LUMEN ET VIRTUS
ISSN: 2177-2789

APPLICATIONS OF FUNCTIONAL MAGNETIC RESONANCE IMAGING IN THE EARLY DIAGNOSIS OF ALZHEIMER'S DISEASE: A SYSTEMATIC REVIEW

APLICAÇÕES DA RESSONÂNCIA MAGNÉTICA FUNCIONAL NO DIAGNÓSTICO PRECOCE DA DOENÇA DE ALZHEIMER: UMA REVISÃO SISTEMÁTICA

APLICACIONES DE LA RESONANCIA MAGNÉTICA FUNCIONAL EN EL DIAGNÓSTICO PRECOZ DE LA ENFERMEDAD DE ALZHEIMER: UNA REVISIÓN SISTEMÁTICA

https://doi.org/10.56238/levv16n53-096

Submission date: 09/23/2025 **Publication date:** 10/23/2025

Leonardo Lucas Pereira Filho[1], Lara Fernanda de Sá Guimarães[2], Carlos Alberto de Mattos[3], Juliana Cristina Levada de Mattos[4], Breno de Amaral Gandini[5], Marcos Alexandre Lima Garcia[6], Lucas Guimarães Grassioli[7]

ABSTRACT

Introduction: Alzheimer's disease (AD) is the most common neurodegenerative disorder globally, characterized by progressive cognitive decline and substantial socioeconomic burden. Early diagnosis is crucial to enable therapeutic interventions before irreversible neuronal loss.

Objective: The primary objective was to systematically review the current evidence on the applications of functional magnetic resonance imaging (fMRI) in the early diagnosis of AD, focusing on diagnostic accuracy, methodological advances, and clinical potential. Secondary objectives included evaluating analytic approaches, such as connectivity metrics and machine learning models, and assessing heterogeneity and gaps in the literature.

Methods: A systematic search was conducted in PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov, and ICTRP for studies published between 2019 and 2025. Inclusion criteria comprised human fMRI studies investigating early AD or mild cognitive impairment (MCI) with quantitative diagnostic metrics. Studies with small samples or non-standardized protocols were included but noted as limitations. Exclusion criteria involved reviews, editorials, and studies without quantitative diagnostic data. The review followed PRISMA guidelines.

Results and Discussion: Most used resting-state fMRI and advanced computational models to differentiate MCI or early AD from healthy controls. Reported diagnostic accuracies ranged

[1] Documentation in Ribeirão Preto.
[2] Child and Adolescent Psychiatry. Einstein
[3] FMRP-USP. E-nail: doutorcarlospediatra@gmail.com
[4] E-mail: jullevada@gmail.com
[5] UNAERP. E-mail: brenogand@hotmail.com
[6] UFGD. E-mail: marcosgarcia1825@gmail.com
[7] Universidade de Fortaleza. E-mail: lucasggrassioli@gmail.com

from 83% to 96%, with consistent sensitivity and specificity above 0.85. Deep learning and graph-based models significantly improved classification performance. However, heterogeneity in acquisition parameters, preprocessing pipelines, and small sample sizes limited generalizability.

Conclusion: Functional MRI demonstrates high potential as a noninvasive biomarker for early AD diagnosis, especially when combined with structural and diffusion imaging or artificial intelligence-based analysis. Standardization of acquisition and preprocessing protocols and multicenter validation remain essential for clinical translation.

Keywords: Alzheimer Disease. Magnetic Resonance Imaging. Functional. Early Diagnosis. Mild Cognitive Impairment.

RESUMO

Introdução: A doença de Alzheimer (DA) é a doença neurodegenerativa mais comum em todo o mundo, caracterizada por declínio cognitivo progressivo e substancial impacto socioeconômico. O diagnóstico precoce é crucial para permitir intervenções terapêuticas antes da perda neuronal irreversível.

Objetivo: O objetivo principal foi revisar sistematicamente as evidências atuais sobre as aplicações da ressonância magnética funcional (RMf) no diagnóstico precoce da DA, com foco na precisão diagnóstica, nos avanços metodológicos e no potencial clínico. Os objetivos secundários incluíram a avaliação de abordagens analíticas, como métricas de conectividade e modelos de aprendizado de máquina, e a avaliação da heterogeneidade e das lacunas na literatura.

Métodos: Uma busca sistemática foi realizada nas bases de dados PubMed, Scopus, Web of Science, Biblioteca Cochrane, LILACS, ClinicalTrials.gov e ICTRP para estudos publicados entre 2019 e 2025. Os critérios de inclusão incluíram estudos de RMf em humanos que investigassem DA precoce ou comprometimento cognitivo leve (CCL) com métricas diagnósticas quantitativas. Estudos com amostras pequenas ou protocolos não padronizados foram incluídos, mas apontados como limitações. Os critérios de exclusão envolveram revisões, editoriais e estudos sem dados diagnósticos quantitativos. A revisão seguiu as diretrizes PRISMA.

Resultados e Discussão: A maioria utilizou fMRI em repouso e modelos computacionais avançados para diferenciar DCL ou DA precoce de controles saudáveis. As acurácias diagnósticas relatadas variaram de 83% a 96%, com sensibilidade e especificidade consistentes acima de 0,85. Modelos de aprendizado profundo e baseados em gráficos melhoraram significativamente o desempenho da classificação. No entanto, a heterogeneidade nos parâmetros de aquisição, nos pipelines de pré-processamento e nos pequenos tamanhos de amostra limitaram a generalização.

Conclusão: A RM funcional demonstra alto potencial como biomarcador não invasivo para o diagnóstico precoce da DA, especialmente quando combinada com imagens estruturais e de difusão ou análise baseada em inteligência artificial. A padronização dos protocolos de aquisição e pré-processamento e a validação multicêntrica continuam sendo essenciais para a tradução clínica.

Palavras-chave: Doença de Alzheimer. Ressonância Magnética. Funcional. Diagnóstico Precoce. Comprometimento Cognitivo Leve.

RESUMEN

Introducción: La enfermedad de Alzheimer (EA) es el trastorno neurodegenerativo más común a nivel mundial, caracterizado por un deterioro cognitivo progresivo y una importante carga socioeconómica. El diagnóstico temprano es crucial para permitir intervenciones terapéuticas antes de la pérdida neuronal irreversible.

Objetivo: El objetivo principal fue revisar sistemáticamente la evidencia actual sobre las aplicaciones de la resonancia magnética funcional (RMf) en el diagnóstico temprano de la EA, centrándose en la precisión diagnóstica, los avances metodológicos y el potencial clínico. Los objetivos secundarios incluyeron la evaluación de enfoques analíticos, como métricas de conectividad y modelos de aprendizaje automático, y la evaluación de la heterogeneidad y las lagunas en la literatura.

Métodos: Se realizó una búsqueda sistemática en PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov e ICTRP de estudios publicados entre 2019 y 2025. Los criterios de inclusión incluyeron estudios de RMf en humanos que investigaran la EA temprana o el deterioro cognitivo leve (DCL) con métricas diagnósticas cuantitativas. Se incluyeron estudios con muestras pequeñas o protocolos no estandarizados, pero se señalaron como limitaciones. Los criterios de exclusión incluyeron revisiones, editoriales y estudios sin datos diagnósticos cuantitativos. La revisión siguió las directrices PRISMA.

Resultados y discusión: La mayoría utilizó fMRI en reposo y modelos computacionales avanzados para diferenciar el deterioro cognitivo leve (DCL) o la EA temprana de los controles sanos. La precisión diagnóstica reportada osciló entre el 83% y el 96%, con una sensibilidad y especificidad consistentes superiores a 0,85. El aprendizaje profundo y los modelos basados en grafos mejoraron significativamente el rendimiento de la clasificación. Sin embargo, la heterogeneidad en los parámetros de adquisición, los procesos de preprocesamiento y el pequeño tamaño de las muestras limitaron la generalización.

Conclusión: La resonancia magnética funcional demuestra un gran potencial como biomarcador no invasivo para el diagnóstico temprano de la EA, especialmente cuando se combina con imágenes estructurales y de difusión o análisis basados en inteligencia artificial. La estandarización de los protocolos de adquisición y preprocesamiento, así como la validación multicéntrica, siguen siendo esenciales para la aplicación clínica.

Palabras clave: Enfermedad de Alzheimer. Resonancia Magnética Funcional. Diagnóstico Temprano. Deterioro Cognitivo Leve.

1 INTRODUCTION

Alzheimer's disease (AD) is the most prevalent form of dementia worldwide, responsible for 60% to 70% of all dementia cases[1]. The disorder is characterized by progressive neuronal loss, synaptic dysfunction, and the accumulation of β-amyloid and tau proteins, leading to cognitive decline and loss of independence[1]. Globally, more than 55 million people live with dementia, and this number is expected to double by 2050 due to aging populations[1].

Early diagnosis is essential for implementing therapeutic interventions before irreversible neuronal damage occurs[2]. Traditional imaging modalities such as structural magnetic resonance imaging (MRI) and positron emission tomography (PET) are often limited to detecting advanced pathological changes[2]. Functional magnetic resonance imaging (fMRI), by measuring blood oxygen level–dependent (BOLD) signals, enables the evaluation of neuronal activity and functional connectivity changes that precede morphological alterations[2].

Functional alterations in AD predominantly affect large-scale brain networks, especially the default mode network (DMN), which includes the posterior cingulate cortex, precuneus, and medial temporal lobe structures[3]. Disruption of connectivity within the DMN has been consistently observed in individuals with mild cognitive impairment (MCI) and early AD[3]. These findings support the hypothesis that fMRI can detect subtle neural dysfunctions before clinical symptoms become evident[3].

Resting-state fMRI (rs-fMRI) evaluates spontaneous low-frequency fluctuations in BOLD signals to map intrinsic connectivity networks[4]. In contrast, task-based fMRI (tb-fMRI) measures task-evoked activations in specific cognitive domains such as memory or attention[4]. Both methods have demonstrated sensitivity in revealing early abnormalities in brain function, but rs-fMRI is more widely used due to its simplicity and reproducibility in clinical research[4].

Advances in computational neuroscience and artificial intelligence have strengthened fMRI's diagnostic potential[5]. Graph theory analysis allows quantification of network efficiency, centrality, and clustering, providing insights into how AD disrupts global communication patterns[5]. Machine learning and deep learning algorithms can process high-dimensional fMRI data to classify individuals with MCI or early AD with high accuracy[5].

Recent studies have achieved classification accuracies exceeding 90% by combining rs-fMRI connectivity metrics with convolutional neural networks (CNNs) or support vector machines (SVMs)[6]. These approaches demonstrate the potential of data-driven fMRI analyses to complement traditional biomarkers such as amyloid PET or cerebrospinal fluid

(CSF) tau levels[6]. Moreover, combining fMRI with structural MRI or diffusion tensor imaging (DTI) enhances diagnostic sensitivity by integrating functional and anatomical information[6].

Despite these promising results, several methodological challenges remain[7]. Variability in image acquisition, preprocessing pipelines, and statistical thresholds complicates cross-study comparisons[7]. Factors such as scanner field strength, temporal resolution, motion correction, and normalization methods can substantially affect functional connectivity estimates[7].

Moreover, the reproducibility of fMRI-based biomarkers across centers and populations is limited by small sample sizes and lack of standardized protocols[8]. Many studies are single-center, retrospective analyses that lack independent validation cohorts[8]. These limitations contribute to uncertainty regarding the generalizability of fMRI findings and hinder its translation into clinical practice[8].

In parallel, consensus is emerging on the importance of multimodal imaging and longitudinal approaches to validate fMRI as a prognostic biomarker[9]. Combining fMRI data with neuropsychological scores, molecular imaging, and fluid biomarkers may enhance diagnostic accuracy[9]. Harmonization initiatives such as the Alzheimer's Disease Neuroimaging Initiative (ADNI) are central to establishing normative datasets and improving reproducibility[9].

Therefore, this systematic review aims to synthesize recent evidence on the diagnostic applications of fMRI in early Alzheimer's disease[10]. The analysis focuses on accuracy, reproducibility, analytic techniques, and clinical implications for early detection[10]. By critically evaluating studies from the past five years, this work seeks to clarify the current state of knowledge and identify priorities for future research[10]

2 OBJECTIVES

The main objective of this systematic review is to critically evaluate the current evidence regarding the use of functional magnetic resonance imaging (fMRI) for the early diagnosis of Alzheimer's disease (AD), including its accuracy, reproducibility, and integration with advanced analytic techniques such as machine learning and graph theory models. Secondary objectives are to (1) compare resting-state and task-based fMRI methodologies in differentiating mild cognitive impairment (MCI) and early AD from healthy controls; (2) assess methodological heterogeneity across acquisition and preprocessing protocols; (3) analyze diagnostic performance metrics such as sensitivity, specificity, and area under the curve (AUC); (4) identify limitations in study design, sample characteristics, and external validation; and (5) propose recommendations for future standardization, multicenter

collaborations, and clinical implementation strategies consistent with PRISMA reporting standards.

3 METHODOLOGY

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. A comprehensive search was performed in PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov, and the International Clinical Trials Registry Platform (ICTRP) for studies published between January 2019 and March 2025. The search strategy combined Medical Subject Headings (MeSH) and free-text terms related to “Alzheimer Disease,” “functional MRI,” “resting-state,” “task-based,” and “early diagnosis.” All titles and abstracts were independently screened by two reviewers using Rayyan QCRI software. Eligible studies included human participants diagnosed with mild cognitive impairment or early Alzheimer’s disease who underwent resting-state or task-based fMRI for diagnostic evaluation. Studies without quantitative diagnostic metrics, lacking control groups, or presenting overlapping datasets were excluded.

Data extraction followed a standardized protocol, collecting study design, population characteristics, fMRI acquisition parameters, preprocessing pipelines, analytic models, and diagnostic outcomes. Quality assessment was performed using the QUADAS-2 tool to evaluate methodological rigor and potential bias. Due to heterogeneity in acquisition parameters, statistical approaches, and machine learning techniques, meta-analysis was not feasible. Instead, a qualitative synthesis was undertaken, with evidence certainty classified according to the GRADE framework. A PRISMA flow diagram summarized the selection process, including the number of studies identified, screened, excluded, and included.

4 RESULTS

Table 1

Summary of included studies on fMRI for early Alzheimer’s disease diagnosis (2019–2025)

Reference	Population / Intervention / Comparison	Outcomes	Main conclusions
Zhang et al., 2020	ADNI cohort; rs-fMRI with graph CNN; MCI vs controls	Accuracy 92.8%, sensitivity 0.90, specificity 0.88	Graph convolutional models effectively identified early AD functional disconnection.
Battineni et al., 2021	Mild AD vs controls; multimodal MRI and fMRI with ML classifier	Accuracy 95.1%	Structural-functional integration improved early classification reliability.

Reference	Population / Intervention / Comparison	Outcomes	Main conclusions
Li et al., 2022	EMCI and LMCI vs normal controls using rs-fMRI + DTI	AUC 0.91	Fusion of structural and functional features enhanced sensitivity for preclinical AD.
Sener et al., 2023	Early MCI vs controls; slice-based ViT	Accuracy 94.3%, specificity 0.90	Vision transformer achieved robust early MCI detection.
Wang et al., 2023	Meta-analysis of 23 rs-fMRI radiomic studies (n=5,554)	Pooled accuracy 0.99 (CI 0.34–1.00)	High diagnostic potential but substantial heterogeneity noted.
Zhao et al., 2023	ADNI data; hybrid CNN on rs-fMRI	Accuracy 93.5%	CNN-based resting-state models reliably differentiated early AD.
Lu et al., 2024	rs-fMRI + clinical metrics; Chinese cohort	Accuracy 88.6%	Combining cognitive scores with connectivity indices improved classification.
Bonarota et al., 2024	Methodological review; MRI segmentation + fMRI	—	Emphasized need for harmonization of preprocessing protocols.
Sener et al., 2024	EMCI vs controls; slice selection with attention model	Accuracy 91.8%	Slice-wise attention enhanced diagnostic precision.
Li et al., 2024	Multi-site rs-fMRI study (three scanners)	Accuracy 85.7%	Multi-center harmonization feasible though scanner variability affected metrics.
Chen et al., 2025	Hybrid graph neural network on rs-fMRI	Accuracy 96.4%	GNN provided superior differentiation of MCI and early AD.
Bonarota et al., 2025	Review on multimodal MRI pipelines	—	Highlighted synergy between segmentation and functional analysis.

5 RESULTS AND DISCUSSION

Zhang et al. (2020) applied graph convolutional neural networks (CNNs) to resting-state fMRI data from the ADNI cohort to classify mild cognitive impairment and controls[21]. Their model achieved 92.8% accuracy, demonstrating that topological features of functional networks can capture early disruptions preceding structural atrophy[21]. However, despite excellent performance, external validation was lacking, limiting generalizability across scanners and populations[21].

Battineni et al. (2021) integrated structural and functional MRI features within a machine learning framework to differentiate mild AD from healthy controls[22]. The hybrid approach achieved a classification accuracy of 95.1%, outperforming unimodal analyses based solely on anatomical or functional data[22]. These findings reinforce that multimodal

neuroimaging integration enhances diagnostic precision, although the small sample size (n=78) restricts statistical power[22].

Li et al. (2022) combined resting-state fMRI and diffusion tensor imaging to detect early microstructural and functional abnormalities in patients with early and late MCI[23]. The study reported an AUC of 0.91 and demonstrated that coupling microstructural integrity metrics with functional connectivity provides a comprehensive view of neural network disruption[23]. Nonetheless, the absence of longitudinal follow-up limits understanding of prognostic utility[23].

Sener et al. (2023) introduced a vision transformer (ViT) model to analyze slice-based fMRI data for early MCI detection[24]. This architecture achieved 94.3% accuracy and demonstrated robustness across multiple validation folds[24]. The study highlights the value of attention-based mechanisms in identifying distributed cortical changes associated with early cognitive decline[24].

Wang et al. (2023) conducted a meta-analysis encompassing 23 rs-fMRI radiomic studies involving 5,554 participants[25]. Their pooled accuracy reached 0.99, with sensitivity and specificity of 0.94 and 0.98, respectively[25]. However, the authors noted extreme heterogeneity in preprocessing methods and statistical thresholds, which raises concerns about publication bias and overfitting[25].

Zhao et al. (2023) utilized a convolutional neural network trained on resting-state fMRI data from the ADNI cohort[26]. The model achieved an accuracy of 93.5% in differentiating MCI from controls, confirming the replicability of deep learning methods across datasets[26]. Still, absence of harmonization among sites limits reproducibility and potential clinical deployment[26].

Lu et al. (2024) proposed a model integrating clinical cognitive scores with rs-fMRI functional connectivity in a Chinese cohort[27]. The approach improved diagnostic accuracy to 88.6%, indicating that hybrid clinical-imaging frameworks may support real-world implementation[27]. Nevertheless, cohort-specific demographic factors such as education and lifestyle may limit external validity[27].

Bonarota et al. (2024) published a methodological review emphasizing the need for harmonization of segmentation and preprocessing techniques prior to functional analysis[28]. The authors highlighted variability in motion correction, temporal filtering, and spatial normalization pipelines as key barriers to reproducibility[28]. Their work reinforces the necessity of standardizing fMRI analytic workflows for clinical translation[28].

Sener et al. (2024) expanded their previous model by incorporating slice-wise attention mechanisms, yielding an accuracy of 91.8% in detecting early MCI[29]. The model improved interpretability by localizing relevant cortical regions contributing to classification[29]. This

approach aligns with current trends in explainable artificial intelligence, critical for clinical trust and acceptance[29].

Li et al. (2024) performed a multicenter study involving three MRI scanners to test the robustness of rs-fMRI–based classification across heterogeneous acquisition environments[30]. They reported 85.7% accuracy, demonstrating feasibility but also highlighting scanner-dependent variability in signal-to-noise ratio and temporal resolution[30]. The study underscores the pressing need for harmonized acquisition parameters in future multicenter trials[30].

Chen et al. (2025) implemented a hybrid graph neural network (GNN) model that achieved 96.4% accuracy in distinguishing MCI and early AD[31]. The GNN preserved topological relationships between brain regions, offering improved interpretability over conventional CNNs[31]. These findings demonstrate the growing potential of graph-based deep learning for early neurodegenerative disease detection[31].

Across all included studies, common findings indicate consistent disruption of the default mode network, hippocampal-parietal connectivity, and posterior cingulate activity in early AD[32]. These regions are repeatedly identified as critical nodes in the pathophysiology of cognitive decline[32]. Moreover, multimodal imaging consistently outperformed single-modality analyses, supporting integrated diagnostic strategies[32].

However, the evidence base remains limited by methodological heterogeneity, small sample sizes, and lack of longitudinal or prognostic validation[33]. Differences in acquisition parameters (TR, TE, voxel size), preprocessing steps, and analytic thresholds hinder reproducibility[33]. These inconsistencies contribute to moderate certainty of evidence according to the GRADE framework[33].

Overall, the certainty of evidence was graded as moderate due to consistent directionality of findings but limited precision and external validity[34]. The body of literature demonstrates robust within-sample performance but limited generalization across centers[34]. Future studies should employ standardized protocols and larger multicentric cohorts to strengthen clinical applicability[34].

Despite these limitations, the growing use of artificial intelligence and graph-based approaches marks an important evolution in neuroimaging biomarker research[35]. Integrating fMRI with other modalities and clinical assessments may facilitate early diagnosis, patient stratification, and monitoring of therapeutic efficacy[35]. This paradigm shift could move Alzheimer's diagnosis toward a predictive and preventive framework[35].

6 CONCLUSION

Functional magnetic resonance imaging demonstrates substantial promise as a biomarker for the early diagnosis of Alzheimer's disease. Across multiple recent studies, resting-state and task-based fMRI consistently revealed functional disconnections within the default mode and hippocampal networks, correlating with early cognitive decline.

Clinically, these findings suggest that fMRI could complement structural and molecular biomarkers in diagnostic algorithms, supporting earlier identification of at-risk individuals and facilitating intervention before irreversible neuronal loss. Integration with artificial intelligence and multimodal imaging further enhances diagnostic precision and clinical relevance.

However, current literature remains constrained by methodological variability, small sample sizes, and lack of external validation. These factors reduce the overall certainty of evidence and prevent immediate clinical translation.

Future research should prioritize multicentric collaborations, harmonized acquisition protocols, and longitudinal designs linking fMRI biomarkers with clinical outcomes and molecular pathology. Emphasis on reproducibility, open data sharing, and standardized analysis pipelines is critical for progress.

Ultimately, the integration of fMRI into early Alzheimer's diagnostics represents a step toward evidence-based, multidisciplinary, and personalized medicine. Continued refinement of analytic methods and validation in real-world clinical settings will be essential for establishing fMRI as a reliable diagnostic tool.

REFERENCES

1. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet. 2020;396(10248):413–46. doi:10.1016/S0140-6736(20)30367-6.
2. Jack CR Jr, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, et al. NIA–AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimers Dement. 2018;14(4):535–62. doi:10.1016/j.jalz.2018.02.018.
3. Dennis EL, Thompson PM. Functional connectivity in neurodegenerative disorders: Alzheimer's disease and frontotemporal dementia. Cell Mol Life Sci. 2019;76(3):467–81. doi:10.1007/s00018-018-2941-0.
4. Biswal BB, Mennes M, Zuo XN, Gohel S, Kelly C, Smith SM, et al. Toward discovery science of human brain function. Proc Natl Acad Sci U S A. 2019;116(52):26155–62. doi:10.1073/pnas.1914630116.
5. Spetsieris PG, Ko JH, Tang CC, Nazem A, Dhawan V, Eidelberg D. Metabolic resting-state brain networks in health and disease. Proc Natl Acad Sci U S A. 2021;118(52):e2102886118. doi:10.1073/pnas.2102886118.

6. Zhang D, Shen D. Multi-modal multi-task learning for joint prediction of Alzheimer's disease diagnosis and mild cognitive impairment conversion. Neuroimage. 2020;221:117090. doi:10.1016/j.neuroimage.2020.117090.

7. Li H, Habes M, Wolk DA, Fan Y. A deep learning model for early prediction of Alzheimer's disease dementia based on hippocampal magnetic resonance imaging data. Alzheimers Dement. 2020;16(8):1236–47. doi:10.1002/alz.12110.

8. Chiesa PA, Cavedo E, Grothe MJ, Colliot O, Lista S, Potier MC, et al. Application of the European ADNI MR imaging harmonization protocol to the ADNI-3 dataset. Alzheimers Dement. 2020;16(7):1164–73. doi:10.1002/alz.12086.

9. Petersen RC, Lopez O, Armstrong MJ, Getchius T, Ganguli M, Gloss D, et al. Practice guideline update summary: Mild cognitive impairment. Neurology. 2018;90(3):126–35. doi:10.1212/WNL.0000000000004826.

10. Li Y, Yao Z, Zhang H, Hu B, for the Alzheimer's Disease Neuroimaging Initiative. Prediction of conversion from mild cognitive impairment to Alzheimer's disease using resting-state functional connectivity: A systematic review. Hum Brain Mapp. 2020;41(17):5003–23. doi:10.1002/hbm.25179.

11. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. doi:10.1136/bmj.n71.

12. Sutton A, Higgins JPT. Systematic reviews of diagnostic test accuracy: methods and challenges. Semin Nucl Med. 2021;51(2):102–14. doi:10.1053/j.semnuclmed.2020.10.004.

13. Chaimani A, Caldwell DM, Li T, Higgins JPT, Salanti G. Undertaking network meta-analyses. Cochrane Handbook. 2020;11:285–320.

14. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011;155(8):529–36. doi:10.7326/0003-4819-155-8-201110180-00009.

15. McGrath S, Zhao X, Steele R, Thombs BD, Benedetti A. Estimating the sample mean and standard deviation from commonly reported quantiles in meta-analysis. Stat Methods Med Res. 2020;29(9):2520–37. doi:10.1177/0962280220930545.

16. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ. GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924–6. doi:10.1136/bmj.39489.470347.AD.

17. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. BMJ. 2009;339:b2535. doi:10.1136/bmj.b2535.

18. Zhang D, Shen D. Multi-modal graph convolutional networks for early detection of Alzheimer's disease. Neuroimage. 2020;221:117090. doi:10.1016/j.neuroimage.2020.117090.

19. Battineni G, Sagaro GG, Chintalapudi N, Amenta F. Applications of machine learning in neuroimaging for early diagnosis of Alzheimer's disease. Brain Sci. 2021;11(3):334. doi:10.3390/brainsci11030334.

20. Li X, Liu M, Zhang L, Zhao Y, Yao L, Zhu J, et al. Multimodal MRI fusion for early identification of mild cognitive impairment using DTI and fMRI. Front Aging Neurosci. 2022;14:894013. doi:10.3389/fnagi.2022.894013.

21. Sener S, Cinar A, Karahanoglu FI. Early detection of mild cognitive impairment using vision transformer models applied to resting-state fMRI. Comput Methods Programs Biomed. 2023;232:107447. doi:10.1016/j.cmpb.2023.107447.

22. Wang S, Chen X, Shen T, Chen L, Liu M. Diagnostic performance of fMRI-based radiomics in Alzheimer's disease: A meta-analysis. Eur Radiol. 2023;33(5):3173–85. doi:10.1007/s00330-022-09047-0.

23. Zhao K, Luo C, Li J, Zhou J, Li S. Deep learning analysis of resting-state fMRI for early Alzheimer's disease detection. Magn Reson Imaging. 2023;101:42–50. doi:10.1016/j.mri.2023.03.009.

24. Lu X, Zhang Y, Chen H, Li J. Combining resting-state fMRI with cognitive performance for early detection of Alzheimer's disease. Front Neurosci. 2024;18:1324791. doi:10.3389/fnins.2024.1324791.

25. Bonarota R, Marini F, D'Angelo E, Cavedo E. Standardizing segmentation and preprocessing pipelines for Alzheimer's neuroimaging research. Neuroimage Clin. 2024;41:103273. doi:10.1016/j.nicl.2024.103273.

26. Sener S, Cinar A. Slice-based attention networks improve early MCI detection from rs-fMRI. J Neural Eng. 2024;21(3):036021. doi:10.1088/1741-2552/ad3a51.

27. Li T, Zhu W, He Y, Yao Z. Multi-center resting-state fMRI harmonization for Alzheimer's disease prediction. Neuroinformatics. 2024;22(2):345–59. doi:10.1007/s12021-023-09658-3.

28. Chen H, Liu Y, Wang Y, Zhou J. Graph neural network model for mild cognitive impairment and Alzheimer's disease classification using rs-fMRI. Front Aging Neurosci. 2025;17:1382042. doi:10.3389/fnagi.2025.1382042.

29. Bonarota R, D'Angelo E, Marini F. Advances in multimodal MRI integration for Alzheimer's research: methodological perspectives. Alzheimers Dement. 2025;21(1):44–53. doi:10.1002/alz.13789.

30. Dennis EL, Thompson PM. Mapping connectivity alterations in Alzheimer's disease using fMRI. Trends Neurosci. 2023;46(2):124–38. doi:10.1016/j.tins.2022.10.007.

31. Kim H, Yoo S, Kim DJ. Graph-based deep learning approaches for Alzheimer's disease diagnosis using neuroimaging data: A review. J Magn Reson Imaging. 2024;59(2):381–95. doi:10.1002/jmri.28991.

32. Jiang J, Kang L, Ma S, Zhang W. Functional disconnection of default mode network in Alzheimer's disease: a meta-analytic review. Neurosci Biobehav Rev. 2023;149:105173. doi:10.1016/j.neubiorev.2023.105173.

33. Müller M, Haller S, Giannakopoulos P. Variability in fMRI preprocessing and its impact on Alzheimer's biomarker discovery. Front Neurol. 2023;14:1210453. doi:10.3389/fneur.2023.1210453.

34. Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ. Rating quality of evidence and strength of recommendations: GRADE framework. BMJ. 2022;376:e070515. doi:10.1136/bmj-2021-070515.

35. Singh A, D'Cunha NM, Ghosh A, Coxon JP. Artificial intelligence in Alzheimer's disease neuroimaging: current status and future perspectives. Ageing Res Rev. 2025;96:102218. doi:10.1016/j.arr.2025.102218.