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REGULAR PAPER

Machine learning applications in Alzheimer's disease research: a comprehensive analysis of data sources, methodologies, and insights

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Abstract

Alzheimer's disease is a debilitating neurological disorder that affects the central nervous system, causing significant disruption to cognitive processes. Predominantly afflicting the elderly, it leads to profound cognitive impairment. This study aims to review the application of machine learning techniques in the diagnosis and progression analysis of Alzheimer's disease. A comprehensive review of 783 papers published from 2009 to 2023 was conducted, focusing on machine learning and deep learning techniques. Data sources included ADNI, OASIS, and localized patient data. The papers were categorized into 18 taxonomic classes and partitioned into five clusters based on neuroimaging and non-imaging methodologies. This categorization was underpinned by topic modeling and text mining methods, analyzing the semantic similarities in the papers. The study provides a detailed landscape of AI applications in Alzheimer's research, highlighting the evolving role of machine learning in enhancing diagnostic accuracy and understanding disease progression.

Keywords Alzheimer's disease (AD) · Mild cognitive impairment (MCI) · Diagnostic accuracy · Dementia · Machine learning · Deep learning

Abbreviations

Acronyms

AD	Alzheimer's disease
MCI	Mild cognitive impairment
ML	Machine learning
AI	Artificial intelligence
ELMS	Exploration of Literature through Machine Learning and Semantics
LDA	Latent Dirichlet allocation
NMF	Non-negative matrix factorization
LSTM	Long short-term memory
RNN	Recurrent neural network
CapsNets	Capsule neural network
CNN	Convolutional neural network
ANN	Artificial neural network
AUC	Area under the ROC curve
EHR	Electronic health record
DTI	Diffusion tensor imaging
SVM	Support vector machines
KNN	K-nearest neighbors
SNP	Single nucleotide polymorphism
CNV ViTs	Copy number variation swin transformer
EEG	Electroencephalogram
PET–MRI	Positron emission tomography–magnetic resonance imaging
ADA	Accuracy of advanced Alzheimer's disease
ADM	Accuracy of moderate Alzheimer's disease
sMRI	Structural magnetic resonance imaging
MRI	Magnetic resonance imaging
OTA-LSTM	Optimized transformer-based attention long short-term memory
GAN	Generative adversarial network
cGAN	Conditional generative adversarial network
DAG-Att	Directed acyclic graph with attention mechanisms
TA-LSTM	Time-attention long short-term memory
dFNC	Dynamic functional network connectivity
rs-fMRI	Resting-state functional magnetic resonance imaging

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VANT-GAN	Visually attributed abnormal-to-normal translation generative adversarial network
MLG-GAN	Multi-level guided generative adversarial network
Mul-T	Multimodal transformer network
BSGAN-ADD	Brain slice generative adversarial network for Alzheimer's disease detection
ROI	Region of interest
ADNI	Alzheimer's Disease Neuroimaging Initiative
OASIS	Open Access Series of Imaging Studies
RMSE	Root-mean-square error
MAE	Mean absolute error
2 T-GCN	Two-task graph convolutional network
MVS-GCN	A multi-view graph convolution network
CIA-HGCN	Characteristic information aggregation hypergraph convolutional network
GNN	Graph neural network
GRN	Template-based graph registration network
MGN-Net	Multi-view graph normalizer network
TTC	Of time-to-conversion
MMSE	Mini mental state examination
BiLSTM	Bidirectional long short-term memory
PET	Positron emission tomography
FAS-norm	Feature-aware sparsity-inducing norm
BGP-MTFL	Bi-graph guided self-paced multi-task feature learning
nMSE	Normalized mean-squared error
FC	Functional connectivity
SC	Structural connectivity
RFE	Recursive feature elimination
DAGs	Directed acyclic graphs

1 1. Introduction

DEMENTIA is a broad term encompassing a decrease in cognitive function significant enough to disrupt daily activities. Alzheimer's disease (AD) is a degenerative neurological disorder associated with aging, which progressively worsens and ultimately leads to fatality. This decline in cognitive abilities primarily affects memory, reasoning, and communication skills, making early diagnosis and management vital in mitigating its impact on the quality of life of those affected. AD is characterized by the accumulation of amyloid deposits and the formation of neurofibrillary tangles within brain cells. AD is one of the most critical healthcare challenges globally [1]. Alzheimer's disease is the most prevalent form of dementia, responsible for at least two-thirds of dementia cases in individuals aged 65 and above. It is a neurodegenerative disorder that gradually deteriorates behavioral and cognitive abilities, such as memory, comprehension, language, attention, reasoning, and judgment. AD has a subtle beginning and progressively worsens over time. In the USA, it ranks as the sixth leading cause of death and the fourth leading cause of disability-adjusted life-years (DALYs) lost among individuals aged 75 years and older. Early onset of the disease, occurring before the age of 65, is typical and affects less than 10% of AD patients [2]. Furthermore, the socioeconomic impact of Alzheimer's disease is immense, not only due to the direct costs of medical care but also because of the significant emotional and financial strain it places on families and caregivers, highlighting the need for comprehensive support systems and policies. As such, the integration of advanced technologies like artificial intelligence (AI) and machine learning (ML) is increasingly being recognized as crucial in this domain, offering innovative approaches for early detection, personalized treatment plans, and improved management of Alzheimer's disease, thereby potentially alleviating its burden on individuals and society.

Every three seconds, a new case of dementia arises globally. In the year 2020, there were more than 55 million individuals worldwide living with dementia. This figure is projected to nearly double every two decades, resulting in an estimated 78 million cases by 2030 and 139 million cases by 2050 [3]. The disease not only impacts patients, but also places a considerable burden on caregivers and healthcare systems. The economic cost of AD is substantial, involving both direct medical costs and indirect costs such as lost productivity and caregiver expenses. This escalating prevalence and its far-reaching implications underscore the urgent need for extensive research in understanding and combating AD. With these staggering statistics in mind, it becomes evident that innovative and scalable solutions are required to address the growing challenge of Alzheimer's disease, necessitating a global effort in medical research, public health policy, and community support to combat this escalating crisis effectively.

Before the emergence of machine learning and deep learning methods, Alzheimer's disease (AD) diagnosis primarily depended on conventional techniques such as neurological examinations, medical history reviews, and brain imaging modalities like magnetic resonance imaging (MRI). These traditional approaches, while valuable, often fell short of providing consistent and universally reliable diagnostic results, particularly in the early stages of the disease. They lacked the ability to effectively integrate the myriad of data sources involved in AD diagnosis, such as imaging, genetic data, and clinical assessments, thus limiting their accuracy and predictive power. This underscored the pressing need for more sophisticated analytical techniques capable of processing complex, high-dimensional data.

Recent advancements in ML and DL methods have revolutionized AD research by enabling the analysis of vast datasets to detect patterns and biomarkers that were previously undetectable using traditional techniques. Numerous studies have highlighted the utility of ML algorithms in areas such as early detection, prediction of disease progression, and development of personalized treatment strategies. For instance, convolutional neural networks (CNNs) have been extensively applied to neuroimaging data, achieving remarkable accuracy in distinguishing between AD and mild cognitive impairment (MCI) [4–7]. Similarly, ensemble learning methods like Random Forests have proven effective in integrating diverse data sources, including MRI, PET, and EEG, alongside electronic health records (EHRs) and cognitive assessments, yielding robust predictive models [8].

A prominent example of this is the ADNI (Alzheimer's Disease Neuroimaging Initiative), which leverages neuroimaging and genetic datasets alongside ML algorithms to identify early biomarkers of AD. By utilizing CNNs and recurrent neural networks (RNNs), researchers have been able to significantly enhance diagnostic accuracy, especially in detecting early-stage AD where traditional methods often falter. Additionally, ML techniques have facilitated the development of multimodal models that combine imaging data with clinical records, thus providing a more holistic view of the disease's progression. This integration allows for the generation of models that can predict cognitive decline years in advance, providing invaluable insights for early intervention [7].

Another breakthrough has been the use of unsupervised learning algorithms, such as clustering techniques, to identify subgroups of patients with distinct disease trajectories, which aids in personalized medicine. For instance, clustering methods have been applied to segment patient populations based on disease progression, facilitating more tailored therapeutic approaches [9]. Moreover, ML models have proven highly beneficial in genomic studies related to AD. Genetic risk factors have been successfully integrated into predictive models, further enhancing the ability to forecast the onset and progression of AD. Techniques like support vector machines (SVM) and principal component analysis (PCA) have been used to analyze gene expression profiles, helping researchers to identify genetic markers that contribute to the disease [7, 10, 11].

In this paper, we delve into the utilization of AI and ML in Alzheimer's research, providing a detailed analysis of data sources, methodologies, and emerging insights. Our comprehensive review of these papers, spanning over a decade, aims to synthesize the existing knowledge, identify trends and gaps in current research, and highlight the transformative potential of ML and AI in enhancing diagnostic accuracy, understanding disease progression, and developing targeted therapeutic strategies. By consolidating and analyzing a vast array of studies, our work not only charts the evolution of technology in Alzheimer's research but also serves as a foundational resource for future investigations seeking to harness the power of AI and ML in the battle against this debilitating disease.

1.1 Data sources in Alzheimer's disease research

Data sources for Alzheimer's disease research include longitudinal data, which tracks disease progression over time, This type of data is crucial for understanding the long-term effects and trajectory of the disease, and cross-sectional data provide a snapshot of Alzheimer's characteristics at a specific time, facilitating the identification of prevalent symptoms and risk factors. This approach helps in comparing different populations and assessing the immediate impact of the disease. Imaging modalities like PET, MRI, and CT scans offer detailed insights into brain structure and function, essential for visualizing amyloid plaques and neurodegeneration. These imaging techniques are pivotal in differentiating Alzheimer's from other types of dementia.3D-MRI provides high-resolution brain images, while fMRI measures brain activity and connectivity. Cognitive assessments evaluate a patient's cognitive abilities and detect declines in memory, language, and problem-solving skills. These tests are critical for establishing a baseline and monitoring changes over time. CSF and blood plasma biomarkers provide biochemical evidence of Alzheimer's pathology, such as tau proteins and amyloid-beta levels. These biomarkers are valuable in confirming diagnosis and tracking disease progression [12]. Genetic data help understand genetic factors and inheritance patterns. EEG abnormalities provide insights into brain function, and electronic health records offer valuable information for screening and tracking the disease [13]. Electronic health records (EHR) compile comprehensive medical histories, including diagnosis, treatment, and laboratory results. This data source is invaluable for screening, tracking disease progression, and assessing treatment outcomes. These data are shown in Fig. 1.

Fig. 1 Methodological approaches and data sources for insights into pathology and progression

1.2 Prominent data sources and initiatives in Alzheimer's disease research.

Prominent data sources like ADNI,[1] OASIS,[2] HABS,[3] MIRIAD,[4] J-ADNI,[5] and AIBL[6] provide neuroimaging and neuropsychology data for Alzheimer's research [14–18]. Challenges and competitions (CAD Dementia, TADPOLE, DREAM, Kaggle)[7] offer pre-selected data, simplifying research participation.

Other sources (UK Bio Bank,[8] NKI,[9] IXI,[10] IGAP,[11] KLOSCAD,[12] and ANMerge[13]) contribute diverse datasets for advancing Alzheimer's research [19]. These data sources are presented in Fig. 2.

[1] ADNI (Alzheimer's Disease Neuroimaging Initiative): https://adni.loni.usc.edu/

[2] OASIS (Open Access Series of Imaging Studies): https://sites.wustl.edu/oasisbrains/

[3] HABS (Harvard Aging Brain Study): https://habs.mgh.harvard.edu/

[4] MIRIAD—Public release of a multiple time point Alzheimer's MR imaging dataset: https://www.ucl.ac.uk/drc/research-clinical-trials/minimal-interval-resonance-imaging-alzheimers-disease-miriad

[5] Japan ADNI: https://www.alz.org/research/for_researchers/partnerships/wwadni/japan_adni

[6] AIBL (Australian Imaging, Biomarkers & Lifestyle Study of Ageing): https://aibl.org.au/

[7] Alzheimer's Disease Prediction Of Longitudinal Evolution (TADPOLE) Challenge: https://tadpole.grand-challenge.org/
https://www.kaggle.com/datasets/ninadaithal/imagesoasis

[8] UK Biobank: https://www.ukbiobank.ac.uk/

[9] NKI (Nathan Kline Institute:

[10] IXI: http://brain-development.org/

[11] NG00036 – IGAP: https://www.niagads.org/datasets/ng00036, https://www.niagads.org/datasets/ng00075

[12] Korean Longitudinal Study on Cognitive Aging and Dementia: https://www.maelstrom-research.org/study/kloscad

[13] ANMerge: A comprehensive and accessible Alzheimer's disease patient-level dataset: https://www.medrxiv.org/content/10.1101/2020.08.04.20168229v1.full

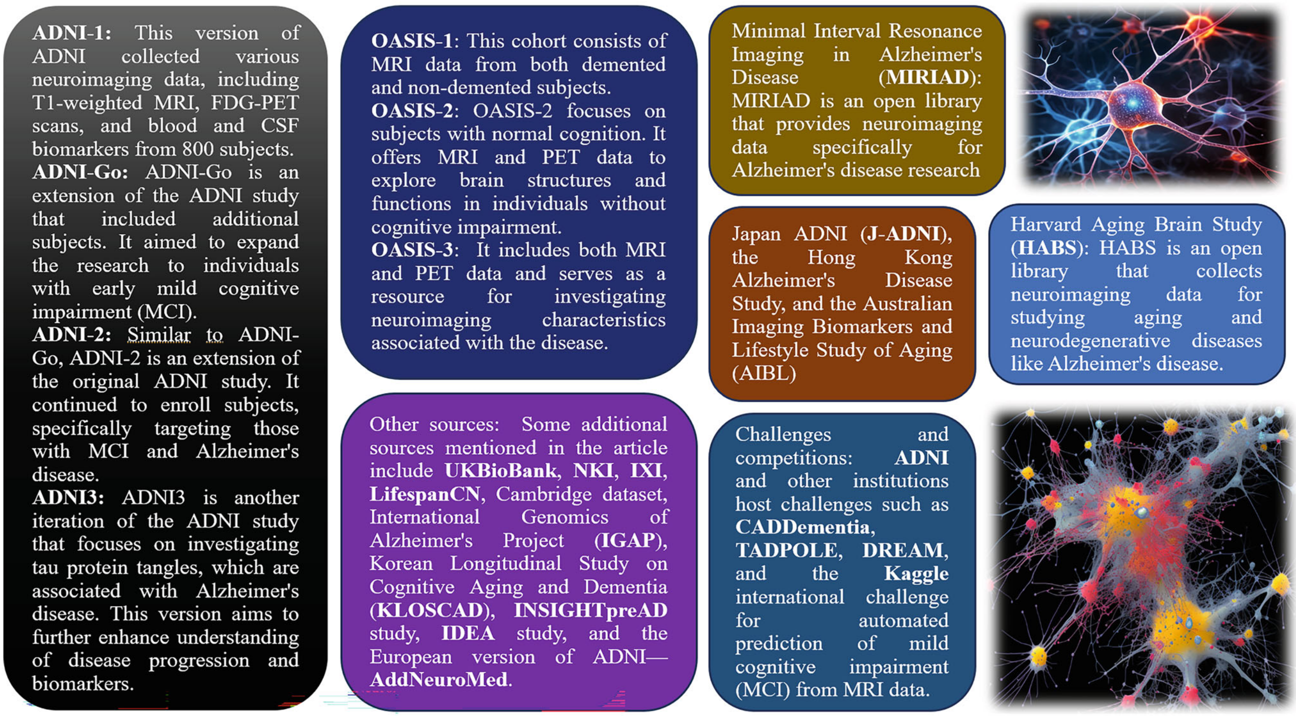

Fig. 2 Data sources for insights into Alzheimer's disease

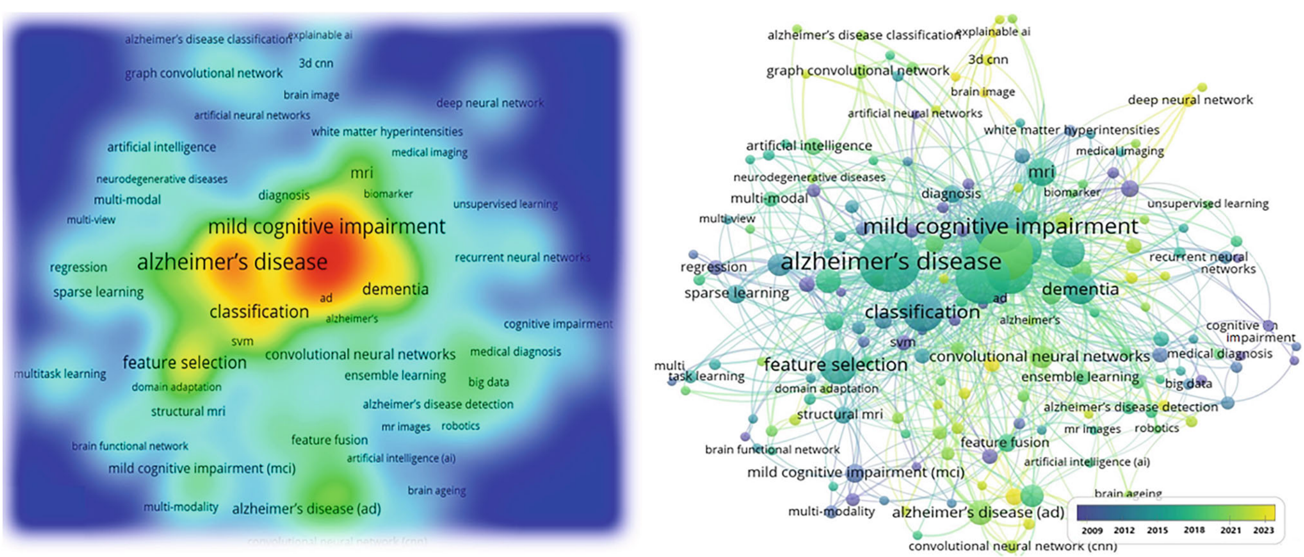

Fig. 3 Temporal evolution and longitudinal analysis of 783 published papers: a comprehensive review from 2009 to 2023

2 Materials and methods

In this paper, a total of 783 papers were extracted and subsequently subjected to an initial review using VOS Viewer, as shown in Fig. 3. The figure maps and visualizes the most frequent terms and keywords used in platform research, revealing major themes and trends. It includes density maps that illustrate the intensity of research activity and highlight hotspots within the field. The terms "mild cognitive impairment" and "Alzheimer's disease" are prominently featured at the center of the hotspot, indicating they are highly researched topics. Other frequently occurring terms include "classification," "dementia," "feature selection," "convolutional neural networks," and "MRI" [20].

Table 1 provides an overview of the keywords used to identify the limitations of the review. In all search areas, the scope of the study focused on Alzheimer's disease, mild cognitive

Table 1 Keywords used for identifying limitations of the review

The key search areas	Criteria	Detail
All search areas	Scope	Alzheimer's disease, mild cognitive impairment (MCI), dementia
All search areas	Study	Machine learning, deep learning, neuroimaging, types of imaging modalities, non-imaging methodologies, brain function, EEG, biomarker discovery
		Alzheimer's disease as a neurological disorder
		Cognitive impairment in Alzheimer's disease
General Topic about the Alzheimer's disease	Application	Machine learning techniques in Alzheimer's disease research
		Deep learning techniques in Alzheimer's disease research
		Non-imaging methodologies in Alzheimer's disease research
		Neuroimaging methodologies in Alzheimer's disease research

Table 2 Filters used for searching strategy

The key search areas	Criteria	Detail
All search areas	Database	Pub med
All search areas	Publisher of	We only filtered the publisher on " Alzheimer's disease" with: Elsevier, Springer Science and Business Media, MDPI, Institute of Electrical and Electronics Engineers (IEEE), Hindawi, Oxford University Press, Springer Nature, SAGE Publications, Wolters Kluwer, Public Library of Science (PLOS)
All search areas	Search Field	In Title & Abstract
General Topic about the pandemic management	Year	We used papers from past 5 years for " Alzheimer's disease" and no filter on other searches
outbreak prediction	Language	English

impairment (MCI), and dementia. The study areas encompassed various aspects, including machine learning, deep learning, neuroimaging, types of imaging modalities, non-imaging methodologies, brain function, EEG, and biomarker discovery. The table highlights the key search criteria and outlines the specific details related to each search area, providing a comprehensive framework for identifying and addressing limitations in the review. Table 2 presents the filters used in the searching strategy. The search areas included the PubMed database as the primary source. In terms of the publisher, the papers were filtered. The search field for all areas focused on the title and abstract of the papers. Additionally, the search was limited to papers published within the past five years for Alzheimer's disease, while no specific filters were applied to other searches. These filters helped streamline the search process and ensure the retrieval of relevant and recent literature for the review.

The quest for insights into Alzheimer's disease, dementia, and MCI has led to a substantial body of scientific literature. The content review model has been developed by integrating diverse techniques in topic modeling and inter-cluster semantic analysis applied to extensive datasets encompassing scientific publications, citations, and keyword metadata. By utilizing the ELMS (Exploration of Literature through Machine Learning and Semantics) process to meticulously scrutinize citation networks, research themes, and collaborative endeavors within the scientific literature, peer reviewers are empowered to provide more astute and constructive feedback to authors. A comprehensive search was conducted across preeminent scientific databases, including PubMed, ScienceDirect, and IEEE, leading to the initial identification of 32,000 papers published between 2000 and 2023. Subsequently, the research focus was refined, with specific emphasis on the interplay between Alzheimer's disease, dementia, MCI, and the fields of artificial intelligence and data science, culminating in the curation of 9347 relevant papers. To streamline the study's scope, review papers and book chapters were excluded from consideration. Furthermore, the review window was constrained to the period spanning from 2009 to 2023, resulting in a final dataset encompassing 783 papers in the field of data science, a comprehensive categorization was undertaken, resulting in the creation of 18 distinct clusters. These clusters were initially devised to facilitate the summation of papers by

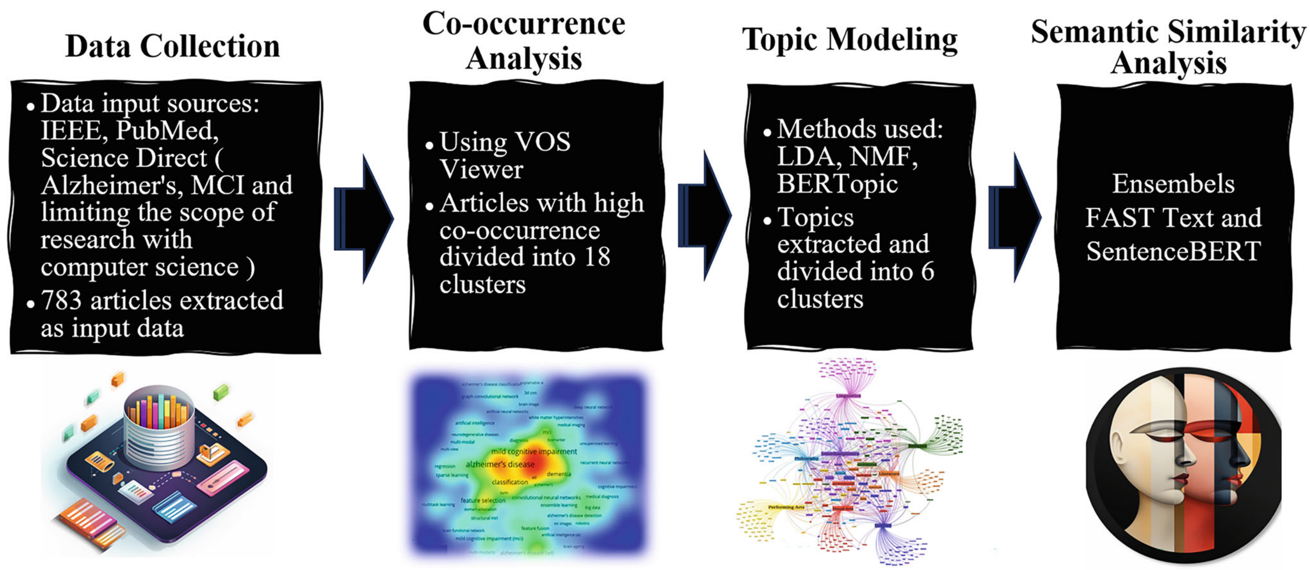

Fig. 4 Survey protocol (data collection, co-occurrence analysis, topic modeling, and semantic similarity analysis workflow considering 783 papers published over the span from 2009 to 2023)

grouping them based on their subject matter, methodologies, and architectural aspects. Subsequently, a more refined categorization was achieved by leveraging topic modeling and semantic similarity techniques. This refined process culminated in reclassifying the 18 initial clusters into five more homogenous clusters, thereby enhancing the organization and summarization of this field's prevalent methods, case methodologies, and architectures. Topic modeling and semantic similarity are commonly used in combination for topic clustering of large volumes of papers. With the ever-increasing amount of scientific literature available, manually organizing and categorizing these papers becomes daunting. Topic modeling allows for the automatic identification and extraction of key themes, while semantic similarity analysis enhances the clustering process by measuring the semantic relatedness between documents. By leveraging these techniques, researchers can efficiently group papers based on their shared topics and explore complex relationships within the literature, providing valuable insights and facilitating further research in specific domains. It is evident that reviewing a sizable volume of papers characterized by concise, text-dense abstracts poses challenges due to methodological complexities in data collection and analysis. In order to bridge the evolving domains of medical science and scientific metric social research, this study seeks to conduct a comprehensive examination of Alzheimer's-related topics through the employment of four thematic modeling techniques. Specifically, latent Dirichlet allocation (LDA), non-negative matrix factorization (NMF), Top2Vec, and BERTopic were utilized in this study. LDA is a probabilistic model that identifies latent topics in a document collection, while NMF is a matrix factorization technique that extracts underlying themes from the data. Top2Vec is an algorithm that combines document clustering and topic modeling, and BERTopic uses the BERT language model to derive topics from the data. Semantic similarity techniques were employed to evaluate the thematic selection. The analysis identified six overarching thematic clusters, paving the way for a comprehensive inquiry into the subject matter. For a more detailed explanation of the methodology, please refer to Fig. 4, which illustrates the data extraction and paper clustering process.

3 Discussion

3.1 Article clustering via semantic similarity: organizing papers based on shared themes

The proposed partitioning of the data into five distinct clusters is associated with specific thematic categories, as represented within the dependency graph. Visually, this graph structure of clusters represents mappings of relevant methodological issues and serves as the foundation for comparative and in-depth discussions in the review paper. Each cluster will demonstrate these categories' interrelationships and hierarchical dependencies, contributing to a more comprehensive understanding of the organizational framework underpinning the data analysis. five clusters based on the similarity of scientific methods are presented in Fig. 5. The clustering of data analysis methods allows for a more targeted approach to identifying potential therapeutic targets or diagnostic markers in AD. systematic review, focusing on the common features and inherent inequalities of the methods within each cluster. Each cluster has been categorized

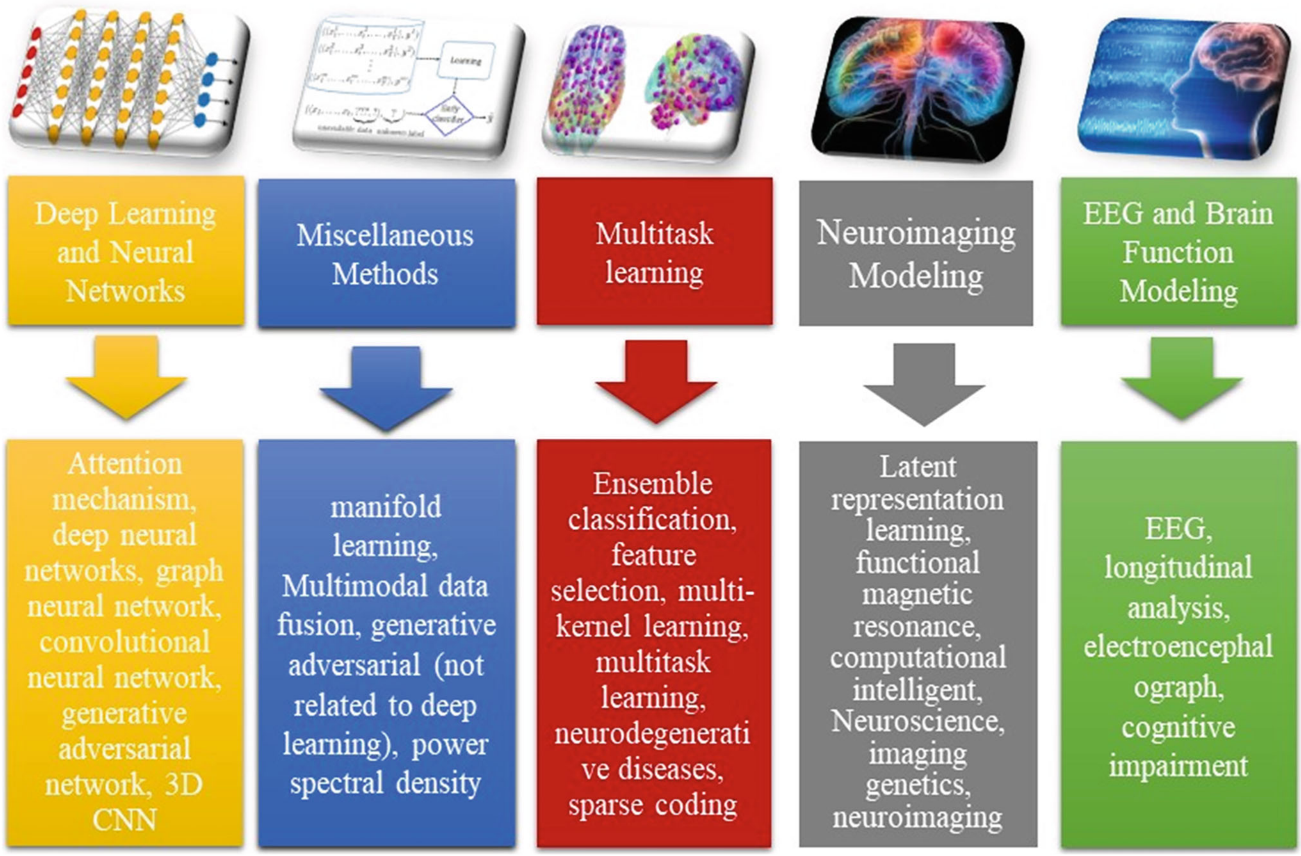

Fig. 5 Thematic categories and hierarchical dependencies: partitioning of data into five clusters based on similar scientific methods

based on the thematic similarity of the papers, enabling the identification of shared themes within each cluster. While there are similarities between clusters, their separation primarily arises from the emphasis placed on specific topics within each cluster. It is important to note that clusters may also have connections or overlaps with other clusters. Additionally, the varying number of papers in each cluster is a result of the frequency of papers associated with those particular themes. The selection and review of papers were driven by the frequency and significance of the topics rather than a predetermined target number of papers. The categories include "Deep Learning and Neural Networks," "Miscellaneous Methods," "Multitask Learning," "Neuroimaging Modeling," and "EEG and Brain Function Modeling." This classification was arrived at through a comprehensive review of existing literature, which revealed how different machine learning techniques are applied across these domains to enhance understanding and diagnosis of Alzheimer's disease. By organizing these methodologies, the article aims to provide clarity on the varied approaches, highlight their specific contributions, and suggest avenues for future research in this critical area of healthcare.

3.2 Deep learning and neural networks: deep learning

Deep learning is a field of study that utilizes artificial neural networks to analyze and extract meaningful patterns and information from large sets of data. It has shown great promise in various domains, including medical image analysis and the diagnosis of diseases like Alzheimer's disease (AD). The common feature among these categories of papers is the utilization of deep learning methods for predicting or diagnosing Alzheimer's disease [21]. They leverage the power of neural networks to extract meaningful patterns and features from various data sources, including electronic medical records, MRI images, and handwriting samples. These methods aim to improve prediction accuracy and enable early detection of AD.

Table 3 provides a concise overview of the comparison of deep learning methods, including evaluation criteria, method innovation, data and modeling challenges, and proposed solutions. Subsequently, the following sections will present comparative tables and figures that may contain some methods or image modalities that overlap. However, the key differences lie in the specific techniques and data used within each category. The LSTM RNN-based methods

Table 3 Comparing deep learning methods based on evaluation criteria, method innovation, data and modeling challenges, and proposed solutions, but the main emphasis is placed on the methodology and approaches discussed in the papers

References	Model	Result	Innovation	Challenges	Proposed improvement
[22]	LSTM, RNN	AUPRC score 0.98, -0.99	Filter unrelated conditions, choose treatment method	Clinical domain, temporal integration	Ratio impact, different training/testing ratios
[23]	CapsNets, 3D CNN, pretrained 3D autoencoder	Accuracy: 98.42%	Advantages over traditional CNNs, handle limited labeled data, class imbalance in biomedical image	Limited labeled data, class imbalance	More diverse datasets, other modalities, further experiments
[4]	CNN, 12 sequential layers, Early Stopping callback	Accuracy of 90.4%	Kinematic analysis of handwriting movements to detect neurodegenerative diseases	Too many trials for hyperparameter tuning	Train on a larger dataset
[5]	CNN T1-weighted	Accuracy, sensitivity, specificity (AUC) 99.68%, 100%, 100%	Efficient deep learning pipeline for AD diagnosis from a small dataset	Limited labeled data, Imbalanced dataset	Combine different datasets
[6]	CNN (mobility data)	Accuracy 90.91%, F1-score 0.897	Mobility data from smartphones, detect complex patterns in patient movement	Limited data available	Cloud-computing architecture to collect accelerometer data in AD stages
[7]	CNN (high-level features from each modality)	Accuracy 98.22%, NC vs. AD 93.11%, NC vs. sMCI 97.35%	Unified framework combining multimodal neuroimaging and genetic data for joint classification and clinical score regression	Incomplete modality data, integration of brain disease identification and clinical score estimation	Explore data imputation techniques, enhance integration
[73]	RNNs (Vanilla RNNs, LSTM, GRU)	TPR and FPR percentages for LSTM: 91.43%, 40.96%	Activity recognition, abnormal behavior detection in elderly with dementia, generate synthetic data	Lack of datasets related to abnormal behavior, complexity of temporal and spatial modeling	Collect data from a smart home for elderly with dementia
[74]	Gray level co-occurrence matrix (GLCM), extreme learning machine (ELM)	Accuracy rate GLCM-ELM 92.30%	Combination of GLCM and ELM for AD	Small dataset size, error in selection and division of ROIs	Transfer learning or GAN methods for data augmentation
[75]	BrainNetCNN with hidden topological features from structural brain networks	Accuracies: 0.96 (NC vs EMCI), 0.98 (NC vs MCI), 0.95 (EMCI vs MCI)	Extracts hidden topological features from structural brain networks	Limited data in neuroimaging, non-interpretability of models	Incorporate multiple neuroimaging modalities
[76]	Multimodal ensemble (random forest using EHR, CNN using DTI scans)	Accuracy of 98.81%, DTI scans better at AD (96.43%) than clinical data alone (92.86%)	Combines multiple modalities (EHR, DTI) for comprehensive disease view	Imbalanced data, apply oversampling techniques	Explore additional modalities, genetic biomarkers, longitudinal studies

Table 3 (continued)

References	Model	Result	Innovation	Challenges	Proposed improvement
[77]	SVM, ELM, KNN	Accuracy: 99.77% (Kaggle), 98.21% (ADNI)	Combines deep residual autoencoder and SVM, multi-scale pooling for segmenting white matter MRI images	Dataset expansion, robustness to variability, integration of clinical data	Evaluate on external datasets
[78]	Ensemble learning (2D CNNs, GAN, VGG16, ResNet50)	Accuracy 90.36% (AD vs CN classification)	Combines ensemble learning, multi-model integration, multi-slice ensemble learning	Limited neuroimaging data	Increase training dataset diversity and size, explore advanced models
[10]	Enhanced deep recurrent neural network	Accuracy 89.5%, AUC 87.7%	EDRNN model and stopping criteria	Low sample size (HDLSS) in molecular data analysis	Analyze various molecular data sets to identify AD-associated genes
[79]	Conv-Swinformer (CNN, Transformer encoder)	ADNI: Accuracy AD vs. CN 0.9356, AD vs. MCI 0.8209, MCI vs. CN 0.7907; OASIS: Accuracy AD vs. CN 0.9231, AD vs. MCI 0.8333, MCI vs. CN 0.7353	Combines CNN and Transformer modules, shift window attention for local lesion feature modeling in MRI	Accurately identifying MCI, small dataset size	Adjust CNN layers to reduce parameters and overfitting, verify clinical value
[80]	CNNs, ViTs, Swin transformer, DO-Conv, CoAtNet, MBConv	Accuracy: 93.23% (OASIS), 97.33% (ADNI), 98.87%	Combining CNNs and ViTs for long-range relationships and global features, multimodal imaging	Different image acquisition techniques, scanner types	Additional fusion methods, optimize training for ViTs
[81]	rankCNN	RMSE: 2.23 (ADNI-1), 2.43 (ADNI-2), Pearson's CC: 0.57 (ADNI-1), 0.43 (ADNI-2)	Transforming regression into binary classifications, ranking layer for MMSE values	Different imaging methods introduce inconsistencies	Combine local and global features, integrate historical record information
[82]	2D CNN, 3D CNN, spatio-temporal (2 + 1)D CNN	(2 + 1)D CNN 85% AUC score, faster convergence than 3D CNN	Spatio-temporal model handles images in spatial and temporal dimensions separately	Selection of appropriate features	Improve model architecture, explore other deep learning techniques
[83]	VGG-TSwinformer, longitudinal brain (sMRI) data	Accuracy: 77.2%, sensitivity: 79.97%, specificity: 71.59%, AUC: 0.8153	Captures progressive nature of disease, extracts spatial features, captures temporal patterns	Deep learning disadvantages in longitudinal medical data, limited multimodal biomarkers	Combine multimodal cross-sectional and longitudinal biomarkers

[22] focus on utilizing EMR data and incorporating medical domain knowledge for preprocessing and dataset selection. The CapsNets and 3D CNN-based methods [23] emphasize the advantages of CapsNets over traditional CNNs in handling challenges such as limited labeled data and class imbalance in biomedical image databases. They utilize MRI images and explore the combination of different modalities for comprehensive AD diagnosis. On the other hand, CNN-based methods [4–7] for early AD diagnosis employ different input data, such as handwriting samples or MRI brain scans, and incorporate specific architectural choices and optimization techniques to achieve accurate classification.

Overall, while all these categories utilize deep learning, they differ in their specific approaches, input data sources,

Table 3 (continued)

References	Model	Result	Innovation	Challenges	Proposed improvement
[84]	Enhanced ICA, segmented gray matter of MRI	AD-CN: 100% accuracy, specificity, sensitivity; AD-MCI: 96.2% accuracy, 93% sensitivity, 100% specificity; CN-MCI: 98.0% accuracy, 96% sensitivity, 100% specificity	Combines CNN-based approach with hybrid ICA segmentation for differentiating brain atrophy	Differentiation between MCI, CN, AD cases, complexities in analyzing brain images	Incorporate data from multiple imaging modalities (PET, fMRI)
[85]	Unsupervised CNNs for feature extraction from MRI	AD vs. MCI: 95.52% (one slice), 97.01% (TOP); MCI vs. NC: 90.63% (one slice), 92.6% (TOP)	Unsupervised deep learning eliminates need for labeled data	Insufficient labeled medical image data	Validate on larger, diverse datasets
[86]	Statistical methods, unsupervised learning, neural network, clustering algorithm	84% accuracy in discriminating CN and AD	Utilizes limited labeled data, identifies AD-relevant regions, accurate diagnosis without large volumes of labeled data	Difficulty in labeling MRI scans, time-consuming and expertise-dependent	Utilize limited labeled data, identify AD-relevant regions, accurate diagnosis without extensive labeled data
[87]	VGG-16 pretrained CNN architecture	95.73% accuracy for 3-way classification (AD, CN, MCI)	Transfer learning from ImageNet, leveraging knowledge from natural images, reduces computational cost	Difficulty in accurately classifying MCI, intermediate stage between AD and CN	Investigate alternative neural network architectures, fine-tune pretrained layers
[88]	IDA-Net (Inheritable Deformable Attention Network)	Accuracy: AD vs NC: 0.927, pMCI vs sMCI: 0.835, pMCI vs NC: 0.913, sMCI vs NC: 0.852	Deformable self-attention modules for precise extraction of microstructural changes	Precise extraction of microstructural changes in sMRI	Validate and test on larger, diverse datasets, explore multimodal data integration
[89]	EAD-DNN (Early Alzheimer's Disease—Deep Neural Network)	98% accuracy	Leveraging deep neural networks and optimization techniques for accurate predictions	Lack of accurate methods for early Alzheimer's diagnosis	Validate on larger, diverse datasets, clinical integration, incorporate multimodal data

and optimization strategies, allowing for diverse methods to address the challenges in predicting and diagnosing Alzheimer's disease. The cluster of reviewed papers encompasses a total of 24 scholarly publications. Each paper within the cluster was analyzed and evaluated based on multiple sections, including the Implementation Model, Implementation Result, Challenge, Innovation, and Data Sets. The findings of each study were carefully examined, and recommendations were provided to enhance the respective papers. Challenges and solutions in deep learning for Alzheimer's diagnosis are summarized in Fig. 6.

3.2.1 Generative adversarial network (GAN)

It is a type of machine learning model that consists of two components: a generator and a discriminator. The generator is responsible for generating new samples, such as images or text, that resemble the training data, while the discriminator tries to distinguish between the generated samples and real samples from the training data. In the context of predicting Alzheimer's disease, GAN models are used to generate realistic and high-quality medical images that capture different stages of the disease progression. These generated images can be valuable for various purposes. The following section

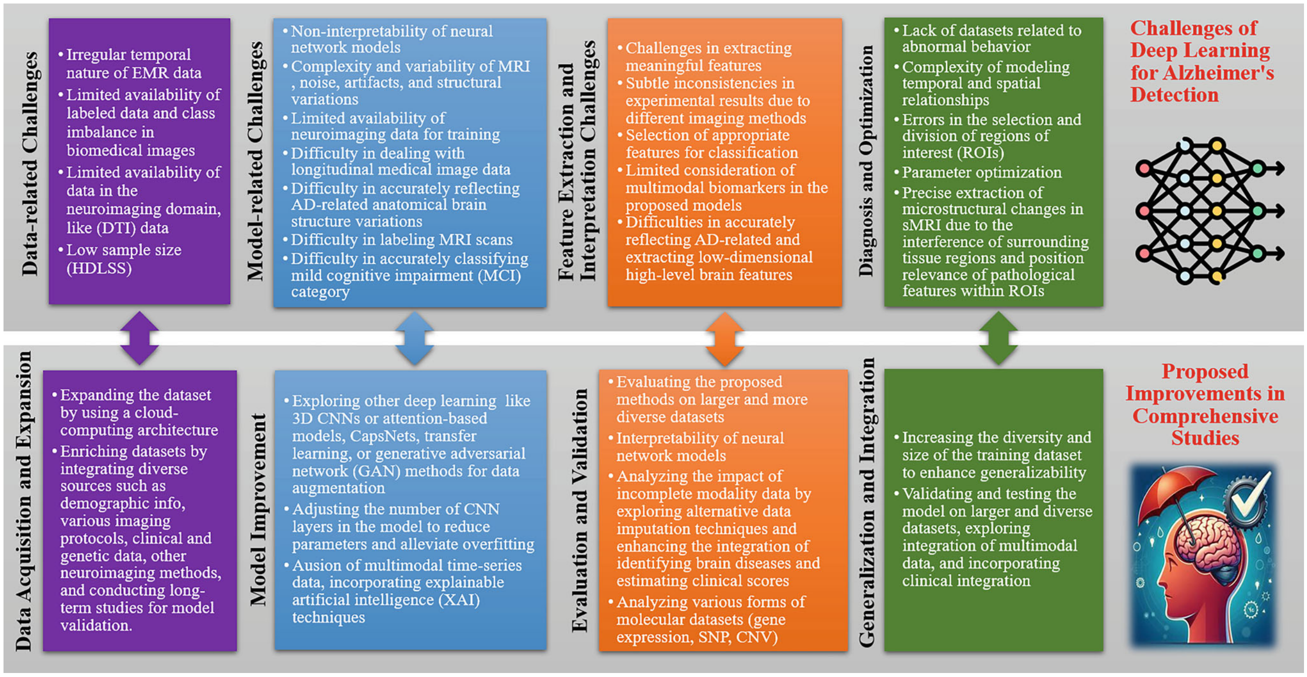

Fig. 6 Navigating challenges and solutions in deep learning for Alzheimer's detection: data, models, features, and diagnosis optimization

briefly explains the different GAN methods mentioned in Table 4. Conditional generative adversarial network (cGAN) [24] for generating 3D MR brain images: This method utilizes a cGAN model to generate high-quality 3D magnetic resonance (MR) brain images by conditioning the generator on target conditions, such as different stages of Alzheimer's disease (AD). Such synthesized 3D MR brain images are instrumental in augmenting datasets for deeper research and provide valuable insights for medical professionals in understanding the progression of Alzheimer's disease at various stages, thereby enhancing diagnostic accuracy and treatment planning. Time-attention long short-term memory (TA-LSTM) [25] network: This model is designed to classify multivariate time series data obtained from dynamic functional network connectivity (dFNC) estimated from resting-state functional magnetic resonance imaging (rs-fMRI) for assessing clinical progression from subjective cognitive decline to (MCI). The TA-LSTM network's capability to effectively process and interpret complex temporal patterns in rs-fMRI data is pivotal in identifying subtle changes in brain function, thus offering a promising tool for early detection of mild cognitive impairment and monitoring its transition to more advanced stages of cognitive decline. Visually Attributed Abnormal-to-Normal Translation Generative Adversarial Network (VANT-GAN) [26]: VANT-GAN is a strategy for visual attribution in medical imaging. It performs unsupervised abnormal-to-normal mapping using the cycle-consistency principle of generative adversarial networks (GANs) to capture disease-related evidence in medical images. This approach enables clinicians and researchers to distinguish and understand the specific abnormalities associated with disvisually eases in medical images, greatly aiding in the accurate diagnosis and in-depth study of pathological features, particularly in complex cases where conventional imaging techniques may fall short.

Multi-level guided generative adversarial network (MLG-GAN) [27] with multimodal transformer network (Mul-T): MLG-GAN utilizes a multimodal transformer network (Mul-T) to guide the generation of realistic and diverse brain images for Alzheimer's disease detection. It combines the power of GANs with transformer-based models for improved performance. This integration of GANs with transformer technology in MLG-GAN allows for a more nuanced and detailed analysis of brain images, significantly enhancing the accuracy of Alzheimer's disease detection and providing deeper insights into its neural correlates through the synthesis of high-quality, varied imaging data.

Brain slice generative adversarial network for Alzheimer's disease detection (BSGAN-ADD) [28]: BSGAN-ADD is an integrated framework that combines GAN-based image enhancement with a CNN-based Alzheimer's disease (AD) detection model. It leverages the strengths of both approaches to improve the accuracy of AD detection. By enhancing image quality and utilizing advanced convolutional neural network (CNN) techniques, BSGAN-ADD significantly increases the reliability and precision of Alzheimer's disease detection, offering a powerful tool for early diagnosis and

Table 4 Comparing GAN methods based on evaluation criteria, method innovation, data and modeling challenges, and proposed solutions

References	Model	Result	Innovation	Challenges	Proposed improvement
[24]	cGAN for generating 3D MR	Outperforms previous methods in image quality and generation performance, Smooth and realistic 3D image	Prediction of brain status at intermediate AD stages, Incorporation of 3D discriminator, adaptive identity loss	Discontinuities and inconsistent transformations in 2D-based methods, Computational requirements for full-size 3D space	Adjust regression weight for enhanced image quality, further comparisons, statistical analysis, ablation studies
[25]	TA-LSTM network, TEAM	AUC in Modality MRI + PET got 0.838	TA-LSTM model for analyzing rs-fMRI data, TEAM framework for gradient-based interpretation	Prediction of qMCI progression in patients, Identifying imaging-based biomarkers, Analyzing and interpreting rs-fMRI data	Use windowless wavelet-based dFNC (WWdFNC), Enhanced temporal and spectral resolution
[26]	VANT-GAN	IoU Score: 91.4, Dice Score: 94 (BraTS dataset)	Approach to visual attribution without pixel-level ground-truth labeling, Leveraging abnormal to normal mapping and discrepancy maps	Limited availability of pixel-level ground-truth labeling, Focus on salient regions in existing interpretation methods	Constrain abnormal-to-normal image translation function, Generate normal counterparts to guide translation
[27]	MLG-GAN, Mul-T	Accuracy: 94.4% (AD vs CN), 77.8% (pMCI vs sMCI) on ADNI-2 trained on ADNI-1	Comprehensive framework for incomplete image generation and disease diagnosis, voxel-level, feature-level, and task-level constraints	Handling incomplete multimodal brain images, Utilizing full potential of multimodality, Properly integrating missing data for accurate diagnosis	Explore additional modalities for enhanced analysis, Incorporate functional MRI and diffusion tensor imaging
[28]	BSGAN-ADD	Accuracy: 0.986 (ADNI), 0.983 (OASIS)	Combination of GAN-based image enhancement and CNN-based AD detection, integration of disease category feedback, extraction of representative high-level brain features	Difficulty in accurately reflecting AD-related anatomical brain structure variations, extraction of low-dimensional high-level features	Explore larger and diverse datasets, optimize model architecture, refine training process
[29]	GAN, ROI mask, ROI loss	MMSE: 2.8040, ADAS-cog: 3.4358	Integration of regression model and GAN for multi-view prediction, Concurrent prediction of cognitive score and MRI volume	Lack of exploration of intra-correlation between cognitive score and MRI prediction	Incorporate additional clinical and demographic features

aiding clinicians in making more informed treatment decisions.

Integrated framework combining regression model and generative adversarial network (GAN) [29] with region-of-interest (ROI) mask and ROI loss: This framework integrates a regression model and GAN for medical image analysis. It incorporates a region-of-interest (ROI) mask and ROI loss to focus on specific regions of interest and improve the accuracy of the analysis. Figure 7 illustrates the challenges encountered in using GANs for Alzheimer's diagnosis along with their corresponding solutions.

3.2.2 3D Deep learning models

3D deep learning models are neural network architectures specifically designed to process and analyze three-dimensional data, such as medical images. These models are tailored to handle the spatial and volumetric nature of 3D data and extract meaningful features for tasks like predicting Alzheimer's disease and (MCI). Various types of 3D deep learning methods are mentioned in the research related to this topic. The first method is the 3D hemisphere-based convolutional neural network (CNN) [30], which segments whole-brain MRI by considering each hemisphere as an independent sample. The second method is the (2 + 1)D CNN [31], which classifies Alzheimer's disease and MCI based on structural MRI using separate spatial and temporal dimensions. The third method is the multimodal 3D CNN framework [32], which predicts MCI by integrating multi-level features obtained through attention mechanisms and spatial pyramid pooling. Lastly, the hybrid multimodal deep learning framework combines a 3D CNN and a bidirectional recurrent neural network (BRNN) [9] to predict Alzheimer's progression using longitudinal MRIs, cognitive scores, and demographic features. Figure 8 provides a summary of the challenges and corresponding solutions in utilizing 3D deep learning models for Alzheimer's diagnosis. Table 5 briefly describes the comparison between three-dimensional deep learning models, focusing on evaluation criteria, method innovation, data and modeling challenges, and proposed solutions.

3.2.3 Graph convolutional networks

1. Two-task graph convolutional network (2 T-GCN) [33] for skeleton-based human action evaluation in Alzheimer's progression: the network constructs a skeleton graph to represent the data and uses deep learning techniques for accurate abnormality detection and action evaluation.
2. The implementation model, hi-GCN [34], is a hierarchical graph convolution network for learning graph embeddings of brain networks and predicting brain disorders. It considers network topology and subject association in the learning process.
3. A multi-view graph convolution network (MVS-GCN) [35] is an implementation model for autism spectrum disorder diagnosis. It combines graph structure learning and multi-task graph embedding learning to improve classification performance and interpretability.
4. The proposed multi-model fusion framework [36] for Alzheimer's disease prediction utilizes a spectral graph attention model and adaptive fusion to enhance prediction accuracy.
5. The paper presents a characteristic information aggregation hypergraph convolutional network (CIA-HGCN) [11] for imaging genetics data fusion. CIA-HGCN utilizes hypergraphs to model high-order associations and improve interpretability.
6. A graph neural network (GNN) [37] framework is proposed for dementia analysis from functional connectivity networks. It combines deep learning, self-attention, and feature selection methods to improve diagnostic performance and interpretability.
7. A template-based graph registration network (GRN) [38] enhances the diagnosis of brain connectivity disorders. It uses a generative adversarial network to register brain graphs to a population-driven template, improving prediction accuracy.
8. A multi-view graph normalizer network (MGN-Net) [39] is a graph neural network-based method for integrating heterogeneous biological network populations. It normalizes and integrates multiple biological networks into a single connectional template.
9. Edge-variational graph convolutional network [40] is used for population-based disease prediction. The framework automatically learns to build a population graph with variational edges, incorporating imaging and non-imaging data for improved diagnostic quality. Three graph convolutional networks have some similarity, while their key differences lie in the specific tasks they address and the approaches they employ:

GCNs [37] focus on skeleton-based human action evaluation, detecting abnormalities, and evaluating the quality of human actions.

hi-GCN [34] is designed for graph embedding learning of brain networks and predicting brain disorders, considering network topology and subject association.

MVS-GCN [35] aims to improve classification performance and interpretability in diagnosing autism spectrum disorder, combining graph structure learning and multi-task graph embedding learning.

Compared to other machine learning methods, such as traditional statistical models or shallow neural networks, these

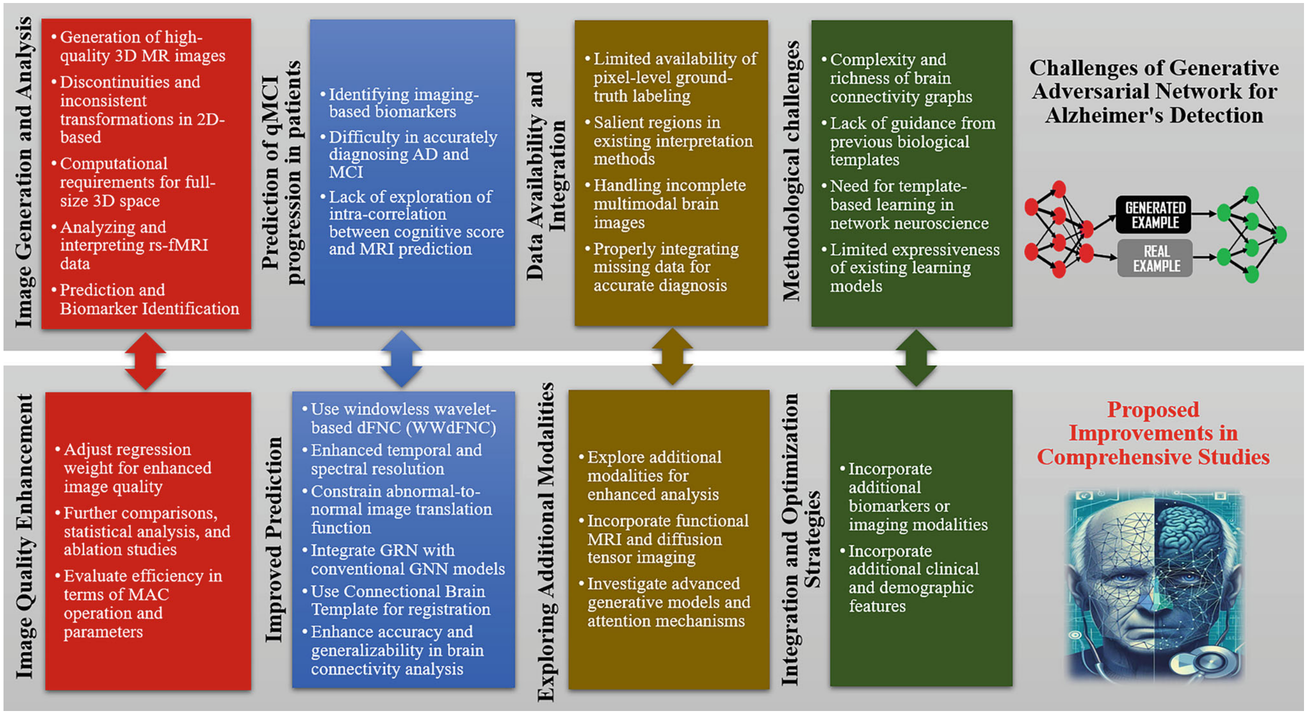

Fig. 7 navigating challenges and solutions in GAN for Alzheimer's detection: image generation, prediction models, data availability, and methodological optimization

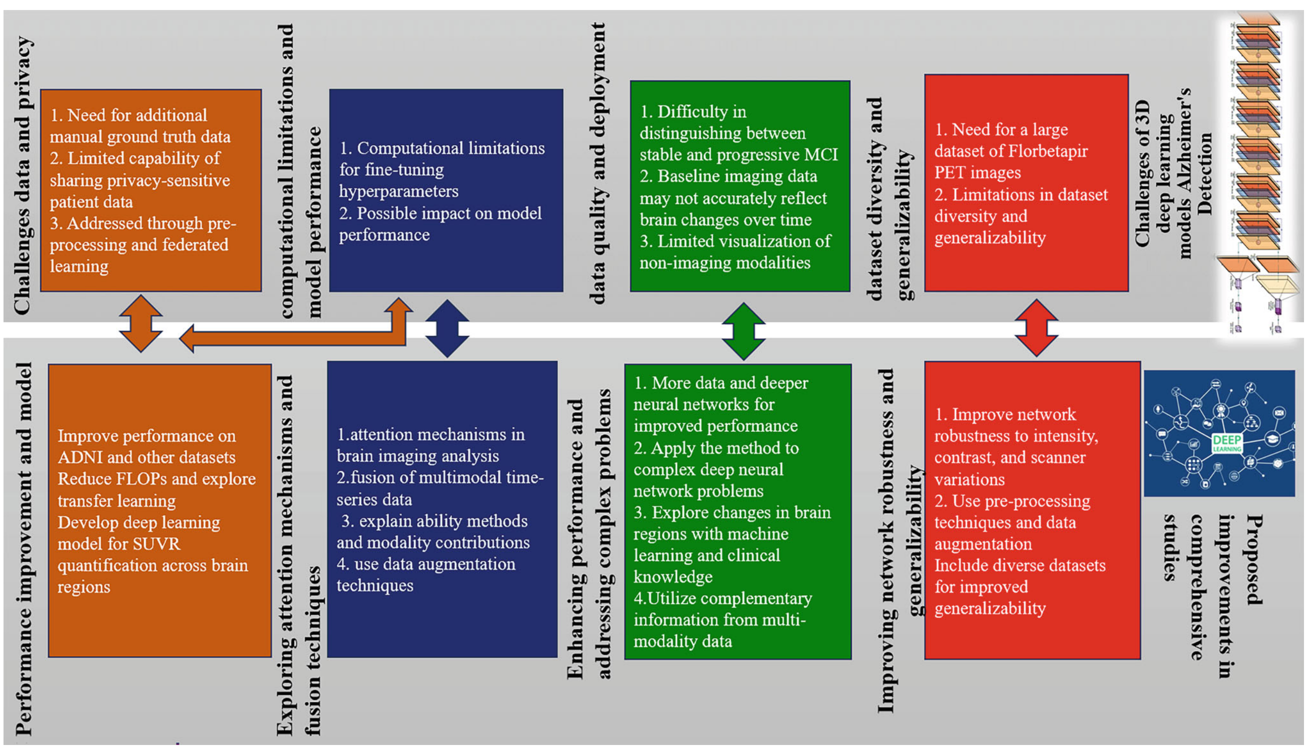

Fig. 8 Navigating challenges and solutions 3D deep learning models for Alzheimer's detection: data privacy, models computational, data qualitied, and data diversity

Table 5 Comparing 3D deep learning models based on evaluation criteria, method innovation, data and modeling challenges, and proposed solutions

References	Model	Result	Innovation	Challenges	Proposed improvement
[30]	Hemisphere-based CNN for whole-brain MRI segmentation	DSC: 0.836, Outperforms patch-based CNN, comparable to other CNN methods	Hemisphere-based, treats each hemisphere as independent, doubles training samples, reduces memory usage	Need for additional manual ground truth data, limited capability of sharing privacy-sensitive patient data	Improve network robustness to intensity contrast and scanner variations
[31]	(2 + 1)D CNN for AD and MCI classification	Average AUC score: 0.85, validation accuracy: 0.78	(2 + 1)D CNN handles spatial and temporal dimensions separately, Improved accuracy and AUC score, faster training	Computational limitations for finetuning hyperparameters	More data and deeper neural networks for improved performance
[32]	End-to-end multimodal 3D CNN framework based on ResNet	Average accuracy: 94.61% (AD diagnosis), 77.19% (MCI)	Integration of multi-level features with attention mechanisms, Twin-based network for multimodality image feature	Difficulty in distinguishing between stable and progressive MCI	Utilize complementary information from multimodality data
[90]	Attention-based 3D CNN	RMSE: 0.0362, MAE: 0.026 (ADNI); RMSE: 0.058, MAE: 0.044 (A4 study)	Attention mechanisms improve accuracy and consider entire scan volume	Need for a large dataset of Florbetapir PET images, Limitations in dataset diversity and generalizability	Reduce FLOPs, transfer learning, develop deep learning model for SUVR quantification across brain regions
[9]	3D-CNN-BRNN	Accuracy: 96%, Precision: 99%, Recall: 92%, AUC: 96% (AD progression prediction)	Utilization of multimodal data (longitudinal MRI, biomarkers, demographics), Novel explainability approach for intuitive and interpretable decision-making visualization	Parameter optimization, availability of longitudinal data, compatibility with other datasets	Fusion of multimodal time series data, XAI techniques incorporating demographics and biomarkers, data augmentation techniques

graph convolutional network models have the advantage of explicitly modeling the graph structure and capturing complex relationships between brain regions or human actions. This allows them to leverage the inherent connectivity and spatial information present in the data. Traditional methods may not be able to effectively capture such complex relationships, making graph convolutional networks particularly suited for tasks involving graph-structured data like brain networks. Figure 9 depicts a diagram illustrating the challenges and solutions in graph convolutional networks for Alzheimer's diagnosis. The diagram encompasses aspects such as data, models, features, and optimization strategies for diagnosis. Table 6 provides a summary of the comparison in graph convolution networks, considering evaluation criteria, method innovation, data and modeling challenges, and proposed solutions. It offers a comprehensive overview of the different aspects related to graph convolution networks in the context of the study.

3.3 Miscellaneous methods

Manifold learning models are mathematical techniques that analyze and represent high-dimensional data in a lower-dimensional space while preserving the intrinsic structure and relationships of the data. These models have significant applications in predicting AD by extracting meaningful features or biomarkers from medical imaging datasets. Four types of manifold learning methods are discussed in this context:

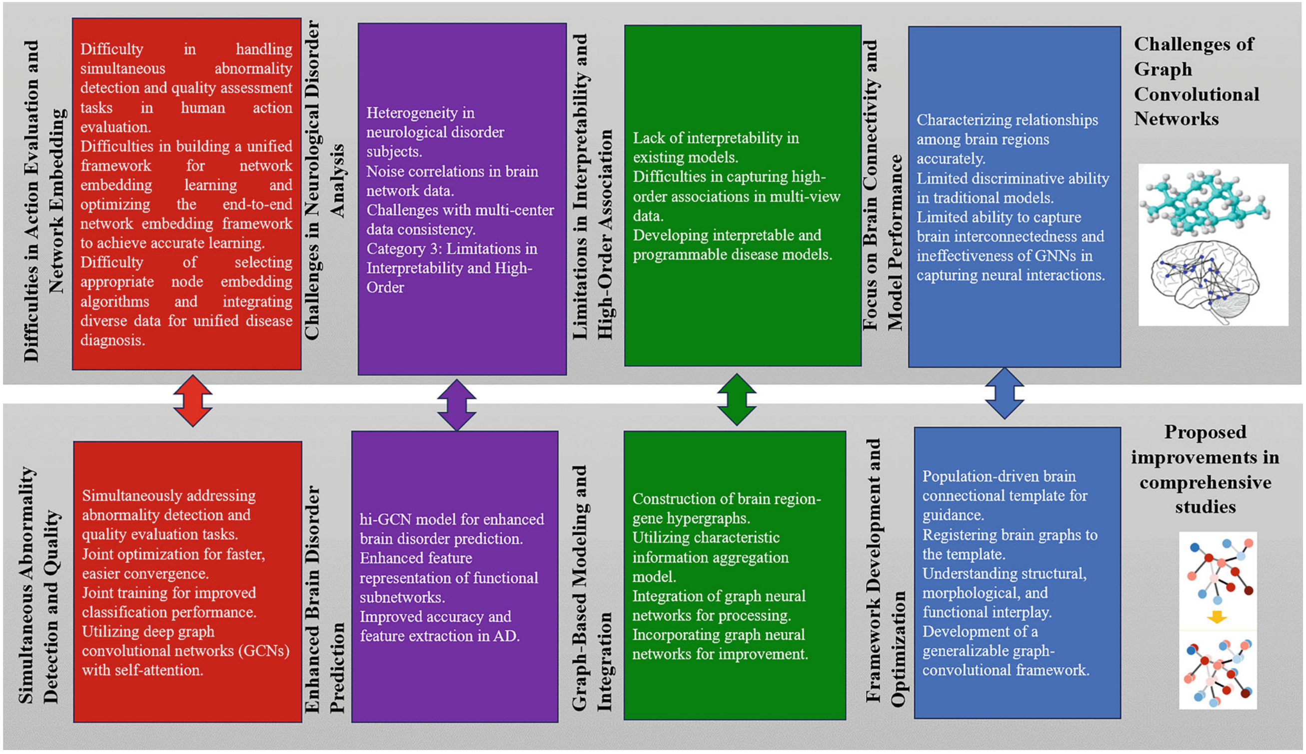

Fig. 9 Challenges and solutions graph convolutional networks for Alzheimer's detection: networks, disorder analysis, interpretability, and model performance

a. Group-constrained manifold learning for AD risk assessment: The model [41]: This approach integrates preexisting grouping information to enhance the estimation of the underlying structure in high-dimensional medical imaging datasets. It adapts the Laplacian eigenmaps and isomap algorithms to integrate group constraints, enabling the creation of longitudinal biomarkers for evaluating an individual's likelihood of developing Alzheimer's disease (AD).
b. Manifold modeling for brain population analysis: The learning model learns a low-dimensional, nonlinear manifold that approximates the space spanned by a set of brain images. The manifold model is generative, allowing the construction of new brain images from a small set of parameters. The manifold coordinates can be used for statistical analysis of the population [42].
c. Nonlinear dimensionality reduction combining MR imaging with non-imaging information: This framework integrates subject-specific meta-information within the manifold learning stage, enhancing a similarity measure derived from pairwise image similarities. It facilitates the creation of a unified representation that encompasses both. Imaging and non-imaging measurements, aiming to enhance data analysis and visualization capabilities [43]. A method for feature selection in Alzheimer's disease (AD) diagnosis that incorporates relational regularization for simultaneous regression and classification tasks: The proposed method [44] introduces a sparse multi-task learning framework that incorporates relational information in AD diagnosis. It preserves feature-feature, response-response, and sample-sample relations to enhance similarity. The objective function includes these relational characteristics and an (l2,1)-norm regularization term. The dimension-reduced data is used to train support vector regression and classification models for predicting clinical scores and determining clinical labels. Figure 10 presents a summary of the challenges and solutions in manifold learning for Alzheimer's diagnosis. It highlights the data, models, features, and diagnosis optimization aspects associated with manifold learning techniques in the context of Alzheimer's diagnosis. Table 7 provides a comprehensive summary of the comparison of manifold learning methods for Alzheimer's diagnosis. It highlights various aspects, including evaluation criteria, method innovation, data and modeling challenges, and proposed solutions, allowing for a thorough understanding of the different approaches in the context of Alzheimer's diagnosis.

Table 6 Comparing graph convolutional networks based on evaluation criteria, method innovation, data and modeling challenges, and proposed solutions

References	Model	Result	Innovation	Challenges	Proposed improvement
[33]	Two-Task Graph convolutional Network (2 T-GCN)	Numerical scores correlate with clinical assessment of AD severity	2 T-GCN, Comprehensive Human Action Assessment, Disease Monitoring	Handling simultaneous abnormality detection and quality assessment tasks	Address abnormality detection and quality evaluation tasks simultaneously
[34]	Hierarchical Graph Convolution Network (hi-GCN)	Average accuracies: 73.1%, 78.5%; AUC: 82.3%, 86.5% (ABIDE, ADNI)	Hierarchical graph embedding, Improved brain network analysis, Fusion of network topology and subject association	Building a unified framework for network embedding learning, Optimizing the end-to-end network embedding framework	Enhanced brain disorder prediction, Hierarchical perspective, Joint optimization for faster convergence
[35]	Multi-view graph convolutional neural network (MVS-GCN)	Average accuracy/AUC: 69.38%/69.01%	Graph structure learning, Multi-task graph embedding learning	Heterogeneity in neurological disorder subjects, Noise correlations in brain network data, Lack of interpretability in existing models, Multi-center data consistency	Multi-view graph embedding for heterogeneity, Enhanced feature representation of functional subnetworks
[36]	Multi-model fusion framework	ACC: 92.80 ± 0.92 (Tadpole), 84.0 (Cora), 72.9 (Citeseer), 80.6 (PubMed)	Integration of multiple models, Spectral graph attention, Bilinear aggregation	Selecting appropriate node embedding algorithms, Integrating diverse data for unified diagnosis	Adaptive fusion module for dynamic integration, Overcoming limitations of single-model methods
[11]	Characteristic Information Aggregation Hypergraph Convolutional Network (CIA-HGCN)	Accuracy: 88.3%	Hypergraph structural information, Addressing black-box nature, Fusion of multi-view information	Integration of macroscopic and microscopic disease manifestations, Limitations of traditional correlation analysis methods, Capturing high-order associations in multi-view data	Construction of brain region-gene hypergraphs, Integration of graph neural networks
[37]	Graph neural network framework (GCNs)	AUC: 89.24 ± 3.44 (OCD), 87.22 ± 2.83 (FTD)	Deep learning techniques, Self-attention mechanisms, Feature selection methods for dementia analysis	Characterizing relationships among brain regions accurately, Limited discriminative ability in traditional models	Iteratively updating graph structure to understand disease attributes

3.4 Biomarker discovery and feature extraction and neuroscience

The models and methods play a crucial role in integrating information from multiple modalities to improve the accuracy of diagnosis and risk assessment.

1. Group-constrained manifold learning [45]: This is an implementation model that incorporates a-priori grouping knowledge of the data to improve the low-dimensional representation of high-dimensional medical imaging datasets. The model includes the modification of the Laplacian eigenmaps and isomap manifold learning algorithms to incorporate group constraints. This

Table 6 (continued)

References	Model	Result	Innovation	Challenges	Proposed improvement
[38]	Template-based graph registration network (GRN)	Boosted prediction accuracy of four conventional GNN models across four neurological datasets	Template-based graph registration, Conventional graph neural networks for brain connectivity disorder diagnosis	Limited ability to capture brain interconnectedness, Ineffectiveness of GNNs in capturing neural interactions, GNN training without guidance from biological templates	Population-driven brain connectional template, Registering brain graphs to the template, Improved connectivity pattern capture
[39]	Multi-view graph normalizer network (MGN-Net)	Average accuracy: 74.23 (σ 2. 91), 54.05 (σ 1. 19), 56.26 (σ 0. 58), 58.13 (σ 1. 05)	Data-driven approach for integral connectional fingerprint, Disentangling typical from atypical variations across population samples	Large variability in connectivity across individuals, need for normalization to reduce inter-subject variability, identifying pathological alterations in brain networks, integrating multimodal connect data	Enhance MGN-Net with deep learning techniques, improve normalization and integration processes, Understand structural, morphological, and functional interplay
[40]	Graph convolutional framework (EV-GCN)	Accuracy: 79.40 (ADNI), 87.79 (TADPOLE), 87.03 (ODIR)	Automatic learning of a population graph, Variational edges enhancing representation learning, Integration of non-imaging data for associations	Integrating diverse modalities for enhanced diagnosis, unifying different data types, Constructing a population graph manually, Automating population graph construction	Develop a generalizable graph convolutional framework, conduct a comprehensive ablation study, Extend framework for multimodal data leverage

approach aims to generate longitudinal biomarkers for assessing the risk of developing AD and estimating time-to-conversion (TTC) and the mini mental state examination (MMSE) of subjects who develop AD. The key innovation of this model is the incorporation of grouping knowledge into manifold learning algorithms, which addresses the limitations of traditional techniques that neglect grouping information. The challenge addressed is capturing temporal relationships and correlations within longitudinal medical imaging datasets.

2. Multimodal fusion in neuroimaging combines data from multiple imaging modalities to overcome the limitations of individual modalities. Neuroimaging fusion can achieve higher temporal and spatial resolution, enhance contrast, correct imaging distortions, and bridge physiological and cognitive information. The most widely used imaging modalities in neuroimaging are magnetic resonance imaging (MRI), computerized tomography (CT), positron emission tomography (PET), and single-photon emission computed tomography (SPECT).Individual imaging modalities provide complementary information on anatomical structure, pathophysiology, metabolism, structural connectivity, and functional connectivity. The authors in [46] analyzed over 450 references covering current challenges in multimodal fusion, medical applications of fusion for specific neurological diseases, strengths and limitations of imaging modalities, fundamental fusion rules, fusion quality assessment methods, and applications of fusion for atlas-based segmentation and quantification.
3. Multiclass classification framework [47]: This implementation model proposes a novel multiclass classification framework for Alzheimer's disease diagnosis using multimodal neuroimaging. The framework integrates embedding feature selection and fusion techniques. It employs regularization terms and multiple kernels learning to select features across all classes

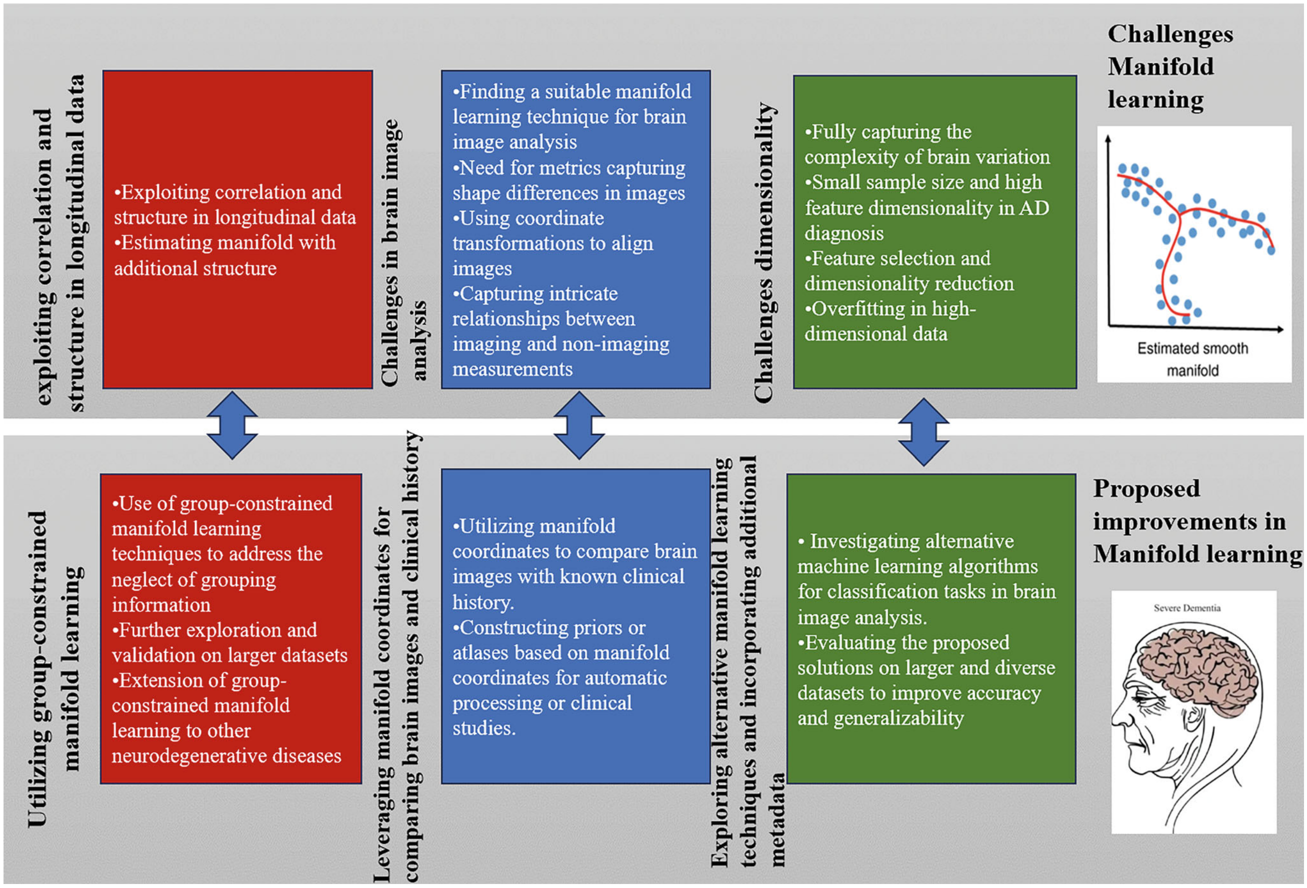

Fig. 10 Challenges and solutions Manifold learning for Alzheimer's detection: exploiting correlation, brain image analysis, dimensionality

and exploit complementary modalities. The innovation lies in the combination of feature selection and fusion techniques and the incorporation of regularization terms for improved classification accuracy. The challenge addressed is the accurate diagnosis of Alzheimer's disease and (MCI) using reliable biomarkers and robust machine learning methods. The potential improvement in this model includes exploring advanced feature selection methods and incorporating additional neuroimaging data and clinical information. The paper [48] focuses on the development of a robust ensemble deep learning model for the detection of Alzheimer's disease (AD) progression based on multimodal time series data. The proposed model combines a stacked convolutional neural network (CNN) and a bidirectional long short-term memory (BiLSTM) network to extract local and longitudinal features from different modalities. The model predicts multiple variables, including AD multiclass progression task and four critical cognitive scores regression tasks.

These methods [45–48] share the goal of leveraging multimodal data to improve Alzheimer's disease diagnosis and risk assessment. They all involve integrating information from multiple sources, such as medical imaging datasets, to capture meaningful patterns and correlations. The key differences lie in the specific techniques employed and the focus of each method. Group-constrained manifold learning focuses on incorporating grouping knowledge into manifold learning algorithms. Manifold learning aims to build efficient representations of brain images using a generative manifold model. The multiclass classification framework combines feature selection and fusion techniques with regularization terms and multiple kernel learning. Compared to other machine learning methods, the methods described in the document have a specific focus on multimodal data fusion, addressing the challenges associated with Alzheimer's disease diagnosis. These methods consider the temporal relationships, correlations, and grouping information present in the data, which are important factors in capturing the underlying disease progression. Traditional machine learning methods may not effectively utilize such information and may result in suboptimal results. Figure 11 presents the challenges and corresponding solutions in multimodal data fusion for Alzheimer's diagnosis. It encompasses aspects such as data integration, models, features, and optimization strategies for improving the accuracy and effectiveness of

Table 7 Comparing manifold learning based on evaluation criteria, method innovation, data and modeling challenges, and proposed solutions

References	Model	Result	Innovation	Challenges	Proposed improvement
[41]	Group-constrained manifold learning for AD risk assessment	Improved estimation of TTC and MMSE, 16% improvement in kNN estimation of TTC, 6% improvement in MMSE on ADNI	Incorporation of group constraints in manifold learning, Improved low-dimensional representation for better disease progression estimation and risk assessment	Neglect of grouping information in traditional techniques, exploiting correlation and structure in longitudinal data, Estimating manifold with additional structure	Use of group-constrained manifold learning, Further exploration and validation on larger datasets, Extension to other neurodegenerative diseases
[42]	Learning a low-dimensional nonlinear manifold from a dataset	Regression models show manifold model is statistically significant descriptor of clinical parameters	Geometric fit assessed qualitatively/quantitatively, Explains clinical measures, statistically significant descriptor of parameter	Finding suitable manifold learning technique for brain image analysis, need for metrics capturing shape differences in images, using coordinate transformations to align images	Utilizing manifold coordinates for comparing brain images and known clinical history, Constructing priors or atlases for automatic processing or clinical studies
[43]	Framework for biomarker extraction from low-dimensional brain image manifolds	Accuracy on 9 methods: AD vs. CN 88% (E-LE: Ab1 42, hippo vol. ApoE), 69% (P-MCI vs. S-MCI), 87% (P-MCI vs. CN)	Combines manifold learning with subject meta-information for biomarker extraction, Extends Laplacian Eigenmap objective function for comprehensive analysis, Provides a unified representation for data analysis and visualization	Complex and high-dimensional nature of brain image data, Capturing intricate relationships between imaging and non-imaging measurements, fully capturing complexity of brain variation	Explore other manifold learning techniques, Incorporate additional metadata, Investigate alternative machine learning algorithms for classification, Evaluate larger and diverse datasets for improved accuracy and generalizability
[44]	Sparse multi-task learning framework for joint regression and classification in AD diagnosis	Regression with MRI for AD vs. NC: Best CCs: 0.669 (ADAS-Cog), 0.679 (MMSE); Best RMSEs: 4.43 (ADAS-Cog), 1.79 (MMSE). Regression with MRI for MCI vs. NC: Best CCs: 0.472 (ADAS-Cog), 0.50 (MMSE); Best RMSEs: 4.23 (ADAS-Cog), 1.63 (MMSE)	Incorporation of relational information into feature selection for AD diagnosis, Consideration of relationships between features, response variables, and samples, Capture of underlying structure and selection of informative features	Small sample size and high feature dimensionality in AD diagnosis, Feature selection and dimensionality reduction, Overfitting in high-dimensional data	

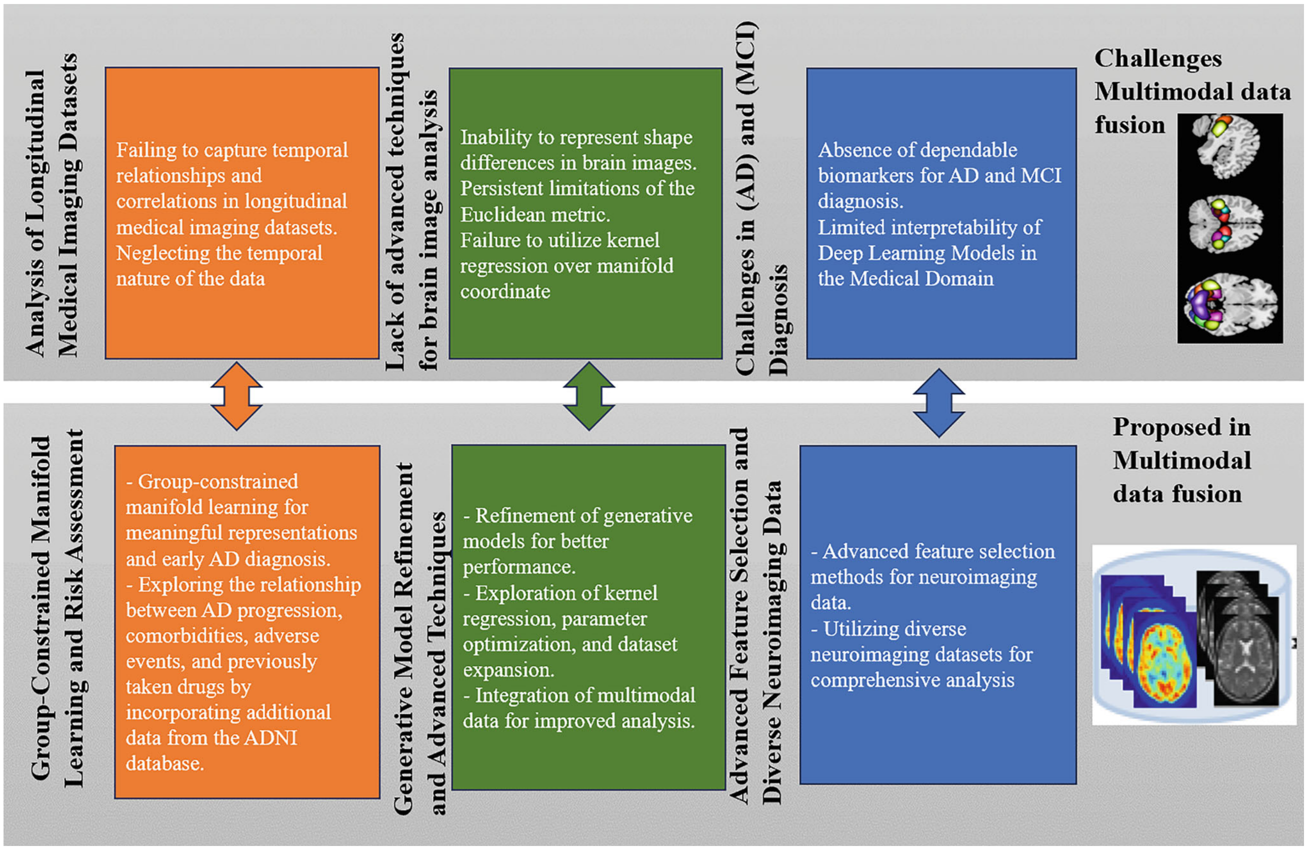

Fig. 11 Challenges and solutions multimodal data fusion for Alzheimer's detection: features, analysis and misdiagnosis

Alzheimer's diagnosis through the fusion of multiple data modalities. Table 8 provides a comprehensive comparison of multimodal data integration methods for Alzheimer's diagnosis. It includes evaluation criteria, method innovation, data and modeling challenges, and proposed solutions. The table serves as a valuable resource for understanding and comparing different approaches to multimodal data integration in the context of Alzheimer's diagnosis.

3.5 Multi-task learning

Multi-task learning is a machine learning approach that aims to improve the performance of multiple related tasks by jointly learning from them. In the context of Alzheimer's prediction, multi-task learning allows for the integration of various cognitive measures and imaging data to enhance the accuracy of predictions.

The multi-task learning models mentioned include:

1.Sparse Shared Structure-based Multi-task Learning for Alzheimer's Disease Prediction [49]:

- Incorporates a mixed norm and sparse shared structure-based multi-task learning for predicting cognitive performance in Alzheimer's disease.
- Considers implicit shared subspace structure, explicit subset of features, and region of interests (ROIs) simultaneously.

2.Deep recurrent neural network for Alzheimer's disease progression modeling [50]:

It utilizes longitudinal data and deep recurrent neural networks to model the progression of Alzheimer's disease and addresses challenges of missing features and small sample size by adaptive imputation and leveraging correlations among different prediction tasks.

3. A multi-task learning approach for Alzheimer's disease (AD) prediction that leverages dual feature correlation guidance [51]:

- Exploits task and feature correlation structures to improve the accuracy of predicting cognitive scores and identifying reliable biomarkers.
- Applies a feature-aware sparsity-inducing norm (FAS-norm) penalty and the alternating direction method of multipliers (ADMM) algorithm for effective implementation.

Table 8 Comparing multimodal data fusion based on evaluation criteria, method innovation, data and modeling challenges, and proposed solutions

References	Model	Result	Innovation	Challenges	Proposed improvement
[45]	Group-constrained manifold learning for AD risk assessment	Improved kNN estimation of TTC and MMSE by approximately 16% and 6% respectively	Incorporation of a-priori grouping knowledge into manifold learning algorithms to improve risk assessment and AD progression prediction	Capturing temporal relationships and correlations in longitudinal medical imaging datasets, Effectively utilizing grouping information, Considering the temporal nature of the data	Group-constrained manifold learning, Risk assessment, Meaningful representations, Early AD diagnosis
[46]	Multimodal fusion in neuroimaging combines data from multiple imaging modalities	Comprehensive analysis of over 450 references, Highlighting challenges and benefits of multimodal fusion in neuroimaging for clinical diagnosis and neuroscience research	Discusses fusion rules, quality assessment methods, specific medical applications	Representing shape differences in brain images, Overcoming limitations of the Euclidean metric, Using kernel regression over manifold coordinates	Investigate Generative model refinement, Kernel regression exploration, Parameter optimization, Dataset expansion, Multimodal integration
[47]	Multiclass support vector machine as the basic classifier framework for AD diagnosis	Promising performance in multiclass AD diagnosis, Accurate classification using T1, T2, T3, T4 multimodal neuroimaging compared to 8 other models	Combination of embedding feature selection and fusion techniques, l21-norm regularization for feature selection, lp-norm regularization for multiple kernel learning, Theorem-based optimization, Convergence proof	Lack of AD and MCI diagnosis using reliable biomarkers	Advanced feature selection, Diverse neuroimaging data
[48]	Multimodal multitask model combining stacked CNN and BiLSTM network	ADNI accuracy: 92.62%, Average F1-score: 92.56%	Stacked CNN-BiLSTM architecture to capture both local and temporal features from time series data	Interpretability of deep learning models in the medical domain	Explore relationship between AD progression and comorbidities, adverse events, and previously taken drugs by incorporating additional data from the ADNI database

4. Multi-task Learning for Alzheimer's Disease Cognitive Score Prediction [52]:

A framework called bi-graph guided self-paced multi-task feature learning (BGP-MTFL) designed to enhance the prediction of cognitive scores. It considers relationships among multiple tasks and incorporates correlation regularization for features and tasks.

5. Multi-task Learning for Survival Analysis with Multi-source Block-wise Missing Data [53]: MSAMB framework for survival analysis in multi-source data with block-wise missing data uses a two-layer multi-task learning framework and partition method to address the missing data challenge.

6. Joint Multi-task Learning for Early Alzheimer's Disease Identification [54]:

It integrates functional and structural brain networks for joint multi-task learning in early Alzheimer's disease identification and combines low-rank self-calibrated functional brain networks with structural brain networks.

7. Auto-weighted Centralized Multi-task Learning for Subjective Cognitive Decline Diagnosis [55]:

- Auto-weighted centralized multi-task learning framework for diagnosing subjective cognitive decline and mild cognitive impairment.
- Integrates functional and structural connectivity information from MRI using a multi-task learning algorithm. Compared to other machine learning methods, multi-task learning models have the advantage of jointly learning from multiple related tasks, which can lead to improved prediction performance compared to learning each task separately. In contrast, traditional machine learning methods typically focus on learning from a single task or dataset. Multi-task learning models also have the ability to incorporate task-specific and shared information, allowing for better integration of heterogeneous data types. Additionally, multi-task learning models can handle missing data and capture correlations among tasks, which are important considerations in Alzheimer's prediction. Figure 12 summarizes the challenges and corresponding solutions in multi-task learning models for Alzheimer's diagnosis. It highlights the key aspects related to data, models, features, and diagnosis optimization, providing a comprehensive overview of the challenges and proposed solutions in this field. Table 9 presents a comparison of papers related to multi-task learning models in the context of Alzheimer's diagnosis. It compares the papers based on the aforementioned criteria, including evaluation criteria, method innovation, data and modeling challenges, and proposed solutions.

3.6 Neuroimaging

3.6.1 Functional magnetic resonance imaging (fMRI) modeling

FMRI models are computational approaches used to analyze and interpret fMRI data. fMRI captures variations in cerebral blood flow and oxygenation levels, enabling examining brain activity and connectivity patterns. Models based on fMRI data strive to elucidate the association between brain function and cognitive processes and also aim to forecast and diagnose neurological disorders like Alzheimer's disease.

1. Interpretable long short-term memory (LSTM) [56] model for cognitive impairment: It utilizes a time-attention LSTM network to analyze dynamic functional network connectivity derived from rs-fMRI, enabling the prediction of cognitive deterioration or recovery.
2. Sparse brain network construction with regularization using weighted graphs [57]: It presents a model using rs-fMRI data to construct brain functional networks for (MCI) identification, incorporating weighted graph Laplacian regularization and addressing convergence issues.
3. MSE-GCN framework [58] is a multi-scale enhanced graph convolutional network. The framework is designed for the detection of (MCI) and combines structural and functional information from (DTI) and resting-state functional MRI (rs-fMRI), respectively. It utilizes locally weighted clustering coefficients and parallel (GCN) layers to integrate the two data types.
4. This paper introduces a graph convolution network (GCN) [59] model incorporating similarity awareness and adaptive calibration to predict disease-induced deterioration. The model takes into account imaging similarity, disease status, and the fusion of functional MRI (fMRI) and diffusion tensor imaging (DTI) information.
5. Alzheimer's disease detection using C3d-LSTM [60]: It implements the C3d-LSTM model by combining 3D CNN and LSTM for processing 4D fMRI data, capturing spatial and temporal features to detect Alzheimer's disease.
6. Weighted correlation kernels in CNNs for brain disease diagnosis [61]: It introduces wc-kernel and wck-CNN framework for functional connectivity-based brain disease diagnosis, learning correlation weights between brain regions and extracting local, global, and temporal features from fMRI data.
7. Spatio-temporal directed acyclic graph learning with attention mechanisms [62]: ST-DAG-Att combines ST-graph-conv and FC-conv networks to predict cognition and disease using fMRI data. The framework captures spatial, temporal, and functional connectivity features by incorporating a functional connectivity-based spatial attention component. This approach enables spatio-temporal directed acyclic graph learning with attention mechanisms.
8. Six-stage approach for Alzheimer's disease diagnosis based on fMRI [63]: It presents a comprehensive approach involving preprocessing, modeling, feature extraction, selection, and classification using machine learning algorithms, specifically random forests and support vector machines, applied to fMRI data.
9. An adaptive approach for constructing a dynamic effective connectivity network through the detection of change points [64]: It detects dynamic changes in brain connectivity using fused lasso regression and Granger causality, providing insights into temporal dynamics and effective connectivity networks in fMRI data.

Figure 13 presents a summary of the challenges and corresponding solutions in utilizing fMRI for Alzheimer's diagnosis. It encompasses various aspects such as data

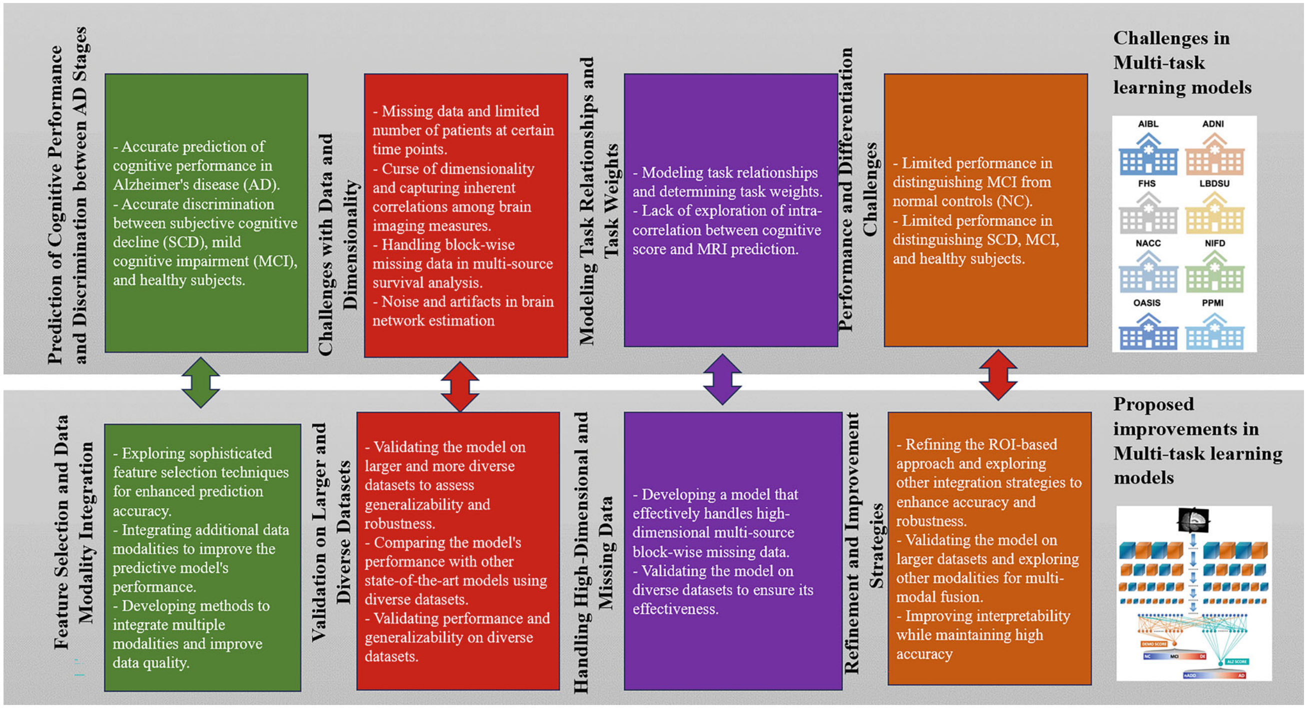

Fig. 12 Challenges and solutions multi-task learning models for Alzheimer's detection: models, data, task weight, and model performance

acquisition, modeling techniques, feature extraction, and optimization strategies for improving the accuracy and effectiveness of Alzheimer's diagnosis using fMRI data. Further elaboration on this topic can be found in Table 10, providing a more comprehensive discussion.

3.6.2 EEG and brain function modeling

EEG data analysis models refer to the computational techniques and algorithms used to analyze and interpret electroencephalography (EEG) data for the purpose of predicting Alzheimer's disease and classifying different cognitive conditions. These models play a crucial role in identifying patterns, features, and biomarkers within EEG signals that are indicative of cognitive decline and can aid in early diagnosis. Several methods can be used for EEG data analysis in the context of Alzheimer's disease and detection.

1. Spectral and complexity analysis of scalp EEG characteristics for MCI and early AD [65]: This study analyzes EEG data to differentiate between normal aging, MCI, and AD using regional spectral and complexity features, achieving high accuracy in classification tasks.
2. Complexity analysis of EEG Dynamics for Early Diagnosis of Alzheimer's Disease using Permutation Entropy Neuro marker [66]: EEG recordings from AD, MCI, and healthy controls are analyzed using permutation entropy values and a multinomial logistic regression model for classification.
3. An improved I-FAST system for the diagnosis of AD from unprocessed electroencephalograms by using robust invariant features [67]: The I-FAST system employs machine learning techniques and invariant features extracted from unprocessed EEG data to classify subjects into AD, MCI, and healthy elderly groups, enhancing classification accuracy.
4. A electroencephalography-based approach for AD and MCI detection [8]: This methodology uses EEG signals along with discrete wavelet transform, power spectral density, and coherence analyses, combined with a bagged trees classification algorithm, for automatic detection of AD and MCI.
5. Alzheimer's disease diagnosis using fusion of high informative BiLSTM and CNN features of EEG signal [68]: A deep learning framework combines BiLSTM networks for temporal feature analysis and CNN for exploring regional relationships in EEG signals, with channel selection and data augmentation techniques to improve diagnostic accuracy.
6. EEG Alzheimer's Net: Development of transformer-based attention LSTM network for detecting AD using EEG signal [69]: This model employs EEG signal decomposition, recurrent neural networks, and a multi-scale dilated CNN to extract temporal and spatial

Table 9 Comparing multi-task learning models based on evaluation criteria, method innovation, data and modeling challenges, and proposed solutions

References	Model	Result	Innovation	Challenges	Proposed improvement
[49]	Sparse shared structure-based multi-task learning	Superior performance in predicting cognitive scores, robust tool for identifying a concise set of imaging biomarkers	Jointly learns multiple related tasks to improve prediction performance	Accurate prediction of cognitive performance in AD, progressive impairment of memory and cognitive functions in AD patients	Advanced feature selection techniques, additional data modalities for enhanced prediction accuracy
[50]	Multi-task learning with deep recurrent neural network	5.6%, 5.7%, 4.0% and 11.8% improvement in mAUC, BCA, and MAE (ADAS-Cog13 and Ventricles)	Uses time-LSTM architecture to capture temporal dependencies	Missing data and limited number of patients at certain time points	Balanced multi-task dynamic weight optimization method, Development of multiple longitudinal prediction models
[51]	Dual feature correlation guided multi-task learning framework	4.28% decrease in overall error in cross-sectional analysis, 7.97% decrease in ADAS-Cog total score longitudinal analysis	Integration of task and feature correlation structures, feature-aware sparsity-inducing norm (FAS-norm) penalty	Curse of dimensionality, Capturing inherent correlation among brain imaging measures	Incorporate additional relevant data sources
[52]	Bi-graph guided self-paced multi-task feature learning framework	nMSE for predicting eighteen cognitive scores: 3.923, wR: 0.416	Incorporates feature and task correlations, utilizes self-paced learning strategy	Modeling task relationships, determining task weights	Validate performance and generalizability on diverse datasets, Compare with other state-of-the-art models
[53]	MSAMB framework for survival analysis in multi-source block-wise missing data	MSAMB.V2: CN-to-MCI Time AUC: 0.8102 ± 0.0263, MCI-to-AD MSAMB.V1: 0.7433 ± 0.0266	Incorporates feature-level and source-level analysis	Handling block-wise missing data in multi-source survival analysis	Develop a model that effectively handles high-dimensional multi-source block-wise missing data, Validate on diverse datasets
[54]	Joint multi-task learning with low-rank self-calibrated functional brain networks and structural brain networks	ACC NC vs. SMC: 82.95, NC vs. EMCI: 85.23, NC vs. LMCI: 87.80	New method for functional brain network estimation, Integration of functional and structural neuroimaging patterns, non-convex regularizer for rank minimization	Limited performance in distinguishing MCI from NC, Noise and artifacts in brain network estimation	Develop methods that integrate multiple modalities, improve data quality, Validate on diverse datasets
[55]	Auto-weighted centralized multi-task learning framework for SCD and MCI diagnosis	NC vs. SCD: BFCN ACC in PC: 74.40, BFCN ACC in SR: 80.80, BFCN ACC in LR: 80.80, BFCN ACC in SLR: 84.80; SCD vs. MCI: BFCN ACC in PC: 79.59, BFCN ACC in SR: 80.95, BFCN ACC in LR: 89.12, BFCN ACC in SLR: 89.12	Integration of functional and structural connectivity information, Multimodal fusion and learning	Accurate discrimination between SCD, MCI, and healthy subjects	Validate on larger datasets, Explore other modalities for multimodal fusion, Improve interpretability

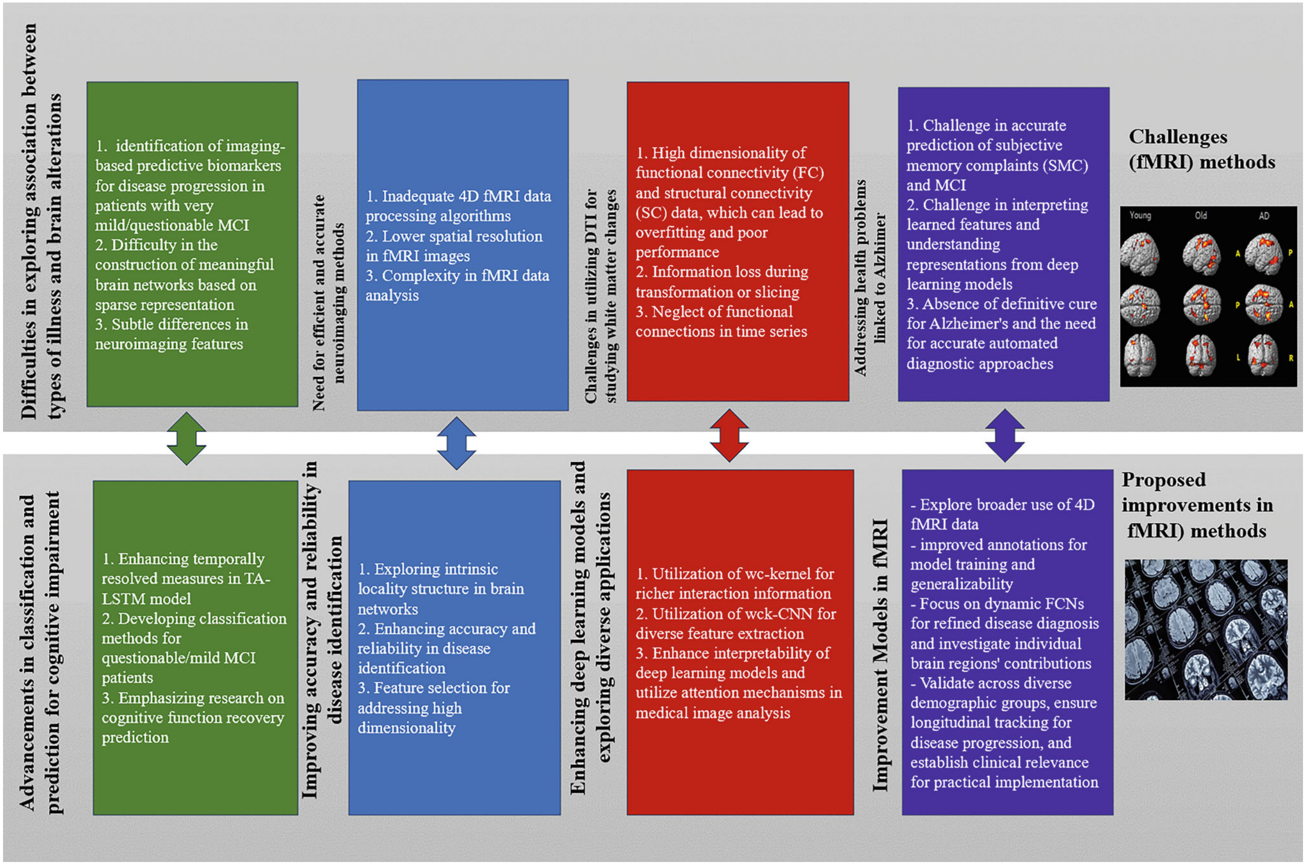

Fig. 13 Challenges and solutions fMRI for Alzheimer's detection: data, models, high dimensionality, and diagnosis optimization

features, and an optimized transformer-based attention LSTM model for AD detection.

7. EEG and cognitive biomarkers-based MCI diagnosis [70]: EEG and cognitive biomarkers are analyzed using a support vector machine classifier to classify MCI, dementia, and healthy subjects, based on data collected during different cognitive tasks.
8. Early detection of AD from EEG signals using Hjorth parameters [71]: This study focuses on Hjorth parameters as novel features in AD detection, comparing different signal decomposition methods and classification algorithms for early diagnosis.

9. An Alzheimer's disease classification methodology [72] for distinguishing between moderate and advanced stages utilizing a neural network model initialized with fuzzy logic and based on radial basis functions. The model is trained on EEG data to achieve accurate classification.

Figure 14 provides a concise summary of the challenges and solutions encountered in the utilization of EEG and brain function for Alzheimer's diagnosis. It incorporates insights from multiple review papers, covering important aspects such as data, models, features, and optimization techniques Furthermore, a more detailed presentation of the challenges and solutions, methods and result, innovation related to EEG and brain function for Alzheimer's diagnosis, along with additional explanations that can be found in Table 11.

4 Conclusion

The analysis of 783 papers published between 2009 and 2023 reveals the evolving landscape of research in this field, highlighting the significance of machine learning and deep learning techniques in early-stage identification of Alzheimer's risk and disease progression. The paper underscores the importance of datasets such as ADNI and OASIS, as well as localized patient data, in deriving valuable insights. It also categorizes the papers into taxonomic classes based on topic modeling methods and explores the strengths, limitations, and procedural modalities of the methodologies employed. This comprehensive analysis sheds light on the complex and multifaceted nature of Alzheimer's disease research. The integration of advanced machine learning techniques with diverse data sources has the potential to significantly

Table 10 Comparing fMRI models based on evaluation criteria, method innovation, data and modeling challenges, and proposed solutions

References	Model	Result	Innovation	Challenges	Proposed improvement
[56]	Time-attention long short-term memory (TA-LSTM) network	Average accuracy: MCI vs. stable MCI: 0.836 (images), 0.863 (learning), Average AUC: 0.789	TA-LSTM model, Gradient-based interpretation framework, Prediction of qMCI progression and biomarkers	Limited data availability, Scalability, Interpretability	Enhance temporally resolved measures in TA-LSTM model, Utilize windowless wavelet-based dFNC, Develop classification methods for questionable/mild MCI patients
[57]	Novel weighted graph regularized sparse brain network	Accuracy: 88.89%, 5% and 9% increase compared to WSGR (84.85%) and WSR (79.80%)	Weighted graph regularization, Sparse representation for brain network construction, Correlation similarity and local structure, Addressing non-convergence in self-representation model	Difficulty in constructing meaningful brain networks based on sparse representation	Explore intrinsic locality structure in brain networks, Enhance accuracy and reliability in disease identification
[58]	Multi-scale Enhanced Graph Convolutional Network (MSE-GCN)	Accuracy: 90.39%	Integration of structural and functional data, Overcoming limitations in subtle neuroimaging differences, LWCC for feature representation, Incorporation of demographic information, Parallel GCN layers	High dimensionality of functional and structural connectivity data, Overfitting and poor performance	Feature selection to address high dimensionality, Use recursive feature elimination (RFE) method
[59]	Graph convolution network (GCN) with similarity awareness and adaptive calibration	Accuracy: 86.83%	Adaptive mechanism for improved similarity evaluation, Calibration mechanism for fusing fMRI and DTI, Leveraging complementary cues from multiple modalities	Inaccurate prediction of SMC and MCI, Subtle differences in neuroimaging features, Limitation impacting prediction accuracy	Design disease status-aware graph, Adaptive mechanism for evaluating similarity, Update similarity using pre-training difference, Calibration mechanism for fMRI and DTI fusion

enhance the accuracy of diagnosis and understanding of disease progression. This requires interdisciplinary collaboration to explore innovative ML methodologies to tackle the challenges posed by Alzheimer's disease. Continued research in this field, building upon the foundation established by studies like the one reviewed here, holds promise for improving early detection, treatment, and care for individuals affected by this debilitating neurological disorder.

Table 10 (continued)

References	Model	Result	Innovation	Challenges	Proposed improvement
[60]	C3d-LSTM: combination of 3D CNN and LSTM network	GRU: AD/MCI: 85.53, AD/NC: 94.74, NC/MCI: 86.84, AD/NC/MCI: 81.58; LSTM: AD/MCI: 92.11, AD/NC: 97.37, NC/MCI: 88.12, AD/NC/MCI: 89.47	Processing 4D fMRI data directly, Combining 3D CNNs and LSTM networks, Simultaneous extraction of spatial and temporal information	Inadequate 4D fMRI data processing algorithms, Information loss during transformation or slicing	Explore broader use of 4D fMRI data, Assess C3d-LSTM model on diverse datasets, Validation of model effectiveness in larger datasets
[61]	Novel weighted correlation kernel (wc-kernel) and corresponding CNN framework (wck-CNN)	Wck-CNN Acc: eMCI vs Hc: 81.1, AD vs Hc: 85.3, AD vs lMCI vs eMCI vs HC: 57.6	Introduction of wc-kernel for brain interactions, Capturing richer interaction information compared to PCC, Learning weighting factors for valuable observation details, Utilizing contributions of different time points, Integration of wc-kernel with CNN for disease diagnosis	Neglecting changing properties in functional connectivity, Focus on low-level measures over high-level features, Assumption of temporal stationarity in FCNs, Overlooking high-order network characteristics in studies	Utilization of wc-kernel for richer interaction information, Incorporation of wck-CNN for diverse feature extraction, Focus on dynamic FCNs for refined disease diagnosis
[62]	Deep learning framework: spatio-temporal directed acyclic graph with attention mechanisms (ST-DAG-Att)	Correlation: 0.288 ± 0.003, MAE: 5.582 ± 0.012, RMSE: 7.046 ± 0.010	Integration of functional time series and connectivity, Analysis across multiple spatio-temporal scales, Utilization of directed acyclic graphs (DAGs), FC-SAtt inclusion for local dependency capture	Inadequacy of deep learning for dual data, Neglect of functional connections in time series, Lack of explicit temporal scale modeling, Limited deep learning for functional connectivity data	Enhance interpretability of deep learning models, Explore individual brain regions' contributions, Investigate DAG structures for model enhancement, Utilize attention mechanisms in medical image analysis
[63]	Generalized Linear Model	Accuracy: 94%, monitoring progression: 97% and 99%	Utilization of fMRI data for analysis, Conversion of Random Forest trees into rules	Need for accurate automated diagnostic approaches, Complexity in fMRI data analysis, Challenge in selecting relevant features	Standardization and Protocol Development on fMRI data, Integration of Multimodal data: Explore the integration of multiple modalities such as fMRI, structural MRI, and clinical data

Table 10 (continued)

References	Model	Result	Innovation	Challenges	Proposed improvement
[64]	Fused lasso regression	Accuracy: 86.24%	Dynamic detection of brain connectivity changes, Fused lasso regression for precise identification, Accurate estimation of effective connectivity networks	Unknown change points in brain connectivity, Frequent dynamic reorganization during fMRI scans, Detecting and understanding temporal brain dynamics, Challenge in analyzing fMRI data's temporal dynamics	Validate across diverse demographic groups, Ensure longitudinal tracking for disease progression, Establish clinical relevance for practical implementation

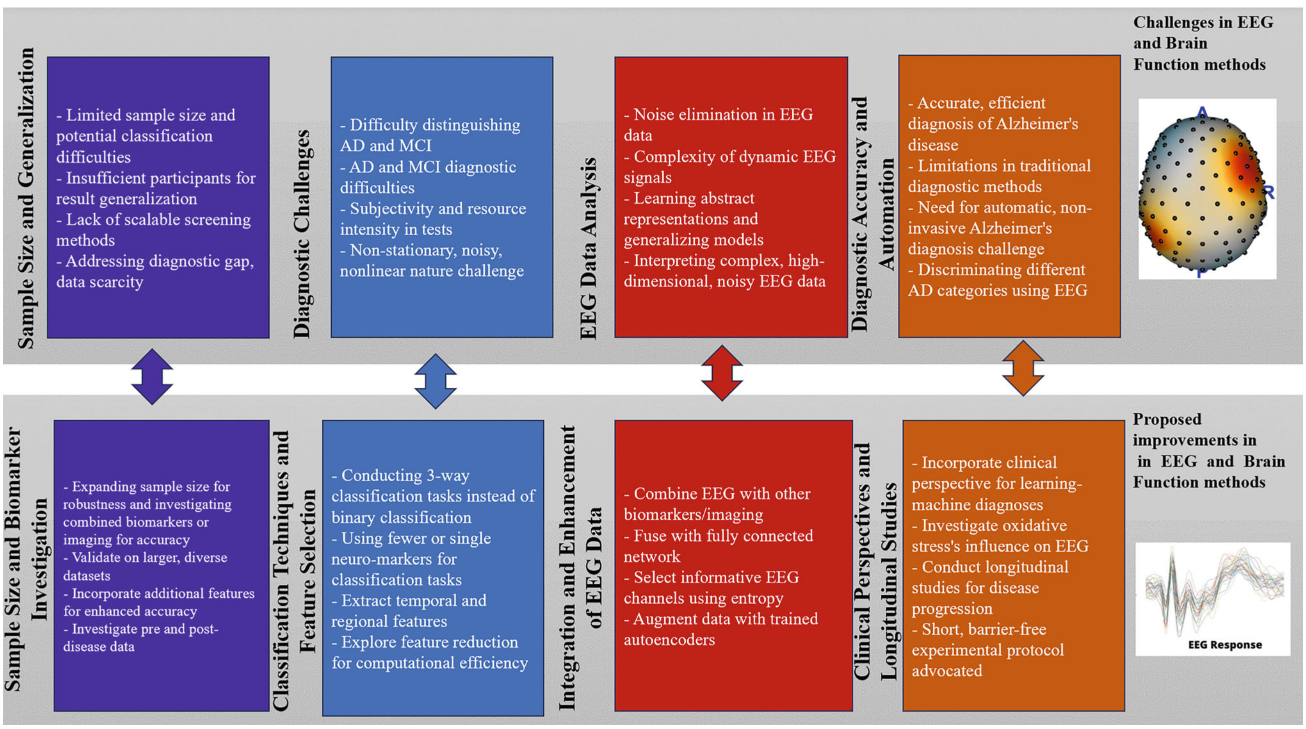

Fig. 14 Challenges and solutions EEG and brain function for Alzheimer's detection: sample size, misdiagnosis, data, and evaluation measurements

Table 11 Comparing EEG and brain function models based on evaluation criteria, method innovation, data and modeling challenges, and proposed solutions

References	Model	Result	Innovation	Challenges	Proposed improvement
[65]	Support vector machine model	Accuracies: 83.3% (resting eyes open), 85.4% (counting eyes closed), 79.2% (resting eyes closed)	EEG exploration as non-invasive markers for early cognitive decline detection	Limited sample size, Potential classification difficulties	Expand sample size for robustness, Investigate combined biomarkers or imaging for accuracy
[66]	Multinomial Logistic Regression (MLR)	F1-scores, sensitivity, specificity: up to 100% for certain electrode locations and eyes open conditions	PE as AD neuro-marker, Novel MLR approach, Eye states' classification performance impact	Insufficient participants for result generalization, Limited metrics for dementia stage classification	Combine both eyes open and eyes closed conditions, conduct 3-way classification tasks instead of binary classification, Use fewer or single neuro-markers
[67]	I-FAST (Intelligent Feature Analysis of Signals and Textures), KNN, QDC, Naïve Bayes	Accuracy: AD vs MCI: 94%-98%, Overall: 98.25% (ANNs)	ANNs leverage connection weights for superior classification	Noise elimination in EEG data, TWIST system with robust classifier, Difficulty distinguishing AD and MCI	Incorporate clinical perspective for machine learning diagnoses, investigate oxidative stress's influence on EEG, Test I-FAST system on Parkinson's, ALS
[8]	Bagged Trees classification model	Accuracy: 96.5%, Sensitivity: 96.21%, Specificity: 97.96%	Decision support for early diagnosis, Utilizing EEG signals in diagnostics, Unique approach using advanced analysis	AD and MCI diagnostic difficulties, Subjectivity and resource intensity in tests, Lack of scalable screening methods	Validate on larger, diverse datasets, Combine EEG with other biomarkers/imaging
[68]	BiLSTM, CNN	Accuracy: 100%	BiLSTM and CNN for EEG analysis, Comprehensive AD diagnosis via brain activity, Entropy-based channel selection, Data augmentation	Limitations in traditional diagnostic methods, Need for automatic	Extract temporal and regional features, Fuse with fully connected network, select informative EEG channels using entropy, Augment data with trained autoencoders
[69]	RNN, CNN, Wild Geese Lemurs Optimizer (EWGLO), optimized transformer-based attention LSTM (OTA-LSTM)	Accuracy: 96%, MCC: 98%	Integrates LWT, RNNs, CNNs, EWGLO algorithm optimizes weight values, OTA-LSTM model enhances detection accuracy	Accurate non-invasive Alzheimer's diagnosis challenge, Complexity of dynamic EEG signals, Learning abstract representations and generalizing models	EWGLO algorithm for optimizing weighted features, Optimize OTA-LSTM model parameters, Embrace end-to-end learning with neural networks

Table 11 (continued)

References	Model	Result	Innovation	Challenges	Proposed improvement
[70]	SVM	Accuracy: 73.4%-89.8% for three binary classes	Novel MCI classification using EEG biomarkers	Early MCI diagnosis in diverse populations, Dialectal cultural barriers in diagnosis, Addressing diagnostic gap data scarcity	EEG-based markers for improved MCI detection, Validation and refinement for clinical use, short barrier-free experimental protocol advocated
[71]	SVM, KNN, LDA	Accuracy: 97.64%	Hjorth parameters enhance accuracy in AD, Exploring effective signal decomposition methods	Non-stationary noisy nonlinear nature challenge, discriminating different AD categories using EEG	Explore feature reduction for computational efficiency, combine brain signals and images, Investigate pre and post-disease data
[72]	RBF-based neural network with fuzzy logic	Accuracy: ADA: 96.66%, ADM: 93.31%	RBF neural network with fuzzy logic, Enhanced accuracy in Alzheimer's classification	Availability and quality of EEG data, Coordination and standardization across multiple hospitals, Interpreting complex high-dimensional noisy EEG data	Expand dataset for improved model generalizability, Incorporate additional features for enhanced accuracy, Conduct longitudinal studies for disease progression

Author contributions Z.R. conducted the data analytics and coding, collected and analyzed the data, and prepared the initial draft of the manuscript. Z.R. was responsible for the review and research activities including the implementation of the data mining procedures. Y.M.B. conceptualized the research project, provided critical insights into the data analytics and methodology, and supervised the entire study. Y.M.B. also contributed to the interpretation of the results and the revision of the manuscript.

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Data availability This paper is a review, and the data discussed are open and available in the published papers reviewed. The datasets analyzed during the current review are available from the corresponding publications, which are cited throughout the text.

Declarations

Competing interests The authors declare that they have no competing interests. There are no financial, personal, or professional interests that could be construed to have influenced the work reported in this paper.

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