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A Review on Structural and Functional Connectivity-Based Alzheimer's Disease Detection and Localization in Functional Magnetic Resonance Imaging

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Abstract
The most prevalent sort of dementia, which accounts for at least two-thirds of cases in individuals aged 65 as well as older, is Alzheimer's disease (AD). AD is a neurodegenerative illness with insidious onset along with advanced impairment of behavioural as well as cognitive functions. Memory, language, comprehension, attention, reasoning, along with judgment is encompassed in those functions. Functional Magnetic Resonance Imaging (fMRI), as a neuroimaging methodology, affords a means of examining the structure along with function of brain connectivity linked with AD. The recent advancements' usage in Machine Learning (ML), Deep Learning (DL), graph theory, along with connection analysis has allowed for the automated identification and localization of aberrant neural activity from fMRI data. Here, the aim is to review existing structural and Functional Connectivity (FC) detection and localization methods of AD using fMRI techniques. As per the outcome, using a combination of structural along with FC analyses with AI-based approaches enhances the accuracy of diagnosing AD, the precision of localizing the disease, and the predictability of the disease at an early stage. Thus, the integration of FMRI with advanced techniques can enhance diagnostic accuracy, enable precise localization of AD, and improve early-stage AD prediction by supporting better clinical outcomes and patient care.

Keywords: *Alzheimer's Disease, Functional Magnetic Resonance Imaging, Structural Connectivity, Functional Connectivity, Brain Localization, Deep Learning, Neuroimaging, and Machine Learning.*

1. Introduction

Computer-assisted algorithms could be wielded to augment diagnosis in hospitals regarding accuracy as well as speed with the development of advanced technologies. In medical imaging as well as medical image analysis, advances have offered influential tools to engender together with excerpt cherished neuroimaging information as well as monitor neurodegeneration. Also, there is an excessive enthusiasm to make habit of medical images for diagnosis along with prediction [1]. AD is a common form of dementia along with neurodegenerative disease. Although AD has no cure, early diagnosis permits patients to entrée accessible treatments that could aid slow disease progression. Unfortunately, detecting early-stage AD in clinical practice can be challenging because structural and functional brain abnormalities mostly seem to progress over time. fMRI aids researchers recognize brain connectivity along with functional networks in AD patients. The accumulation of evidence shows that changes in FC together with Structural Connectivity (SC) are the prominent hallmarks of AD in the Default Mode Network (DMN) [2]. SC along with FC's usage with fMRI has expected a lot of attention in medical imaging and Artificial Intelligence (AI) research. There are numerous techniques (e.g., ML as well as DL that have been applied to evaluate brain connectivity networks for the purpose of accurate diagnosis and localization of disease through the use of fMRI analysis [3]. This review investigates the current methods, including the methodologies related to fMRI analysis, connectivity models, feature extraction methods, classification algorithms, and localization techniques, to detect AD by means of fMRI analysis. Therefore, in the area of medical imaging analysis along with the diagnosis of neurological disorders, this review analyzes and summarizes the available literature on structural and FC -based methods of detecting and localising AD using fMRI data. The review's overall objective is to present previous research's overview on structural along with FC-based methods of detecting and localising AD using fMRI techniques. Early diagnosis of AD, cognitive impairment evaluation, brain disorders monitoring systems, and intelligent medical decision support systems are some of the examples of how those methods can be applied. The limitations and challenges associated with these methods include: high computational time/costs to perform fMRI analysis, limited datasets available for training large models based on fMRI data, and variability in brain connectivity patterns across individuals. The review paper is arranged as: Research Questions (RQs) along with Article Selection Strategy (Section 2), Literature Review Section (Section 3), Review Summary (Section 4), and Conclusion (Section 5).

2. RQs and Article Selection Strategy

The significant RQs, which provide the review's objectives, are framed as follows: 1. What is the SC -based AD detection in fMRI?, 2. What is the FC -based AD detection in fMRI, and 3. What are the localization procedures using fMRI for AD detection? In order to conduct this review, the articles were collected from diverse databases like "ScienceDirect", "Web of Science (WoS)", "IEEE", etc. As per the inclusion criteria, the articles that aligned with the objective of structural and FC -based AD detection and localization in fMRI, which were published from the year 2016 to 2025, were included in this review. On the other hand, some of the articles that did not align with the objective of this review were excluded, as per the exclusion criteria. The articles published before the year 2016 and the articles with incomplete and outdated information were also excluded. Further, to make this review more efficient, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was wielded. The identification, evaluation, along with selection of eligible articles and sources were included in the PRISMA framework for inclusion in literature reviews. In Figure 1, the PRISMA framework's representation is depicted.

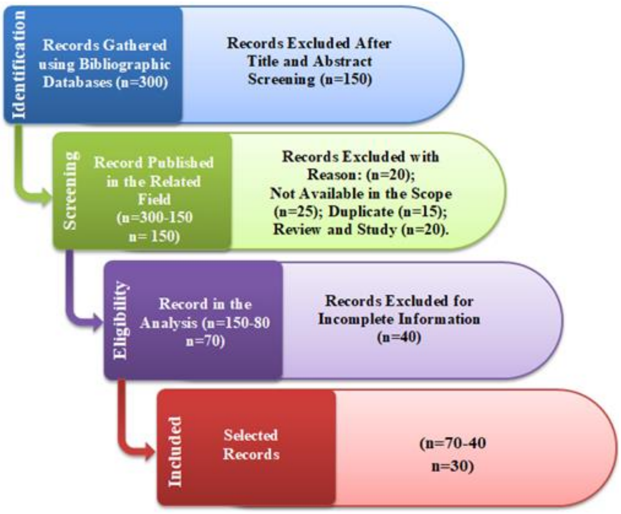

Figure 1 PRISMA Framework

3. Literature Review

The review's literature review section aims to offer an overview of AD and its significance, SC -based AD detection, and FC-based AD detection. Also, the localization of AD using the FMRI techniques, along with their challenges and advantages, is explained in this review.

3.1.Structural connectivity-based AD detection

SC in the DMN is AD's noticeable hallmark. The mutual structural MRI markers are the hippocampal along with medial temporal atrophies, which are convoluted in AD's progression. This degradation impairs how the brain communicates and acts as the physical "road map" along which toxic amyloid-beta and tau proteins spread, causing AD [4]. [5] analysed MRI biomarkers for AD and FC's impact in the DMN along with SC betwixt lobes on diagnostic accuracy. For the AD analysis, resting-state fMRI was wielded. As per the outcome, brain connectivity fluctuations resulted by AD were reflected in multiple Magnetic Resonance Imaging (MRI) biomarkers. Yet, due to the limited number of extracted features, the number of connectivity features was impacted. [6] appraised the disrupted functional as well as SC within the DMN that donated to WMH-linked AD using resting-state FMRI imaging. The results showed that the alterations in FC as well as SC in the DMN attributed

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to AD advance were accountable for cognitive impairment expansion. Yet, the analyses were not performed on each thalamic nucleus. [7] appraised the patterns of alterations in AD by using structural and functional connectomics. To identify the functional cortical network nodes, the resting state fMRI was wielded. The findings indicated that cognitive debits in AD might be allied with cortical modifications along with subcortical alterations, which extended beyond the areas primarily scratched by neurodegeneration. Yet, the Diffusion Tensor Imaging (DTI) sequence was run in a clinical setting without an advanced diffusion model. [8] analysed the SC alterations with the AD continuum, reproducibility across ‘2’ independent samples, along with association with cerebrospinal fluid amyloid along with tau. By using the fMRIB Software Library, the diffusion-weighted images were corrected. In the temporal lobe, preclinical individuals were mainly situated. Disconnection spread pattern to the parietal along with frontal lobes at the MCI stage as well as convoluted almost each brain images in AD. However, the cross-sectional nature was the major limitation in the present system. [9] examined the link betwixt SC as well as the generalized cognitive spectrum in AD using the fMRIB Software Library. Here, the connectivity patterns extracted from DTI were used to classify AD. A few regions’ efficiency and centrality could track cognitive damage in AD, screening a weighty association with the widespread cognitive score. But, features’ subsets were not representative in the collected data. [10] conducted the experiment on structural atrophy changes as well as FC measures in AD using the fMRIB software library. The DMN’s resting-state FC was appraised betwixt the groups employing the FC toolbox. From the results, it was found that the presented model had an advanced association betwixt MMSE as well as functional metrics when compared to atrophy measures. However, a lack of demonstration of connectivity measures was observed. [11] examined the SC centrality variations that marked the path toward AD using fMRI data as of the AD Neuroimaging Initiative database. It was evident from the results that the discriminative network features were related with the medial temporal, along with DMN’s subcortical brain regions and posterior structures and occipital areas. Nevertheless, the dataset features were not extracted from the prodromal phase. [12] developed a hybrid Convolutional Neural Network – Support Vector Machine (CNN-SVM) for AD classification from structural FMRI. Principal Component Analysis (PCA) along with Sequential Feature Selection (SFS) was implemented for feature selection, while a Support Vector Machine (SVM) was assumed to appraise the classification accuracy. As a result, it achieved 90% (classification accuracy) for binary classification of AD as well as HC, 81% for AD together with MCI, along with 72% for MCI. However, additional higher-dimensional kernels were not explored in this study. Further, the result metrics associated with the SC -based AD detection that is composed as of the research articles are tabulated in Table 1.

Table 1 Result metrics associated with the structural connectivity-based AD detection that are collected from the research articles

Method	Time	Dataset	Sample	Accuracy	Sensitivity	MMSE	Significance	Challenges	Ref
MRI and FMRI scanning	Nil	DWI dataset	20 AD Patients	74%	74%	Nil	0.01	Limited number of features due to small sample size.	[5]
FMRI scanning	30 ms	Not reported	116 subjects	Nil	Nil	29	< 0.001	Limited computational scalability.	[6]

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Probabilistic tractography	69.1 ms	HCB Dataset	183 subjects	Nil	Nil	< 26	0.05	Limited sample size.	[8]
Diffusion Tensor Imaging (DTI)	400 ms	AD Neuro Imaging (ADNI)	191 subjects	<70%	Nil	0.42 ± 0.15	0.09	A subset of features was not represented in the overall population.	[9]
FMRIB	30 ms	ADNI	80 subjects	Nil	Nil	36.4	0.006	Lack of demonstration of connectivity measures.	[10]
DMRI	3000 ms	Nathan Kline Institute (NKI) dataset	39 subjects	89.07%	79.16%	28.6761 ± 42	0.14	Network features did not provide further information for diagnosis.	[11]
MRI	Nil	ANOVA	422 records	90%	87%	22.9 ±2.0	0.633	No higher-dimensional kernels were explored.	[12]

The comparative analysis of SC studies highlighted various performance metrics. Research study [11] achieved high accuracy (89.07%) and specificity (98.90%) due to the use of strong imaging resolution. However, the network features added little diagnostic value. On the other hand, the research study [12] reported 90% accuracy and strong sensitivity due to the large dataset modelling. However, it did not explore the higher-dimensional kernels. Subsequently, the research study [9] showed accuracy below 70% due to the limited population representation. The research [10] showed a statistical significance of 0.006. Yet, it failed to analyse the connectivity measures.

3.2. Functional connectivity-based AD detection using FMRI

FC in AD is analysed using fMRI, which is a non-invasive neuroimaging methodology to appraise brain functions via lower-frequency variations (termed the Blood-Oxygen-Level Dependent (BOLD) signals) [13]. In brain networks, FC measurement is done by the fMRI time-series via PCC [14]. [15] appraised the dynamic FC changes in dementia regarding Lewy bodies along with AD using resting-state fMRI data. As per the outcome, AD patients spent huge time in sparse connectivity configurations. Also, sturdy positive as well as negative connections' absence along with motor networks' relative isolation as of other networks were found. Yet, dynamic connectivity measures were sensitive to variations in data. [16] conducted a longitudinal study on different resting-state FC in individuals at risk for AD. FC was analysed employing a group Independent Component Analysis (ICA) and fMRI. Inferior standard insular connectivity foreseen advanced depressive symptoms in MCI subjects. Yet, the research remained susceptible to modulation by functional network changes. [17] analysed the differential medial temporal lobe, default-mode network FC, along with morphometric changes in AD using fMRI analyses. The results indicated dual-functional as

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well as higher-resolution morphometric biomarkers' potential for detecting the earliest stages in the AD pathophysiology. Nevertheless, the global or else large-scale regional neuronal fluctuations were not controlled. [18] developed a longitudinal system for FC in the brain networks for AD detection employing resting-state fMRI. Here, a series of simulations was applied to longitudinal fMRI data collected as of the ADNI database. Thus, no difference was found betwixt AD patients as well as healthy controls in the global FC network. But, differing local aging patterns betwixt the left hippocampus together with the posterior cingulate cortex in the FC were identified. Yet, the model's high computational demands were the challenge. [19] evaluated the executive control network's FC along with the fronto-parietal network in AD. Here, R-fMRI images' protocol was implemented to every subject. The experimental results showed that several functional networks, like the fronto-parietal network along with the executive control network, showed significant changes in AD detection. Nevertheless, the study just adopted resting-state data along with a relatively short sample of patients, which posed a challenge. [20] examined the brain functional network, which correlated with Alzheimer's neuropsychological test scores using fMRI along with graph analysis. The associations betwixt the brain network measures along with the AD psychological charge test scores were appraised. The outcomes showed an optimistic association betwixt the MMSE as well as nodal strength in the left insula along with a negative association betwixt the left olfactory cortex's Clinical Dementia Rating (CDR) score along with local efficiency. Yet, huge sample size was desired to surge the results' accuracy. [21] aimed to determine passive music exposure's impact on brain activation as well as FC employing FMRI in patients with early AD. The findings offered evidence that acquainted music activated a widespread bilateral network and frontal and prefrontal emotional processing areas in AD persons. However, the combination of AD and music intervention did not increase mean cognitive scores. [22] examined the hypothesis of an early as well as selective connection of neural networks centered on AAO in AD. Here, the brain networks' FC was analysed using fMRI. The findings indicated that aberrant link in memory networks was allied with pLOAD, while networks essential for executive as well as visual-spatial functions were affected in pEOAD. Nevertheless, the sensorimotor network didn't display differences between groups. Further, the result metrics related to the FC -based AD detection using FMRI that are composed as of the research articles are tabularized in Table 2.

Table 2 Result metrics related to the functional connectivity-based AD detection using FMRI that are collected from the research articles

Study Type	Method	Dataset	Samples	Time	Frequency	Region Of Inter-section score	Significance	Challenges	Ref
Applied research study	FMRI scanning	Not reported	62 Subjects	25 ms	Nil	Nil	0.013	A limited number of FMRI studies.	[16]
Experimental evaluation	Free surfer estimation	ADNI2	105 subjects	Nil	Nil	36	0.007	Limited imaging data and image processing methods.	[17]

Experimental evaluation	Linear Mixed Effects	ADNI	30 patients	3.8 seconds	3.7 GHz	10	0.008	The cross-sectional models only considered a single time point.	[18]
Applied research study	DMN	ADNI	183 subjects	30 ms	0.01–0.08 Hz	116 regions	Nil	The study had relatively short sample of patients.	[19]
Observational study	Functional Connectivity Network	Not reported	21 patients	Nil	0.01 to 0.08 Hz	Nil	0.05	Decreased continuity was spotted in the limbic system.	[20]
Observational study	AD+MI	Not reported	9 Subjects	Nil	Nil	Nil	0.37	Indication of lower mean cognitive scores.	[21]
Applied research study	Age at Symptom Onset (AAO)	TOMC dataset	30 subjects	12 ms	0.01 Hz	21	<0.05	No evidence of cognitive impairment was seen in the control group.	[22]

The comparative analysis of FC studies revealed various results across the methods. Research study [16] showed high statistical significance (0.013). However, it was inadequate by fewer studies. Yet, the research study [17] achieved a higher ROI score of 36 but struggled with limited imaging data. The [18] reported a implication of 0.008. Yet, the developed cross-sectional design restricted temporal insights. Further, the research study [19], which used DMN, achieved broad coverage (116 regions). However, it lacked longitudinal depth. Subsequently, the research studies [20] and [21] highlighted continuity issues and cognitive decline due to the presence of small samples. Finally, the research study [22] demonstrated a significance score (<0.05). However, it had no cognitive impairment in controls. Overall, these studies showed the trade-off between statistical power, dataset size, and methodological scope. Yet, small sample sizes and limited imaging data remained as challenges.

3.3.Localization techniques of AD using fMRI

fMRI offers a non-invasive technique for language-dominant areas' localisation employing task-specific brain activation maps. The maps are engendered by analyzing alterations in the BOLD signal linked to fluctuations in neural activity regarding a task. Resting-state fMRI is commonly applied to identify deviations from normal functioning within intrinsic brain networks, particularly the DMN, which is one of the first and most clearly used methods for AD

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Page No: 4906-4917
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relative to other brain networks. [23] elucidated the voxel-centric feature detection as well as AD analysis employing SVM. Linear regression model, Least absolute shrinkage along with selection operator (Lasso), Partial Least Squares (PLS), SVM, as well as RS-SVM were the techniques wielded to test along with compare these features' accuracy. The experimental results employing '5' ML methods indicated that the recognized features were effectual for AD as well as HC classification. High-dimensional data, computational costs, and complex manual feature extraction were the limitations. [24] described resting-state fMRI's random SVM cluster analysis in AD. From the AD Neuroimaging Initiative database, the subjects, like 25 AD individuals along with 35 HC individuals, were gained. The classification accuracy might attain better results. Applying a random SVM cluster could help in the diagnosis of AD. The performance did not show excellent results in FC. [25] elucidated the volumetric feature-centric AD diagnosis as of sMRI data employing a CNN as well as a Deep Neural Network (DNN). For extracting volumetric features as of each slice, the pre-processed 2-D patches were wielded by employing a Discrete Volume Estimation-CNN (DVE-CNN). The applied approach achieved average weighted classification accuracies. The applied method was validated on a comparatively trivial private dataset. [26] defined the ROI-centric CNN classifiers' ensemble to stage the AD spectrum as of MRI. Three-View Patches (TVPs) as of these regions were given into the CNN meant for training. Distinctive features were given by Hippocampi, amygdalae, along with insulae for ADD diagnosis. In diagnosing AD, the maximum false positive rate along with bottom true positive rate indirect that the ROI-centric models didn't offer adequate info for AD diagnosis as of the sMRI modality. [27] explained the DL framework for identifying AD using an fMRI-based brain network. The 2D-CNN was implemented on the PSI matrix for exploring the network connectivity's local along with global patterns. 2D-CNN recognized AD by employing a SVM with a 5-fold cross-validation strategy. The techniques' classification accuracy was 98.869%. Overfitting wasn't widely lectured, thus limiting the applied methods' applicability. [28] described the DL-centric classification as well as voxel-centric visualization of frontotemporal dementia and AD. 3D T1-weighted structural MRI volumes' large cohort (n = 4,099) was composed as of '2' publicly available databases. DL-centric networks can resolve the differential diagnosis of diseases' enigma deprived of any hypothesis-centric preprocessing. Performances on the multiclassification tasks weren't satisfactory. [29] explained the voxel extraction as well as multiclass classification of identified brain regions thru numerous stages of AD employing ML approaches. The voxel dataset was used to train as well as test ten ML algorithms for categorizing the MCI into mild, moderate, along with severe stages of AD. AdaBoost performed better than the other algorithms and obtained 98.61% (phenomenal accuracy), 99.00% (precision), and 98.00% (recall and F1 scores). Intricate neuroimaging data's translation into meaningful clinical insights remained a challenge. [30] explored voxel-centric morphometry to improve AD diagnosis centered on an exciting learning machine as of the ADNI cohort. The calculated characteristics were regarded as the classification features. The applied method was optimal in distinguishing patients with AD as of NCs. There was a key betwixt-group alteration in sex; nevertheless, the classification factor wasn't modified in the later model construction, thus affecting its diagnostic efficacy. Further, the localization metrics associated with the AD detection collected from the research articles are tabulated in Table 3.

Table 3 Localization metrics associated with the AD detection collected from the research articles

Approach	Datasets	Samples	Precision	Recall	Accuracy	F-1 Score	Error	Challenges	Ref
Random SVM	ADNI	136 features	91%	91%	91%	91%	0.50%	Limited ROI score.	[23]

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Page No: 4906-4917
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Random SVM	AD/HC	35 participants	Nil	Nil	95.44%	Nil	Nil	High-dimensional feature limitations.	[24]
CNN and DNN	GARD	Not reported	84%	58%	94.82%	73%	Nil	The presented model was highly dependent on accuracy.	[25]
ROI-based CNN	GARD and ADNI	99.925 parameters	46.66 %	93.44%	90.77%	89.06 %	0.10%	A limited number of samples from each class.	[26]
CNN	ADNI	137 subjects	Nil	Nil	95.83±2.34	71.40 %	3.36%	Presence of overfitting issues.	[27]
DL approach	Independent test dataset	1250 FTD	Nil	Nil	70.47%	Nil	0.001	Generalizability was limited to a specific dataset.	[28]
ML-based approaches	Voxel dataset	7560 samples	96.50 %	95.50%	96.36%	96.50 %	0.2	Limited depth of each decision tree.	[29
Voxel-based morphometric method	Nil	57 centres	Nil	Nil	96%	Nil	Nil	Weakened diagnostic efficacy.	[30]

The comparative analysis of localization approaches for AD revealed various results. Research study [23] achieved strong precision and recall (91% each). However, it was limited by ROI scoring. On the other hand, [24] reported high accuracy (95.44%) with fewer participants. Nevertheless, it struggled with

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high-dimensional feature constraints. In the research study [25], CNN and DNN models attained 94.82% accuracy. Yet, the recall of CNN and DNN models was low when compared to the other models (58%). This showed the dependence of the study [25] on accuracy. ROI-based CNN used in the research study [26] achieved high recall (93.44%) but faced challenges due to limited samples. Similarly, the research study [27] demonstrated high accuracy (95.83%) but suffered from overfitting issues. Overall, these studies highlighted persistent trade-offs between dataset size and generalizability.

4. Review Summary

The analysis of 30 studies around fMRI-based analyses using connectivity and structural metrics showed that both of these approaches improved the detection and accuracy of localising AD significantly. The majority of studies used ML, DL, graph theory, and connectivity mapping as tools for detecting abnormal brain networks that were associated with cognitive decline. While progress was made in developing and implementing automated methods for detection and localisation, there remained several technical and clinical limitations that undermined the reliability, interpretability, and scalability of existing systems. Existing studies had mostly been restricted to either structural or functional analysis independently. However, limited studies existed on an integrated hybrid system to diagnose AD comprehensively using both techniques. Many DL models achieved high accuracy when performing classification but lacked interpretability and clinical explainability, detracting from trust in the use of automated systems to make decisions. Most studies also employed small and imbalanced datasets representing small numbers of patients, causing challenges with generalisation and robustness of their models across a variety of clinical environments. Certain limitations imposed on these systems included high computational complexity, noise sensitivity, feature redundancy, and lack of standardized preprocessing pipelines. Because of these limitations, the clinical implementation of many systems was limited by intensive computing resources or expert interpretation. The existing frameworks for the detection and localization of early-stage AD had many issues, including poor multimodal integration, lack of AI model interpretability, limited real-time analysis capabilities, and limited adaptability across different imaging datasets and different clinical settings. In addition to these issues, the existing frameworks also had difficulty in striking the proper balance between localization accuracy, computational efficiency, and the model's generalization at the same time. Finally, the lack of standardized benchmark datasets or validation protocols limited the large-scale implementation of connectivity-based diagnostic systems and the ability to make fair comparisons among different methods.

Conclusion

Here, the review purpose was to explore the use of structural and FC approaches to detect as well as localize AD. A variety of methodologies that were developed for this purpose, including ML, DL, graph theory-based methods, frameworks for connectivity analysis, and multimodal neuroimaging approaches, were examined. As per the findings, the utilization of structural and FC analyses enhances the ability to detect disruption in neural networks in patients with AD. Also, when weighed against conventional statistical approaches, DL and AI-based models achieved higher classification accuracy and localization performance. Numerous studies depicted that FC approaches like seed-centric analysis, independent component analysis, and graph neural networks, were successful in detecting abnormal activity in key brain regions associated with AD. There were still many limitations to working with AI, including a lack of diversity in datasets, no clear methods for explaining AI, computer power being too complicated, and the need for standardization in imaging methods and preprocessing. Also, in this review, significant research gaps were identified. Gaps included insufficient model interpretability along with the lack of standardized imaging protocols, which limited the clinical applicability of AD detection and localization techniques. These gaps will motivate the need for large-scale multicenter validation and standardized benchmark datasets in future research. Also, the dynamic FC analysis and effective models will be concentrated in the future to allow clinically applicable AD diagnosis.

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