OR "neuropsychological evaluation" OR "Cognitive Assessment" OR "Screening Instrument" OR "Neurocognitive Tests" OR "cognitive test" OR "assess*" OR "screen*"OR "neuropsychological performance" OR "cognit"
Biomarkers	"PET" OR "CSF" OR "Cerebrospinal fluid" OR "Tau" OR "T-Tau" OR "Phospho-tau" or "Phosphorylated tau" OR "Amyloid" OR "beta protein" OR "Abeta-42" OR "beta peptides"
Resting-state	"rsfc" OR "resting state" OR "resting-state" OR "resting" OR "ongoing activity" OR "task- free" OR "task free"
Neuroimaging technique	"EEG" OR "electroence*"OR "MEG" OR "magnetoence*" OR "fMRI" OR "Functional magnetic resonance imaging" OR "Brain oscillat*" OR "neural oscillat*" or "functional connectivity" OR "network" OR "alpha peak" OR "electrophysiology"

2.4. Quality assessment

Two independent reviewers (BC and SA) assessed the quality of the selected articles using the tool for cross-sectional studies using biomarker data (BIOCROSS) (Wirsching et al., 2018) and a third researcher was appointed to solve emerging conflicts (JF). The specific assessment of the items was performed under the adaptation described in Chino et al. (Chino et al., 2024) as some of the original items could not be easily applied due to the nature of the specific research field studied. This information included neurophysiological technical specifications, research and data processing protocol modeling details. Furthermore, we incorporated additional specifications to improve quality standards within our study population, patients within the AD continuum (for more information, see "Quality Assessment" in Appendix A). Quality assessment was conducted over the 30 selected studies; no articles were excluded based on the quality assessment. The reviewers' final scores for the 30 articles for each quality item are reported in Supplementary Materials.

2.4.1. Risk of Bias assessment

To ensure methodological rigor in accordance with PRISMA 2020 recommendations, risk of bias was independently assessed by two reviewers for all included studies. Given that most of the selected articles were observational, different Joanna Briggs Institute (JBI) critical appraisal tools were applied depending on the study type.

For cross-sectional studies, the JBI Critical Appraisal Checklist for Analytical Cross-Sectional Studies (8 items) was used; for longitudinal cohort studies, the JBI Critical Appraisal Checklist for Cohort Studies (11 items) was used. The tools evaluate methodological domains including clarity of inclusion criteria, validity and reliability of exposure and outcome measurements, identification and management of confounding factors, appropriateness of statistical analyses, and (where applicable) group comparability, follow-up adequacy, and handling of attrition.

Each item was rated as "Yes", "No", "Unclear", or "Not applicable". For descriptive purposes, a proportional scoring approach was applied. The percentage of "Yes" responses relative to applicable items was calculated for each study (excluding items rated as "Not applicable"). Studies scoring $\geq$75% were classified as low risk of bias, those between 50 and 74% as moderate risk, and those $<$50% as high risk. This categorization was defined a priori to facilitate synthesis and does not represent an official JBI scoring recommendation. Discrepancies between reviewers were resolved through discussion. No studies were excluded based on risk of bias; rather, appraisal results were used to contextualize the interpretation of findings. A detailed summary of risk of bias assessments is provided in Supplementary Materials.

2.5. Data extraction

The information extracted from each full-text article reviewed is summarized in two tables, categorized by the type of signal analysis performed: spectral analysis (Table 2) and connectivity analysis (Table 3). In these tables, the most relevant information was extracted for each of the articles, following the same structure:

- Authors and publication date.
- Sample characteristics: including the number of subjects and basic demographic information (age and distribution by sex).
- Methods: referring to the neuroimaging technique used in each article: Magnetoencephalography (MEG), Electroencephalography (EEG), or Functional Magnetic Resonance Imaging (fMRI); signal acquisition condition (eyes closed, eyes opened) and cognitive test (classified by cognitive process) were also included.
- Main findings: where main results, conclusions, and limitations were reported.

Table 2
Summary of studies included in spectral power analysis.

Authors (Year)	N	Mean Age ± SD (Range)	Sex (M/F)	Biomarker (s)	Neuroimaging Technique	Experimental condition	Cognitive domain	Type of signal analysis	Main Findings	Quality Assessment Score
Avants et al. (2019)	62	**MCI** Aβ - 70.7 ± 9.0 Aβ + 71.0 ± 6.8	(33/29)	Aβ42 (CSF) Aβ (PET)	fMRI	EO (7 min)	Episodic memory (immediate and delayed recall)	Amplitude of Low Frequency Fluctuations (ALFF)	Aβ- subjects stable SBA-rr is associated with stable immediate recall performance. Aβ + reduced SBA-rr is also associated with stable immediate recall performance. The most robust effects were located in the right precuneus and right angular gyrus.	15.5
Chino et al. (2022)	27	**MCI** 75.48 + 5.57	(15/12)	Aβ42 (CSF) t-tau (CSF) p-tau181 (CSF)	EEG	EC (5 min)	Episodic memory (immediate and delayed recall), attention/working memory, language and global cognition	Cluster-based statistics (CBS)	In MCI males, higher theta power in central-posterior regions is associated with lower Aβ42, worse global cognition, poorer episodic memory and higher t-tau. Reduced alpha power correlated with higher t-tau. In MCI females, reduced beta power correlates with higher t-tau levels and older age.	16.5
Cui et al. (2025)	1002	**HC** 64.46 ± 8.53 **SCD** 63.35 ± 7.77 **MCI** 66.50 ± 7.04 **ADD** 67.50 ± 8.45	(390/612)	Aβ (PET)	fMRI	EC (7 min)	Verbal and visual episodic memory, executive function and visual perception	Fractional Amplitude of Low Frequency Fluctuations (fALFF)	ADD reduced right intraparietal cortex fALFF is associated with higher precuneus Aβ burden. Higher precuneus Aβ burden is associated with increased parahippocampal ReHo in MCI.	14
Jiao et al. (2023)	890	**HC** 63.85 ± 8.20 **MCI** 64.77 ± 9.30 **ADD** 64.60 ± 9.75	(360/530)	Aβ40 (CSF) Aβ42 (CSF) t-tau (CSF) p-tau181 (CSF) APOE ε4	EEG	EC (10 min)	Global cognition	Power spectral density (PSD) Hjorth parameters	EEG biomarkers achieve over 70% accuracy in the classification of HC/MCI/ADD, with 80–85% accuracy in binary comparisons (HC vs MCI, HC vs ADD). Most prominent alterations are localized in parieto-occipital, involving theta power and Hjorth mobility. EEG biomarkers are more effective than CSF/APOE measures in predicting age of onset and disease course, while CSF/APOE measures outperformed EEG in estimating global cognition. The best performance across all targets is achieved by combining EEG, CSF, APOE and demographic features. EEG also differentiates ADD/MCI from other	14.5

(*continued on next page*)

Table 2 (*continued*)

Authors (Year)	N	Mean Age ± SD (Range)	Sex (M/F)	Biomarker (s)	Neuroimaging Technique	Experimental condition	Cognitive domain	Type of signal analysis	Main Findings	Quality Assessment Score
Nakamura et al. (2018)	66	**HC** Aβ - 72.5 ± 3.4 Aβ + 71.8 ± 4.4 **MCI** Aβ - 73.8 ± 8.8 Aβ + 74.7 ± 5.4	(35/31)	Aβ (PET) APOE ε4	MEG	EC (5 min)	Episodic memory (immediate and delayed recall) and global cognition	Power spectral density (PSD)	dementias and shows significant correlations with Aβ42/p-tau and global cognition. Increased alpha power in medial-frontal regions is associated with Amyloid-β deposition. Increased delta power in medial-frontal areas reflects disease progression, correlating with entorhinal atrophy, AD-like hypometabolism and cognitive decline. Global theta power augmentation is linked to general cognitive decline and hippocampal atrophy, but it lacks specificity for Alzheimer's disease (similar changes are observed in Aβ -).	14.5
Ren et al. (2016)	35	**HC** 79.33 ± 5 **MCI** 75.35 ± 8.57	(16/19)	Aβ42 (CSF) p-tau181 (CSF)	fMRI	EO (7 min)	Verbal and visual episodic memory and executive function	Amplitude of Low Frequency Fluctuations (ALFF)	MCI participants show a significantly greater longitudinal decline of ALFF in the right putamen (compared with HC) and is associated with memory decline. Baseline CSF Aβ/pTau ratio predicts the decline of right putaminal ALFF across groups, with the slow-4 band showing the strongest sensitivity. MCI higher hippocampal DFA is correlated to lower global cognition.	12.5
Van Nifterick et al. (2023)	131	**HC** 57 ± 8.4 **SCD** 60 ± 8.0 **MCI** 65 ± 5.9 **ADD** 64 ± 7.6	(71/54)	Aβ42 (CSF) Aβ (PET)	MEG	EC (5 min)	Global cognition	Power spectral density (PSD) E/I balance metrics	ADD hippocampal and parieto-occipital DFA, as well as aperiodic gamma exponent in these regions, are positively correlated to global cognition. Posterior cortical aperiodic exponent differs between AD and controls, suggesting altered excitation-inhibition balance. MCI/ADD higher delta activity in the right temporal pole and left superior temporal cortex predicts poorer processing speed.	14.5
Wiesman et al. (2021)	58	**HC** 72.7 ± 4.73 **MCI/ADD** 69.21 ± 6.91	(28/30)	Aβ (PET)	MEG	EC (8 min)	Memory, learning, language, attention/executive function, processing speed and global cognition	Power spectral density (PSD)	MCI/ADD increased theta activity in the right superior temporal cortex and supramarginal gyrus predicts better memory performance. MCI/ADD reduced beta	15

(*continued on next page*)

Table 2 (*continued*)

Authors (Year)	N	Mean Age ± SD (Range)	Sex (M/F)	Biomarker (s)	Neuroimaging Technique	Experimental condition	Cognitive domain	Type of signal analysis	Main Findings	Quality Assessment Score
									activity in the right and left inferior parietal cortices predicts poorer attention, in the left middle temporal cortex predicted poorer processing speed. MCI/ADD shows neural slowing (increased low-frequency and decreased high-frequency amplitude) compared with controls.	
Wiesman et al. (2022)	58	**HC** 72.7 ± 4.73 **MCI/ADD** 69.21 ± 6.91	(28/30)	Aβ (PET)	MEG	EC (8 min)	Memory, learning, language, attention, processing speed and global cognition	Power spectral density (PSD) Pathological Oscillatory Slowing Index (POSI)	POSI has a significant relationship with global cognition in a left-lateralized network (temporo-parietal cortex and supramarginal gyrus) in which greater slowing implies worse cognition. POSI is a better predictor of global cognition than band-limited power. Pathological slowing predicts poorer attention, processing speed, verbal function and is associated with higher regional amyloid-β burden.	14
Zeng et al. (2019)	77	**HC** 75.36 ± 8.22 **SCD Aβ +** 74.62 ± 6.11 **MCI** 71.48 ± 6.20 **ADD** 75.51 ± 4.06	(37/40)	Aβ42 (CSF) t-tau (CSF) p-tau181 (CSF)	fMRI	EO (7 min)	Attention, cognitive flexibility and global cognition	Fractional Amplitude of Low Frequency Fluctuations (fALFF)	MCI displays reduced fALFF in the posterior cingulate cortex/precuneus (DMN) compared to HC. ADD exhibits a mixed pattern with reduced fALFF in posterior cingulate cortex/precuneus, cuneus and occipital cortex, but increased fALFF in hippocampus, parahippocampus, fusiform and inferior temporal regions. fALFF in PCC/precuneus correlated positively with global cognition and CSF Aβ + and negatively with attention, cognitive flexibility and CSF p-tau.	11

2.6. Data synthesis

Due to the diversity in recording conditions and analysis methods utilized in the 30 selected articles, we employed the synthesis without meta-analysis (SWiM) guidelines described by Campbell et al. (Campbell et al., 2020). Data synthesis was conducted by attending to the primary type of analysis employed (i.e., spectral analysis vs. connectivity analysis) and the cognitive process involved (global cognition, memory, attention, visuospatial abilities, language, and executive functions). Fig. 1 shows the number of papers included in each category.

EEG, MEG, and resting-state fMRI were integrated within a common resting-state framework because all three characterize spontaneous brain activity or interregional statistical dependencies in the absence of an explicit task. However, the modalities were not treated as physiologically interchangeable. EEG and MEG directly measure electromagnetic neuronal activity, whereas fMRI reflects slower BOLD fluctuations indirectly related to neural activity through neurovascular coupling. Findings were therefore organized by analytical construct and interpreted in light of the physiological differences among modalities.

To improve the transparency of the narrative synthesis, descriptive study-level counts and proportions were calculated for the principal recurring findings. Each study was counted once within a given category when it reported at least one result consistent with that pattern, regardless of the number of regions, contrasts, or cognitive outcomes

Table 3
Summary of studies included in functional connectivity analysis.

Authors (Year)	N	Mean Age ± SD (Range)	Sex (M/F)	Biomarker(s)	Neuroimaging Technique	Experimental condition	Cognitive domain	Type of signal analysis	Main Findings	Quality Assessment Score
Banks et al. (2018)	123	**HC** Aβ- 72.72 ± 5.76 Aβ + 74.91 ± 6.92 **MCI** Aβ + 73.21 ± 7.00 **ADD** Aβ + 74.17 ± 6.73	(58/65)	Aβ (PET)	fMRI	EO (6 min)	Episodic memory (learning and delayed recall)	Functional lateralization index (FLI)	Aβ-HC group was significantly more pDMN left-lateralized than MCI and ADD groups. This was associated with better delayed recall performance, with effects mediated by amyloid burden. Older subjects in the ADD group had less left functional lateralization of the aDMN. Higher left-lateralization of the aDMN was also associated with better delayed recall.	15
Behfar et al. (2020)	45	**HC** YA 24.4 ± 2.85 OA 67.26 ± 8.11 **MCI** 71.13 ± 5.76	(27/18)	Aβ42 (CSF) t-tau (CSF) p-tau181 (CSF) Aβ (PET)	fMRI	EO (7 min)	Episodic memory and cognitive flexibility	Graph Theory Analysis (DC)	Observable structural atrophy in the right middle frontal gyrus, bilateral precentral gyri and the right superior parietal lobule co-occurred with significant increase in DC. This increase in connectivity in the MCI group was positively associated with episodic memory and cognitive flexibility.	15
Berron et al. (2020)	442	**HC** Aβ- 72.72 ± 5.6 Aβ + 72.4 ± 5.4 **MCI** Aβ + 72.2 ± 4.8	(182/260)	Aβ40 (CSF) Aβ42 (CSF) p-tau181 (CSF)	fMRI	EC (6 min)	Episodic memory (immediate and delayed recall)	BOLD signal correlation	Aβ + HC show reduced MTL-AT connectivity. In those with higher p-tau levels, also reduced connectivity in MTL-PM. MCI group has a strong reduction of MTL-PM and MTL-mPFC connectivity while hippocampal hyperconnectivity. Lower MTL-PM and MTL-AT connectivity linked to worse delayed memory. Both networks predict steeper longitudinal decline in immediate and delayed recall.	15
Blujus et al. (2025)	363	**HC** Aβ- 72.91 ± 6.94 Aβ + 75.77 ± 6.92 **MCI** Aβ- 75.49 ± 7.99 Aβ + 74.54 ± 7.70	(176/187)	Aβ (PET)	fMRI	EO (7 min)	Episodic memory and executive function	Graph Theory Analysis (Redundancy)	Posterior hippocampal redundancy was significantly lower in Aβ + than Aβ-groups, regardless of diagnosis Posterior HC redundancy was related to higher education and better episodic memory, but it did not moderate the Aβ-cognition relationships across the diagnostic groups	16
Canuet et al. (2015)	12	**MCI** p-tau+69.86 ± 6.51 p-tau- 68.80 ± 10.96 Aβ + 66.50 + 7.03 Aβ- 75.25 + 7.93	(2/10)	Aβ42 (CSF) p-tau181 (CSF)	MEG	EC (5 min)	Global cognition and episodic memory	Phase-Locking Value (PLV)	P-tau+ was associated with beta hyperconnectivity in limbic areas and correlated negatively with global cognition and free recall; alpha hypoconnectivity between the right posterior cingulate cortex and the paracentral lobule correlated positively with immediate recall. Aβ + was associated with beta hypoconnectivity between the right inferior temporal and	12

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Table 3 (*continued*)

Authors (Year)	N	Mean Age ± SD (Range)	Sex (M/F)	Biomarker(s)	Neuroimaging Technique	Experimental condition	Cognitive domain	Type of signal analysis	Main Findings	Quality Assessment Score
Chauveau et al. (2025)	116	**HC** 69.8 ± 6.56 **MCI** 74.5 ± 6.7 **ADD** 67.2 ± 9.8	(61/55)	Aβ (PET)	fMRI	EC (11 min)	Global cognition	BOLD signal correlation	precentral cortices, which correlated positively with global cognition. Advancing age was linked to lower PM connectivity and more regionally heterogeneous AT changes. AD was characterized by AT hyperconnectivity without global changes in PM connectivity. AT connectivity was higher in MCI and AD patients compared with older HC and was positively associated with amyloid burden, glucose hypometabolism, hippocampal atrophy, global cognitive deficits and faster progression to dementia.	12
Chen et al. (2025)	173	**HC** 68.25 ± 5.55 **MCI/ADD** 71.32 ± 8.52	(71/102)	Aβ40 (plasma) Aβ42 (plasma) p-tau181 (plasma) NfL (plasma) GFAP(plasma) Aβ (PET)	fMRI	EC (16 min)	Episodic memory, executive function, language and global cognition	BOLD signal correlation Structure-function coupling (SFC)	Compared to HC, MCI/AD participants exhibited increased regional SFC in DMN regions. MCI/AD amyloid pathology correlated with SFC in occipital, precuneus, temporoparietal and medial prefrontal regions, with APOE ε4+ subjects showing stronger associations in occipital and temporoparietal. SFC partially mediated the impact of amyloid on executive function, episodic memory, language and global cognition (MoCA) and findings were replicated with plasma biomarkers.	13
Cui et al. (2025)	1002	**HC** 64.46 ± 8.53 **SCD** 63.35 ± 7.77 **MCI** 66.50 ± 7.04 **ADD** 67.50 ± 8.45	(390/612)	Aβ (PET)	fMRI	EC (7 min)	Verbal and visual episodic memory, executive function and visual perception	Graph Theory Analysis (DC) Regional Homogeneity (ReHo)	MCI high precuneus Aβ burden was associated with increased parahippocampal ReHo/DC. Reduced intraparietal-lateral temporal/parahippocampal connectivity was linked to impaired executive function. ADD higher precuneus Aβ burden was associated with widespread disruptions of DMN connectivity, which correlated with deficits in executive function and memory.	14
Dautricourt et al. (2021)	121	**HC** 68.2 ± 7.8 **MCI/ADD** 70.8 ± 8.8	(60/61)	Aβ (PET)	fMRI	EC (11 min)	Episodic memory, semantic memory, executive function and visual perception	BOLD signal correlation	Decreased FC between MTL and PM network was associated with lower global cognition, episodic memory and semantic memory. Increased FC between MTL and AT was associated with lower global cognition, episodic memory and executive functions.	15
Ersoezlue et al. (2023)	228	**HC** 68 ± 5 **SCD** 71 ± 5 **MCI** 73 ± 6	(111/117)	Aβ42 (CSF) t-tau (CSF) p-tau181 (CSF) APOE ε4	fMRI	EC (8 min)	Episodic memory, executive function and global cognition	BOLD signal correlation	In the MCI/ADD group, the association between intrinsic DMN connectivity and memory was attenuated by higher lifetime of experiences questionnaire (LEQ). MCI years of education significantly moderated the relationship between memory with DMN and DAN intrinsic connectivity, indicating that	16.5

(*continued on next page*)

Table 3 (*continued*)

Authors (Year)	N	Mean Age ± SD (Range)	Sex (M/F)	Biomarker(s)	Neuroimaging Technique	Experimental condition	Cognitive domain	Type of signal analysis	Main Findings	Quality Assessment Score
Huang et al. (2024)	404	**ADD** 75 ± 6 **HC** 66.7 ± 8.8 **MCI** 68.7 ± 7.5 **ADD** 67.6 ± 8.6	(170/234)	Aβ (PET) Aβ (CSF) APOE ε4	fMRI	EC (6 min)	Language and global cognition	BOLD signal correlation	participants with higher education showed stronger memory-network coupling Temporo-frontoparietal FC (in bilateral superior temporal pole, left inferior frontal and supramarginal gyri) was consistently reduced in ilMCI compared with aMCI and normal controls and linked to semantic impairment. Positive correlations were observed between temporo-frontoparietal FC and language/global cognition. Temporo-frontoparietal FC achieved good accuracy in classifying MCI subtypes.	14.5
Koch et al. (2015)	40	**HC** 64.8 ± 5.4 **MCI** 68.2 ± 8.4	(21/19)	Aβ (PET)	fMRI	EC (10 min)	Global cognition	Independent Component Analysis (ICA)	MCI showed reduced FC in the precuneus of the pDMN and the inferior parietal lobule of the right ATN; the pDMN effect remained significant after controlling for atrophy and was associated with poorer global cognition. Higher amyloid burden in medial/lateral posterior parietal cortex overlapped with areas of reduced FC, and pDMN FC moderated the impact of amyloid pathology on global cognition.	15
Leng et al. (2023)	42	**HC** 63.1 ± 8.2 **MCI** 75.8 ± 7.6 **ADD** 73.7 ± 7.7	(21/21)	Aβ (PET) Neuroinflammation (PET)	fMRI	EC (10 min)	Global cognition	BOLD signal correlation Graph Theory Analysis (global efficiency, local efficiency and small-worldness)	ADD shows increased PET uptake of the neuroinflammation tracer (reflecting microglial activation) and reduced network small-worldness and local efficiency. MCI/ADD cortical neuroinflammation correlates negatively with network local efficiency, independent of cortical thickness and amyloid deposition. Local efficiency and cortical thickness correlate positively with global cognition. Mediation analyses indicate that neuroinflammation disrupts functional network organization both directly and indirectly through structural network damage.	14.5
Malotaux et al. (2023)	60	**HC** 72.12 ± 5.16 **Stable MCI** Aβ- 71.49 ± 5.88 Aβ + 73.13 ± 7.60 **Progressive MCI** Aβ- 77.76 ± 4.24	(31/29)	Aβ (PET) APOE ε4	fMRI	EC (7 min)	Global cognition	BOLD signal correlation	Progressive MCI exhibits a longitudinal increase in intra-DMN connectivity compared to stable MCI. That increase is associated with more cognitive decline and subsequent dementia diagnosis. Aβ status is not significantly associated with DMN connectivity at follow-up. Aβ + MCI shows a progressive increase in SMN connectivity. Lower baseline MMSE predicts a future increase in intra-DMN connectivity, and faster MMSE	17.5

(*continued on next page*)

Table 3 (*continued*)

Authors (Year)	N	Mean Age ± SD (Range)	Sex (M/F)	Biomarker(s)	Neuroimaging Technique	Experimental condition	Cognitive domain	Type of signal analysis	Main Findings	Quality Assessment Score
		Aβ + 74.04 ± 8.58							decline is paralleled by greater DMN hyperconnectivity. HC and MCI higher entorhinal tau PET is strongly associated with worse delayed recall performance. Global left frontal-cortex connectivity significantly moderates this association: at higher connectivity, the negative impact of entorhinal tau on memory is attenuated.	
Neitzel et al. (2019)	125	**HC** Aβ- 72.6 ± 6.7 Aβ + 74.3 ± 4.4 **MCI** Aβ- 74.9 ± 8.5 Aβ + 72.8 ± 7.6	(52/73)	Aβ (PET) Tau (PET)	fMRI	EC (10 min)	Episodic memory (immediate and delayed recall)	Seed-based BOLD signal correlation	This moderating effect is also with frontoparietal control network connectivity linked to greater resilience against tau-related memory impairment. There are no moderating effects of amyloid status.	16.5
Scherr et al. (2018)	90	**HC** Aβ- 74.6 ± 7.8 Aβ + 76.3 ± 5.6 **MCI** Early 71.2 ± 5.6 Late 73.6 ± 7.3 **ADD** 73.3 ± 7.9	(42/48)	Aβ (PET)	fMRI	EO (7 min)	Attention, episodic memory (immediate and delayed recall) and executive function (cognitive flexibility)	Independent Component Analysis (ICA)	Coupling between local metabolic activity (LMA) and FC was lower across Aβ + groups with greater clinical impairment, with the lowest coupling observed in late MCI and ADD. This decoupling is strongly associated with poorer delayed recall and outperforms other markers (global Aβ, pDMN Aβ, pDMN LMA and pDMN FC) in multiple regression analyses. Associations with cognitive speed and cognitive flexibility are present in univariate analyses but are not significant in multivariate models (indicating specificity for memory). Decoupling correlated negatively with local pDMN Aβ but not with global Aβ.	16.5
Sintini et al. (2024)	243	**HC** 65 ± 7 **ADD** 65 ± 7	(88/155)	Aβ (PET) Tau (PET) APOE ε4	fMRI	EO (8 min)	Language, visopercepción and global cognition	Independent Component Analysis (ICA) Network Failure Quotient (NFQ)	ADD shows reduced pDMN/vDMN connectivity and increased adDMN connectivity/NFQ compared with HC. HC connectivity declined with age, whereas in ADD younger participants exhibited greater disruption, particularly in the vDMN. In atypical ADD, vDMN connectivity declined longitudinally, with faster decline in older participants and in those with lower baseline tau. Cross-sectionally, higher tau-PET uptake was associated with lower vDMN connectivity, and longitudinally with lower avDMN connectivity. Lower vDMN connectivity correlated with poorer global cognition and visuospatial performance, the latter linked to disruptions in avDMN/vDMN. APOE ε4 carriers exhibited lower vDMN connectivity and higher NFQ.	14

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Table 3 (*continued*)

		HC 59.82 + 6.62							
Skouras et al. (2019)	96	**SCD Aβ +** 68.0 ± 7.1 **MCI** 69.6 ± 7.9 **ADD** 65.7 ± 9.9	(36/60)	Aβ42 (CSF) p-tau181 (CSF) APOE ε4	fMRI	EO (10 min)	Episodic memory (immediate and delayed recall)	Graph Theory Analysis (Eigenvector Centrality)	Eigenvector Centrality in parieto-occipital cortex (BA39-BA19) decreases with higher CSF p-tau/Aβ42 and is positively associated with episodic memory across the AD continuum. Conversely, Eigenvector Centrality in the middle cingulate cortex and thalamus increases with higher p-tau/Aβ42 but is negatively associated with episodic memory.	12.5
Teng et al. (2024)	289	**HC** 72.6 ± 7.0 **MCI** 71.5 ± 7.3 **ADD** 73.5 ± 7.9	(139/150)	Aβ42 (CSF) p-tau181 (CSF)	fMRI	EO (7 min)	Episodic memory, executive function and global cognition	Connectome-Based Predictive Modeling (CPM)	Connectivity strength in the high response time variability connectome model correlates positively with CSF p-tau/Aβ42 ratio and negatively with global cognition and episodic memory. Lesion analyses show that these associations remain significant even after removing major canonical networks (DMN, DAN, VAN, FPN).	15
Wei et al. (2025)	348	**HC** Aβ- 70.4 ± 7.3 Aβ + 72.0 ± 7.8 **ADD** 74.7 ± 9.1	(143/205)	Aβ40 (plasma) Aβ42 (plasma) p-tau181 (plasma) p-tau217 (plasma) NfL (plasma) GFAP (plasma) Aβ (PET) APOE ε4	fMRI	EO (7 min)	Episodic memory (immediate and delayed recall), attention, language, executive function and global cognition	ROI-to-ROI correlations	P-tau217 and p-tau181 show strong correlations with global Aβ PET and FC across multiple networks (DMN, DAN, FPN, VAN, LN, SMN, VN). Mediation analyses reveal that p-tau217/p-tau181 fully mediates the relationship between Aβ deposition and network connectivity alterations. Aβ + HC show significantly reduced DMN connectivity compared with Aβ-HC. FC is significantly lower in AD participants compared with HC across all networks. P-tau217/p-tau181 levels correlate negatively with episodic memory, executive function, global cognition and language. DAN FC connectivity is positively linked to attentional control and working memory.	12
Zhang et al. (2024)	132	**HC** 71.29 ± 6.85 **SCD** 71.97 ± 6.47 **MCI** 73.58 ± 6.66	(67/65)	Aβ42 (CSF) t-tau (CSF) p-tau181 (CSF) NfL (plasma)	fMRI	EO (7 min)	Episodic memory, attention, language, executive function and global cognition	Graph Theory Analysis (Eigenvector Centrality/ Degree Centrality)	Between-group differences were observed in Eigenvector Centrality (left superior temporal gyrus) and DC (left precuneus). EC in the left superior temporal gyrus was positively associated with episodic memory recognition. DC in the left precuneus correlates with global cognition and language performance.	13

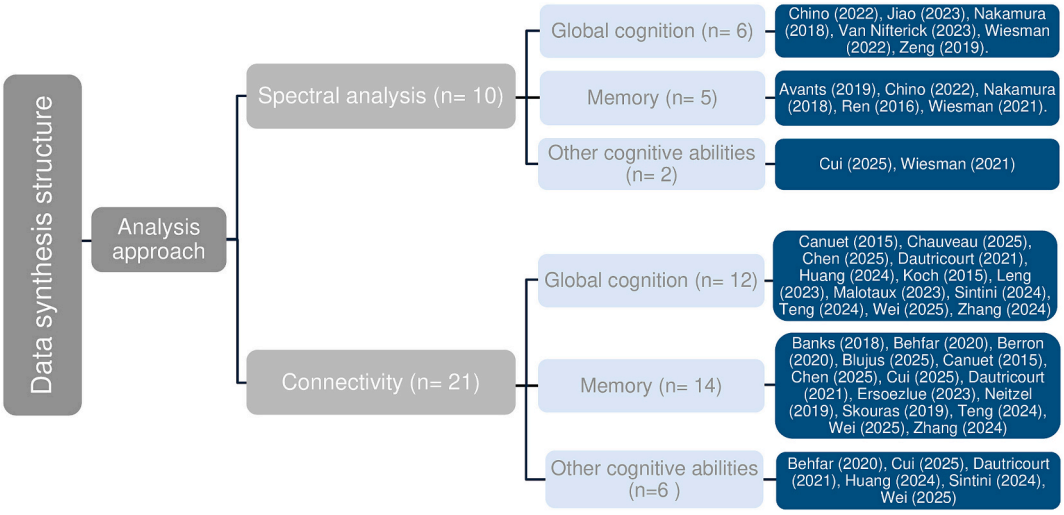


Fig. 1. *Data synthesis structure.* Classification of the papers included in each category. *One of the studies analyzed the acquired signal with both methods (spectral analysis and connectivity).

examined. Because individual studies could report both increased and decreased connectivity across different networks, metrics, or clinical groups, connectivity categories were not mutually exclusive. Percentages were calculated using the number of studies contributing to the relevant analytical modality as the denominator. These counts were used to describe consistency across studies and should not be interpreted as pooled effect estimates.

3. Results

The initial search identified 2718 articles in the first screening. After removing those duplicates and those irrelevant to this systematic review, 38 studies were assessed for eligibility. Eight studies were excluded based on the exclusion criteria: six due to incompatible study designs and two due to lack of availability. Finally, 30 studies with 5898 participants were considered for analysis in the systematic review (see Fig. 2).

3.1. Risk of Bias across studies

Using the predefined proportional scoring approach (≥75% "Yes" responses), all 30 included studies met the threshold for an overall low risk of bias classification, including 25 cross-sectional studies and five longitudinal cohort studies. Across the evidence base, eligibility criteria were generally clearly defined, biomarker-supported diagnostic procedures were adequately described, and resting-state, biomarker, and cognitive outcomes were typically assessed using valid and established methods under the JBI appraisal framework. Nevertheless, the item-level assessment identified recurrent methodological limitations that were not fully captured by the overall proportional classification.

Confounder management was particularly heterogeneous. As detailed in Appendix Table 4, age was included in at least one analysis relevant to the review question in 26 of 30 studies (86.7%), whereas sex and education were included in 19 (63.3%) and 18 studies (60.0%), respectively. Direct covariate adjustment for APOE ε4 status was

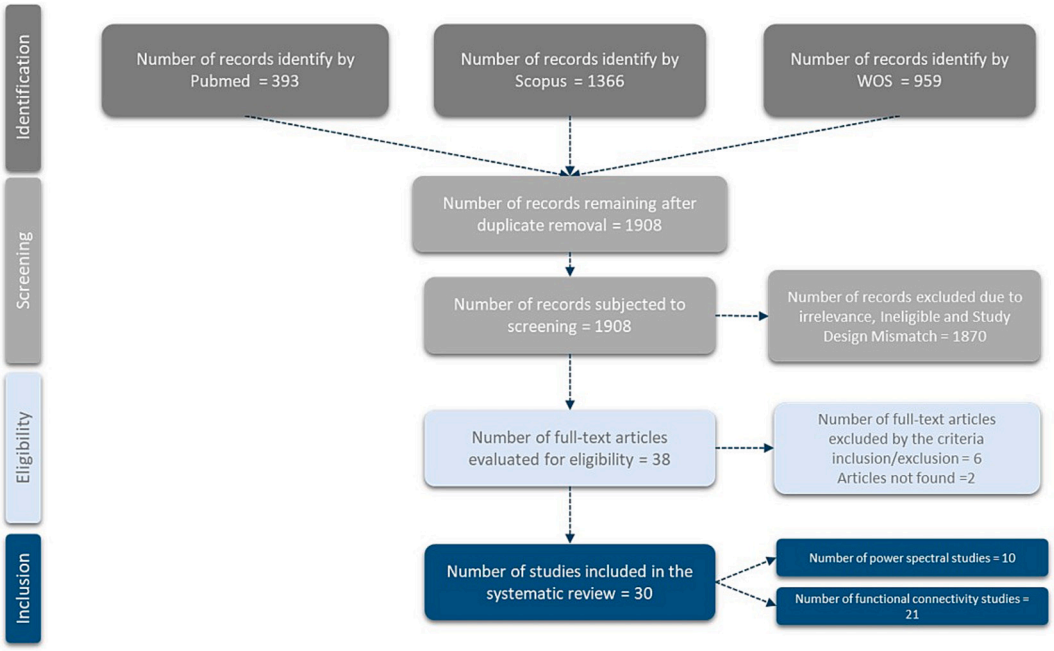


Fig. 2. *Selection process overview.* Flow chart of included and excluded articles through the screening process, following the PRISMA presentation guidelines.

substantially less frequent, being reported in seven studies (23.3%). In several additional studies, sex or APOE status was considered through stratified analyses, subgroup comparisons, or predictive modeling rather than through direct statistical adjustment; these approaches were therefore not considered equivalent to covariate control. None of the included studies explicitly adjusted its primary resting-state models for vascular comorbidities or aggregate vascular-risk burden. Although some studies excluded participants with stroke, major vascular lesions, or alternative neurological disorders, these eligibility restrictions reduce overt comorbidity but do not account for residual confounding related to hypertension, diabetes, dyslipidemia, cardiovascular disease, or subclinical cerebrovascular burden.

Imaging-related nuisance and structural variables were addressed more consistently than demographic or clinical confounders. Several fMRI studies controlled for head motion, scanner or acquisition site, MRI sequence, total intracranial volume, cortical or regional grey-matter measures, hippocampal or entorhinal volume, or tissue-derived nuisance signals. These procedures reduce measurement- and model-related bias but should be distinguished from adjustment for demographic, genetic, and vascular confounding.

Additional limitations were identified in the outcome-measurement and reporting domains. Cognitive assessment strategies varied considerably, and 14 of the 30 studies primarily relied on global screening instruments, such as the MMSE or MoCA, as their main cognitive outcomes. This reliance may have reduced sensitivity to domain-specific impairments, particularly in executive, language, attentional, and visuospatial functions. Among the five longitudinal studies, follow-up duration was generally sufficient, but attrition and missing-data procedures were explicitly described in only three studies. Formal a priori power calculations were reported in fewer than one-third of the included studies.

Overall, although all studies met the predefined threshold for an overall low risk of bias classification, incomplete and inconsistent confounder adjustment, restricted cognitive phenotyping, and variability in statistical reporting should be considered when interpreting associations among Alzheimer's disease biomarkers, resting-state neural measures, and cognitive performance. Study-level details are provided in Appendix Table 4 of the Supplementary Materials.

3.2. Spectral analysis and cognition

Ten studies contributed to the spectral/amplitude synthesis: six electrophysiological studies (two EEG and four MEG) and four fMRI studies using amplitude-based resting-state metrics. At the study level, five of the six electrophysiological studies (83.3%) reported increased delta and/or theta activity, whereas three (50.0%) reported reduced alpha and/or beta activity. All four fMRI studies reported reduced spontaneous activity in at least one region.

3.2.1. Global cognition

Six studies investigated the relationship between spectral power and global cognitive performance. Increases in low-frequency activity were the most consistent feature. Nakamura et al. (Nakamura et al., 2018) reported that global theta augmentation in MCI participants was linked to poorer global cognition (ADAS-Jcog) and hippocampal atrophy. In male MCI participants, Chino et al. (Chino-Vilca et al., 2022) observed a central-posterior theta cluster associated with worse global cognition (ADAS-Cog). Jiao et al. (Jiao et al., 2023) further showed that global theta power achieved over 70% classification accuracy across HC, MCI and ADD, correlating negatively with global cognition. Wiesman et al. (Wiesman et al., 2022) similarly identified POSI (reflecting higher low-frequency and lower high-frequency amplitudes) which strongly predicted poorer global cognition. Reduced fALFF in precuneus/occipital regions correlated with lower global cognitive scores (Zeng et al., 2019). In ADD participants, higher Mini-Mental State Examination (MMSE) scores correlated positively with excitation-inhibition indices in parieto-occipital and hippocampal regions, while the opposite relationship emerged in MCI participants (Van Nifterick et al., 2023).

3.2.2. Episodic memory

Comparable relationships emerged for episodic memory. Low-frequency increases (delta/theta) were negatively associated with immediate and delayed recall performance (Nakamura et al., 2018; Chino-Vilca et al., 2022), whereas higher theta activity in the right superior temporal cortex and supramarginal gyrus predicted better memory performance in the AD spectrum (Wiesman et al., 2021). Convergent evidence across imaging modalities highlights the precuneus as a key posterior hub linking spontaneous activity to memory function. In amyloid-negative MCI participants, stable SBA-rr within the precuneus predicted preserved immediate recall, whereas Aβ-positive individuals showed reduced activity despite comparable performance (Avants et al., 2019). Longitudinally, ALFF reductions in the right putamen have been shown to accompany progressive memory decline in amnestic MCI (Ren et al., 2016).

3.2.3. Other cognitive domains

Beyond global and memory domains, in amnestic MCI decreased beta power in bilateral inferior parietal cortices predicted poorer attention, while beta slowing in temporal cortices corresponded to reduced processing speed (Wiesman et al., 2021). Consistently, reduced precuneus fALFF was also linked to poorer executive function performance in early stages of the AD continuum (Cui et al., 2025). Increased delta activity in temporal regions was also linked to slower processing speed (Wiesman et al., 2021).

Across studies, delta/theta increases consistently accompany poorer global cognition and memory whereas alpha/beta decreases correspond to poorer attention and slower processing speed. Together, these findings converge on a characteristic pattern of pathological spectral slowing that parallels cognitive deterioration along the Alzheimer's continuum.

3.3. Functional connectivity and cognition

Twenty-one studies examining resting-state FC in relation to cognitive performance were included in this section. Twenty studies used BOLD fMRI-derived connectivity measures, whereas one used MEG phase-locking. Accordingly, the terms hyperconnectivity and hypoconnectivity in this section primarily refer to stronger or weaker statistical dependencies among regional BOLD time series and should not be interpreted as direct measures of synaptic coupling. At the study level, 10 of the 21 studies (47.6%) contributed at least one finding to the hyperconnectivity or higher-connectivity synthesis, whereas 13 (61.9%) contributed at least one finding to the hypoconnectivity or lower-connectivity synthesis. These categories were not mutually exclusive because individual studies could report opposing connectivity patterns across different networks, metrics, or clinical groups.

3.3.1. Hyperconnectivity: Global cognition, episodic memory and other cognitive domains

In line with spectral analyses, several studies explored how functional hyperconnectivity relates to cognitive performance.

For global cognition, increased beta connectivity within cingulum-MT circuits and enhanced coupling within MTL subregions and the AT network were consistently associated with poorer overall cognitive status in MCI and ADD (Canuet et al., 2015; Dautricourt et al., 2021; Chauveau et al., 2025). Amyloid-positive MCI participants exhibited rising intra-DMN connectivity and greater SMN coupling, which predicted lower baseline MMSE and steeper global decline over time (Malotaux et al., 2023).

Regarding memory performance, MCI participants with beta hyperconnectivity between the anterior-cingulate and MT cortices correlated negatively with free-recall scores (Canuet et al., 2015), and

stronger MTL-AT coupling was linked to poorer semantic-memory performance, particularly involving posterior hippocampal regions (Dautricourt et al., 2021). Likewise, increased Degree Centrality (DC) within right frontal-parietal regions related positively to verbal-learning and memory performance (Behfar et al., 2020).

Other studies emphasized protective mechanisms of hyperconnectivity on memory performance. Greater left-frontal integration mitigated memory impairment in amnestic MCI (Neitzel et al., 2019), and higher posterior-hippocampal redundancy predicted better episodic-memory performance (Blujus et al., 2025). Similarly, MCI's stronger left-lateralization of DMN organization was associated with improved learning and delayed recall (Banks et al., 2018). At the network level, enhanced posterior connectivity and higher eigenvector centrality within parieto-occipital clusters correlated positively with delayed free-recall performance in MCI and ADD participants (Skouras et al., 2019), while broader coupling between DMN, Salience Network (SN), and FPN predicted better memory outcomes (moderated by education and lifetime experiences) (Ersoezlue et al., 2023).

Beyond mnemonic domains, hyperconnectivity in MTL-AT and motor-parietal regions was associated with poorer executive functions and attentional efficiency (Dautricourt et al., 2021; Behfar et al., 2020). Chen et al. (Chen et al., 2025) further reported increased regional structure–function coupling (SFC) within DMN regions in cognitively impaired participants, with regional SFC associated with executive and language performance.

3.3.2. *Hypoconnectivity: Global cognition, episodic memory and other cognitive domains*

In contrast, several studies described widespread hypoconnectivity associated with cognitive decline.

About global cognition, lower posterior DMN (pDMN) and right AT network FC was associated with greater general cognitive impairment (CERAD) in MCI participants (Koch et al., 2015). Similarly, decreased MTL-PM coupling and reduced global efficiency (linked to microglial activation) were associated with lower MMSE and CERAD scores in MCI and ADD participants (Canuet et al., 2015; Dautricourt et al., 2021; Leng et al., 2023). Connectome-based modeling further showed that weaker network connectivity robustly predicted global cognitive impairment across the AD continuum (Teng et al., 2024).

As for memory performance, multiple studies converged on the association between diminished MTL-PM and MTL-AT connectivity and poorer episodic or semantic recall (Canuet et al., 2015; Dautricourt et al., 2021; Berron et al., 2020). Reduced connectivity in these networks also predicted future memory decline and accelerated disease progression (Berron et al., 2020). Complementing these results, Teng et al. (Teng et al., 2024) found that connectivity strength within the high response time variability connectome model correlated positively with CSF p-tau/Aβ42 and negatively with global cognition and episodic memory.

Other cognitive domains were also related to hypoconnectivity. Temporo-frontoparietal disconnection marks isolated language impairment in MCI (Huang et al., 2024) and reduced ventral DMN connectivity correlated with poorer visuospatial and global performance in atypical ADD variants (Sintini et al., 2024). Decreases in network efficiency further extend to executive and attentional control, as diminished MTL-PM coupling and widespread FC loss corresponded to slower processing and reduced task switching (Dautricourt et al., 2021).

Complementarily, multimodal analyses revealed that functional-metabolic decoupling in the pDMN strongly correlated with delayed-recall deficits (Scherr et al., 2018), while decreased parieto-occipital and frontotemporal connectivity predicted lower memory performance (Skouras et al., 2019). Reduced eigenvector centrality in the precuneus and superior temporal gyrus also related to lower memory and global cognition (Zhang et al., 2024). Similarly, reduced local ReHo/DC and widespread DMN disruptions were associated with poorer executive functions, memory, and visuoperceptual outcomes (Cui et al., 2025). Extending these findings, higher DAN connectivity was positively associated with attentional control and working memory (Wei et al., 2025).

Taken together, these studies suggest a stage-related pattern in which hyperconnectivity was reported more frequently in earlier clinical stages, whereas broader hypoconnectivity was more prominent in participants at more advanced stages of the AD continuum.

3.4. *Resting-state alterations and biomarker associations across the AD continuum*

Across included studies, resting-state alterations converged on two principal patterns: a characteristic pattern of neural slowing and connectivity reorganization. These neural alterations were consistently associated with biomarker burden and cognitive performance.

Spectral findings revealed a shift toward increased low-frequency (delta/theta) and reduced high-frequency (alpha/beta) activity across MCI due to AD and ADD (Nakamura et al., 2018; Chino-Vilca et al., 2022; Van Nifterick et al., 2023; Wiesman et al., 2021). Low-frequency augmentation, particularly in posterior and medial temporal regions, was associated with poorer global cognition and episodic memory (Nakamura et al., 2018; Chino-Vilca et al., 2022; Jiao et al., 2023; Wiesman et al., 2022). Conversely, reductions in alpha and beta power were related to impairments in attention and processing speed (Wiesman et al., 2022; Wiesman et al., 2021). Importantly, these oscillatory changes scaled with biomarker status: higher theta and delta power correlated with lower CSF Aβ42 and higher tau levels (Chino-Vilca et al., 2022; Jiao et al., 2023), whereas reductions in alpha and beta power were associated with greater tau burden and amyloid deposition (Nakamura et al., 2018; Chino-Vilca et al., 2022). Global electrophysiological indices of pathological slowing further showed strong spatial correspondence with regional amyloid accumulation (Wiesman et al., 2022).

Amplitude-based fMRI metrics (ALFF/fALFF/SBA-rr) provided convergent evidence of reduced spontaneous activity in posterior default mode regions, particularly the precuneus and posterior cingulate cortex (Zeng et al., 2019; Avants et al., 2019; Ren et al., 2016). These reductions were associated with greater amyloid accumulation and predicted memory decline over time (Zeng et al., 2019; Avants et al., 2019; Ren et al., 2016), supporting posterior hub vulnerability as an early functional correlate of AD pathology. Longitudinal data additionally indicated subcortical involvement, with ALFF reductions in the putamen linked to CSF Aβ/p-tau ratios (Ren et al., 2016).

Connectivity analyses suggested stage-related differences in functional network organization. In early or prodromal stages, hyperconnectivity (especially within anterior temporal and medial temporal circuits) was observed (Canuet et al., 2015; Dautricourt et al., 2021; Chauveau et al., 2025; Malotaux et al., 2023). In several studies, this hyperconnectivity correlated with poorer global cognition and memory (Canuet et al., 2015; Dautricourt et al., 2021; Chauveau et al., 2025), a pattern interpreted in some studies as potentially reflecting maladaptive network overactivation. However, other investigations indicated that increased frontal or hippocampal integration moderated the impact of tau pathology on memory, consistent with interpretations of compensatory network organization (Neitzel et al., 2019; Blujus et al., 2025; Skouras et al., 2019; Ersoezlue et al., 2023). Studies examining participants at more advanced clinical or pathological stages more frequently reported widespread hypoconnectivity, particularly across posterior DMN, medial temporal-posterior medial networks, and frontoparietal systems (Dautricourt et al., 2021; Koch et al., 2015; Leng et al., 2023; Berron et al., 2020; Wei et al., 2025).

Altered network organization also included reduced DMN lateralization in Aβ-positive individuals (Banks et al., 2018), decreased parieto-occipital centrality associated with neurodegeneration markers (Skouras et al., 2019; Zhang et al., 2024), and connectome-level evidence of frontoparietal reconfiguration in earlier-stage groups and more

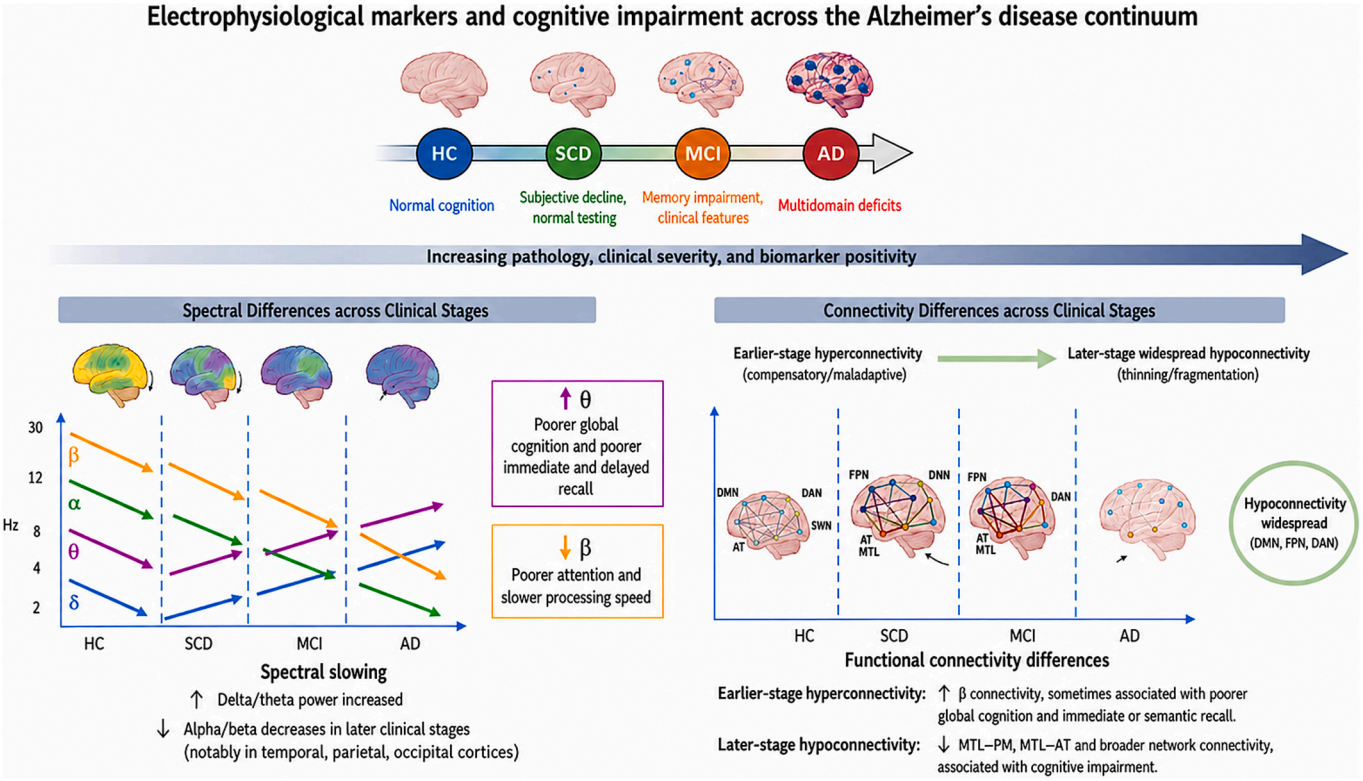


Fig. 3. *Conceptual summary of resting-state spectral and functional connectivity alterations across the Alzheimer's disease continuum.* The upper panel depicts increasing pathology, biomarker positivity, and cognitive impairment across clinical stages. The left panel summarizes spectral slowing, characterized by increased delta/theta and reduced alpha/beta activity. The right panel summarizes a proposed stage-related contrast: hyperconnectivity is reported more frequently in earlier-stage groups, whereas widespread hypoconnectivity is reported more frequently in later-stage groups. Thinning refers to reduced connection strength or density, and fragmentation to loss of network integration. The schematic integrates primarily cross-sectional differences between SCD, MCI, and AD dementia, together with the limited longitudinal evidence, and should not be interpreted as demonstrating a within-person transition between connectivity patterns.

extensive multi-network disconnection in ADD (Teng et al., 2024; Wei et al., 2025). Amyloid pathology was also associated with regional SFC alterations across occipital, precuneus, temporoparietal, and medial prefrontal regions (Chen et al., 2025).

These reductions were consistently associated with worse global cognition, episodic memory, executive dysfunction, and language impairment (Cui et al., 2025; Canuet et al., 2015; Dautricourt et al., 2021; Koch et al., 2015; Berron et al., 2020; Sintini et al., 2024; Wei et al., 2025).

At the molecular level, amyloid deposition overlapped spatially with posterior DMN hypoconnectivity (Koch et al., 2015; Scherr et al., 2018), while tau pathology showed strong associations with medial temporal disconnection (Dautricourt et al., 2021; Berron et al., 2020; Sintini et al., 2024). Emerging evidence further indicates that plasma p-tau mediates the relationship between amyloid burden and large-scale connectivity loss (Wei et al., 2025), and that neuroinflammatory markers are independently associated with reduced network efficiency (Leng et al., 2023).

4. Discussion

The present systematic review examined the relationship between resting-state neural alterations and domain-specific cognitive performance across biomarker-characterized stages of Alzheimer's disease. Across 30 studies involving 5898 participants, evidence from EEG, MEG, and resting-state fMRI converged on two broad features of resting-state dysfunction: pathological spectral slowing and stage-related differences in large-scale functional network organization. Both were associated with cognitive performance and AD biomarker measures. However, because 25 of the 30 studies were cross-sectional, these findings primarily reflect differences across clinical and biomarker-characterized groups rather than within-person changes over time. Within this context, two broad patterns emerged: pathological spectral slowing and stage-related differences in large-scale functional network organization, both associated with cognitive performance and AD biomarker measures.

The spectral findings identify pathological neural slowing as a prominent resting-state feature across biomarker-characterized stages of the AD continuum (Nakamura et al., 2018; Chino-Vilca et al., 2022; Jiao et al., 2023; Wiesman et al., 2022; Van Nifterick et al., 2023; Wiesman et al., 2021). Rather than representing only a correlate of clinical severity, the shift toward increased low-frequency and reduced high-frequency activity may reflect disruption of the neurophysiological systems required for efficient neuronal coordination. In particular, reductions in higher-frequency activity are consistent with cumulative synaptic and cholinergic dysfunction that may impair rapid neuronal synchronization (Fernández-Rubio et al., 2025), while alterations in excitation–inhibition balance may further contribute to the predominance of slower oscillatory activity (Osipova et al., 2005).

Similar patterns of increased delta/theta and reduced alpha activity have been described in previous reviews that did not require biomarker characterization (Maestú et al., 2021). The present synthesis extends this literature by showing that spectral slowing is also associated with amyloid and tau measures (Nakamura et al., 2018; Chino-Vilca et al., 2022; Jiao et al., 2023; Wiesman et al., 2022), supporting its relevance to AD-related pathology rather than interpreting it solely as an expression of healthy aging (Chino et al., 2024). Nevertheless, biomarker association does not establish disease specificity, and the predominance of global cognitive screening and episodic-memory measures prevents determining whether distinct spectral alterations are differentially related to

executive, attentional, language, or visuospatial dysfunction.

The connectivity findings suggest heterogeneous network reorganization rather than a uniform increase or decrease in functional coupling across the AD continuum. Hyperconnectivity in earlier-stage groups was associated with both poorer and better-preserved cognitive performance across studies (Canuet et al., 2015; Dautricourt et al., 2021; Chauveau et al., 2025; Malotaux et al., 2023; Neitzel et al., 2019; Blujus et al., 2025; Skouras et al., 2019; Ersoezlue et al., 2023), indicating that it should not be attributed to a single compensatory or maladaptive process. Instead, these findings may reflect varying contributions from excitation–inhibition imbalance, network dedifferentiation, altered recruitment, and individual differences in cognitive reserve (Skouras et al., 2019; Ersoezlue et al., 2023; Osipova et al., 2005). By contrast, the broader hypoconnectivity reported more frequently in later-stage groups was more consistently associated with multidomain cognitive impairment (Cui et al., 2025; Canuet et al., 2015; Dautricourt et al., 2021; Skouras et al., 2019; Koch et al., 2015; Leng et al., 2023; Teng et al., 2024; Berron et al., 2020; Huang et al., 2024; Sintini et al., 2024; Scherr et al., 2018; Zhang et al., 2024; Wei et al., 2025), compatible with reduced network integration in groups with greater clinical impairment. However, because most included studies were cross-sectional, these patterns represent differences across clinical groups rather than a demonstrated intraindividual sequence.

This stage-related interpretation is consistent with previous conceptual models. Schultz et al. (Schultz et al., 2017) described differences in DMN and salience-network connectivity according to amyloid and tau burden, while Pusil et al. (Pusil et al., 2019) proposed the "X" model of hypersynchronization, according to which hyperconnectivity in MCI may be related to excitation–inhibition imbalance and subsequent clinical progression. The framework summarized in Fig. 3 integrates these models with the present evidence but remains primarily based on cross-sectional differences across clinical and biomarker-defined groups.

Interpretation of the fMRI connectivity findings nevertheless requires caution because BOLD is an indirect hemodynamic signal shaped by cerebral blood flow, blood volume, oxygen extraction, and metabolism (Tsvetanov et al., 2021). Age- and AD-related alterations in cerebrovascular function, neurovascular coupling, and hemodynamic-response characteristics may therefore influence correlations among regional BOLD time series without equivalent changes in neuronal coupling (Tsvetanov et al., 2021; Rangaprakash et al., 2023; Chiarelli et al., 2021). Consistent with this complexity, Epp et al. reported discordance between task-related BOLD responses and oxygen-metabolism changes in a substantial proportion of cortical voxels, including within the DMN (Epp et al., 2026). Although these findings were obtained in healthy adults during task performance, they illustrate why hyperconnectivity and hypoconnectivity should be interpreted as BOLD-derived patterns of network organization with potentially mixed neuronal and neurovascular determinants, rather than as direct measures of synaptic connectivity.

An apparent divergence exists between BOLD hyperconnectivity and FDG-PET hypometabolism in overlapping AD-vulnerable regions. These findings are not necessarily contradictory because resting-state functional connectivity measures temporal dependence among regional BOLD signals, whereas FDG-PET reflects regional glucose uptake over a longer integration period. Accordingly, stronger BOLD coupling does not imply increased local metabolism. Within the included evidence, greater anterior-temporal connectivity was associated with glucose hypometabolism and hippocampal atrophy (Chauveau et al., 2025), while Scherr et al. (Scherr et al., 2018) reported lower coupling between pDMN local metabolic activity and functional connectivity in groups with greater clinical impairment, which was associated with local amyloid burden and poorer delayed recall. More generally, simultaneous PET-fMRI evidence has demonstrated dissociation between BOLD and glucose-metabolic responses within the DMN (Stiernman et al., 2021). Hyperconnectivity should therefore be interpreted as a BOLD-derived pattern of network reorganization that may coexist with metabolic dysfunction, rather than as evidence of preserved or increased regional metabolism. Accordingly, convergence between electrophysiological and fMRI connectivity findings should be interpreted at the level of large-scale network organization rather than physiological equivalence. EEG and MEG can resolve frequency-specific coupling that may reflect distinct oscillatory processes, whereas BOLD fMRI captures slower hemodynamic fluctuations and cannot distinguish these frequency-specific mechanisms. Thus, similar patterns of hyperconnectivity or hypoconnectivity across modalities may be compatible at a systems level while arising from different underlying physiological processes.

Taken together, spectral slowing and functional-connectivity alterations may represent complementary manifestations of large-scale neural vulnerability in AD. The former may reflect reduced efficiency and temporal precision of neuronal coordination, whereas the latter captures changes in the organization and integration of distributed networks. Their consistent associations with cognitive performance and AD biomarkers support their clinical and biological relevance, but neither pattern should be interpreted as a direct or disease-specific measure of a single pathological mechanism.

5. Limitations and future directions

Overall, this review extends our understanding of resting-state electrophysiological and functional differences associated with cognitive impairment across biomarker-characterized stages of the AD continuum. Nevertheless, the existing literature presents certain limitations that future studies should address. For example, many studies investigating resting-state alterations associated with cognitive impairment do not include biological confirmation of AD pathology. Although AD is the most common cause of dementia, not all cases of dementia or MCI are due to AD (Lethin et al., 2019). To avoid confusion, we strictly excluded relevant sources of data that did not include this important confirmatory test that complements clinical diagnosis. Additionally, within selected studies the majority focused on memory or global cognition, while other cognitive domains warrant further attention. Moreover, the most frequently used global cognition test was MMSE, which is a useful screening tool for a quick clinical evaluation, but not the most accurate measure to discriminate different levels of impairment along the continuum (Truong et al., 2024). On top of that, lack of standardization in study design hindered comparison across similar studies, where a clear preference in the protocol for eyes closed or open during the recordings has not been established (see Tables 2 and 3).

An important limitation is that 25 of the 30 included studies used cross-sectional designs, whereas only five were longitudinal cohort studies. Consequently, the proposed stage-related pattern of hyperconnectivity in earlier clinical stages and more widespread hypoconnectivity in later stages is derived predominantly from between-group comparisons. It should therefore not be interpreted as evidence of a within-person transition between these connectivity patterns. Longitudinal studies incorporating repeated resting-state, biomarker, and cognitive assessments are needed to establish the temporal ordering and intraindividual evolution of these alterations.

Moreover, because the included evidence was predominantly observational, the reported associations among AD biomarkers, resting-state alterations, and cognitive performance should not be interpreted as demonstrating causal or mechanistic pathways. Statistical mediation or moderation findings reported by individual studies identify model-based relationships but do not, by themselves, establish biological causality.

Remarkably, a substantial number of published studies did not report statistical power and effect size measurements, despite recurrent criticisms of insufficient sample sizes in neuroscience (Button et al., 2013). In line with this, studies with a larger sample size would enable the analysis of factors that could influence the relationship studied. In this sense, only one article compared participants based on sex (Chino-Vilca et al., 2022), which could be an interesting factor given how AD disproportionately affects women. Other relevant variables could

include educational attainment, lifestyle or genetic factors, which have been described to exert an effect on cognitive and brain reserve (Stephan et al., 2024).

Although overall methodological quality was acceptable, heterogeneity in confounder adjustment and limited reporting of statistical power remain important constraints when interpreting associations between biomarkers, resting-state metrics and cognition. These methodological limitations, together with variability in demographic characteristics, cognitive assessment protocols and statistical reporting, may partly explain the heterogeneity observed across studies examining resting-state alterations in AD.

Future studies would therefore benefit from larger and better characterized cohorts, improved statistical transparency, and systematic consideration of moderating variables such as sex, education, genetic background and lifestyle factors. Such approaches will be essential to clarify how resting-state alterations relate to the emergence and progression of cognitive impairment along the Alzheimer's disease continuum.

The integration of EEG, MEG, and fMRI findings requires caution because these modalities capture signals with different physiological origins and temporal and spatial scales. The present synthesis should therefore be interpreted as identifying convergent or complementary patterns across modalities rather than equivalent physiological processes. In particular, BOLD-derived connectivity should not be interpreted as a direct measure of synaptic dysfunction, because residual vascular and hemodynamic variability may persist despite age adjustment, exclusion of overt cerebrovascular disease, and control of motion or regional atrophy in some studies. Future multimodal studies should seek to separate neuronal and hemodynamic contributions to BOLD connectivity.

Beyond methodological variability, interpretational challenges also arise from the complex and multifactorial nature of AD pathology. Resting-state alterations are unlikely to reflect a single pathological cascade and instead may capture the cumulative impact of interacting biological processes. In addition to amyloid and tau pathology, increasing evidence indicates that vascular dysfunction, neuroinflammatory mechanisms and mixed neuropathologies frequently coexist with AD and may contribute to early network disruption (Jack Jr et al., 2018; Iturria-Medina et al., 2016; Sweeney et al., 2018; Heneka et al., 2015; Schneider et al., 2007; Kapasi et al., 2017; Livingston et al., 2020). From this perspective, spectral slowing and connectivity alterations should be interpreted as indicators of large-scale neural vulnerability and network reorganization, rather than as disease-specific markers of a single pathological pathway. Importantly, the present synthesis highlights that these neural alterations show consistent relationships with cognitive performance across multiple domains when biomarker-confirmed AD samples are considered.

6. Conclusions

This systematic review highlights that resting-state neural alterations are consistently associated with cognitive impairment across biomarker-characterized stages of the Alzheimer's disease continuum. Importantly, unlike previous reviews, this synthesis specifically included studies incorporating AD biomarker information to support clinical characterization, strengthening the evidence for associations among resting-state alterations, AD pathology, and cognitive symptoms.

A pattern of spectral slowing, characterized by increased delta/theta and reduced alpha/beta activity, was accompanied by stage-related differences in functional connectivity. Hyperconnectivity was reported more frequently in earlier clinical stages, whereas widespread hypoconnectivity was more prominent in later stages. However, the predominance of cross-sectional evidence prevents establishing this pattern as an intraindividual sequence. Across these resting-state measures, poorer global cognition and episodic memory were most consistently associated with spectral slowing and reduced FC; associations involving hyperconnectivity were more heterogeneous. Evidence for other cognitive abilities was more limited. Overall, these findings support resting-state alterations as functional correlates of cognitive impairment in biomarker-characterized AD, while highlighting the need for more comprehensive domain-specific cognitive assessments.

Future research using larger, standardized and longitudinal designs will be crucial to clarify their role as potential markers for early detection and disease monitoring.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work, the authors used ChatGPT (OpenAI, GPT-5.3) to improve the clarity, grammar, and overall readability of the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Credit authorship contribution statement

Soraya Alfonsín: Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Formal analysis, Conceptualization. **Brenda Chino:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Formal analysis, Conceptualization. **Jaisalmer de Frutos Lucas:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **María Luisa Delgado-Losada:** Writing – review & editing, Supervision. **Natalia Ojeda:** Writing – review & editing, Supervision. **Fernando Maestú:** Writing – review & editing, Supervision, Conceptualization.

Ethics declaration

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2026.104070.

Data availability

No data was used for the research described in the article.

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