CSE3042 - Machine Intelligence for Medical Image Analysis
Digital Assignment 1

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Title of Project : Prediction of Cognitive Decline from Brain MRI Scans

S.No	Title	Journal	Year	Method Used	Dataset Link	No. of Images Used	Advantages	Limitations	Special Remarks
1	Machine Learning Framework for Early MRI-based Alzheimer's Conversion Prediction in MCI Subjects	NeuroImage	2015	Semi-Supervised Learning, Novel Random Forest-Based Data Integration Scheme	Alzheimer's Disease Neuroimaging Initiative (ADNI)	AD: 200 NC: 231 pMCI: 164 sMCI: 100 uMCI: 130	**Use of Semi Supervised Learning:** Most of the earlier studies were based on supervised learning methods, where only labeled data samples are used for learning the model. Semi-supervised learning (SSL) approaches are able to use unlabeled data in conjunction with labeled data in a learning procedure for improving the classification performance. **Feature Selection:** A feature selection was conducted on MRI data derived from both AD subjects and normal controls, excluding data from MCI subjects. This was achieved	**Lack of Validation on External Datasets:** The study primarily focuses on internal validation or cross-validation within the same dataset. It would be beneficial to validate the model's performance on external datasets to assess its generalizability to different populations and imaging protocols. **Clinical Interpretability:** While the paper emphasizes the accuracy of the prediction model, it does not delve into the clinical interpretability of the features or factors	The paper aims to predict whether an MCI (Mild cognitive impairment) patient will convert to an AD patient over a 3-year period. Introduction of a novel biomarker was made, exclusively utilizing MRI data, employing a semi-supervised learning approach termed low density separation (LDS). The adoption of LDS, in contrast to more conventional supervised learning methods

							through regularized logistic regression. **Removal of Aging Effects:** The aging effects within the MRI data were eliminated before the training of the classifier to avoid potential confounding arising from age-related atrophies. **Incorporation of Cognitive Measurements with MRI Scans**: An aggregate biomarker was formulated by initially deriving a distinct MRI biomarker and subsequently integrating it with age and cognitive measures pertaining to MCI subjects at the baseline, accomplished through the application of a random forest classifier. The added value of these innovative features in predicting the conversion from MCI to AD was empirically demonstrated using data acquired from the Alzheimer's Disease Neuroimaging	contributing to the predictions. Understanding the biological or anatomical basis of the predictions can enhance the clinical utility of the model. **Longitudinal Data:** The paper does not discuss the utilization of longitudinal MRI data. Cognitive decline and Alzheimer's disease progression are dynamic processes, and incorporating longitudinal information may improve prediction accuracy. **Feature Importance and Explainability:** The paper does not provide insights into which features or regions of interest contributed most to the predictions. Understanding feature importance could aid in the clinical interpretation of the results.	such as support vector machines, demonstrated advantages, as evidenced by significantly elevated cross-validated AUC scores. Subsequently, a new technique for amalgamating MRI-biomarker with age and cognitive measurements was presented. This involved incorporating the score generated by the MRI-biomarker as a feature for the learning algorithm, specifically the Random Forest (RF) algorithm in this instance. The resulting aggregate biomarker yielded a cross-validated AUC score of 0.9020 averaged across 100 distinct cross-validation runs.

							Initiative (ADNI) database.		Given the proper nesting of cross-validation, wherein testing data was not utilized for feature or parameter selection, this AUC score holds promise for the early prediction of Alzheimer's Disease (AD) conversion.
2	Hierarchical Feature Representation and Multimodal Fusion with Deep Learning for AD/MCI Diagnosis	NeuroImage	2014	Deep Boltzmann Machine Model	Alzheimer's Disease Neuroimaging Initiative (ADNI)	AD: 93 NC: 101 MCI: 204	**Feature Extraction:** A patch-based approach is employed, positioned as an intermediary level between a voxel-based approach and an ROI-based approach. This strategy proves efficient in addressing concerns related to high feature dimensions and sensitivity to subtle changes. Also patch-based approaches adeptly manages region-wide pathologies, extending beyond specific ROIs. This aligns with the perspective of neurologists or radiologists, who analyze images by	**Visualization of Trained Weights:** From a clinical standpoint, interpreting resulting feature representations, particularly in investigating neurodegenerative diseases like AD or MCI, is challenging. The method lacks utility in providing clinically relevant information. Exploring the extension of the proposed method to identify brain abnormalities in terms of regions or areas is suggested for easier	A novel method for a high-level latent feature representation from neuroimaging data A systematic method for joint feature representation of multimodal neuroimaging data Hierarchical patch-level information fusion via an ensemble classifier

							investigating local patterns and subsequently integrating distributed local information across the entire brain to formulate clinical decisions. **Multi Modal Data Fusion:** The paper explores the fusion of multiple modalities like MRI and PET. This is done through analysis of their inherent shared features. **Use of DBM:** Deep Boltzmann Machine model can hierarchically find feature representations in a probabilistic manner. Rather than using the noisy voxel intensities as features the high-level representation obtained via DBM is more robust to noises and thus helps enhance diagnostic performances. Meanwhile, from a multimodal data fusion perspective, unlike the conventional multimodal feature	comprehension by clinicians. **Small Dataset for Deep Learning Model:** In experiments, the number of hidden units in each layer was manually determined, and relatively small data samples (93 AD, 76 MCI-C, 128 MCI-NC, and 101 NC) were used. Consequently, the network structures employed for discovering high-level feature representations may not be optimal. Emphasizing the need for more intensive studies, such as learning optimal network structures from larger datasets, is highlighted for practical implementation of deep learning in clinical settings. **Fusion of Different Modalities:** The current method solely considers the bi-modalities of MRI and PET. Acknowledging	Maximal diagnostic accuracies of 93.52% (AD vs. NC), 85.19% (MCI vs. NC), and 74.58% (MCI converter vs. MCI non-converter)

							combination methods that first extract modality-specific features and then fuse their complementary information during classifier learning, the proposed multimodal DBM fuses the complementary information from different modalities during a feature representation step. Also in such a multimodal data fusion method, the methodological characteristic of the DBM, allows the bidirectional information flow from one modality (e.g., MRI) to the other modality (e.g., PET) and vice versa. Therefore, feature representations can be distributed over different layers in the path between modalities and thus efficiently discover a shared representation while still utilizing the full information in the observations.	the benefits of combining multiple modalities for richer information, a more systematic model is deemed necessary to efficiently find and utilize complementary information from genetics, proteomics, imaging, cognition, disease status, and other phenotypic modalities. **Dataset Limitations:** Recent studies indicate subjective cognitive complaints as a significant genetic risk factor for progression to MCI or AD. In the ADNI dataset, however, relevant information is lacking. Consequently, in experiments, the NC group may include both genuine controls and those with subjective cognitive complaints.	

3	Multimodal Classification of Alzheimer's Disease and Mild Cognitive Impairment	NeuroImage	2011		Alzheimer's Disease Neuroimaging Initiative (ADNI)	AD: 51 NC: 52 MCI: 99	**Use of Multiple Modalities:** The authors used a multi-kernel SVM to integrate multiple modalities, namely MRI, PET and CSF. 93 features each were extracted from MRI and PET each and 3 features from CSF biomarkers. Such integration is advantageous as different biomarkers provide complementary information which is helpful in diagnosis of AD or MCI. **Consideration of Diversity of Individual Modalities:** Jaccard Similarity Coefficient and Kappa Index were used as quantitative measurements of diversity on any two modalities (MRI vs PET, PET vs CSF and CSF vs MRI). These results indicate that CSF and PET have the highest complementary information, while MRI and PET have the highest similar information for classification.	**Lack of Data:** Besides MRI, PET, and CSF, there are also other modalities of data, i.e., APOE. However, since not every subject has data on all modalities and the number of subjects with all modalities available is too small for reasonable classification, the current study does not consider APOE for multimodal classification. **Unable to discriminate among multiple stages of dementia:** In the current study, investigation has been done only on the classification between one stage of dementia (either MCI or AD) and healthy controls. It does not test the ability of the classifier to simultaneously discriminate multiple stages of dementia, i.e., multi-class classification of AD, MCI, and healthy controls.	The paper proposes to combine MRI, FDG-PET, and CSF biomarkers, to discriminate between AD (or MCI) and healthy controls, using a kernel combination method. A high accuracy of 93.2% for AD classification and a high sensitivity of 91.5% (for MCI converters) for MCI classification. CSF and PET have the highest complementary information and MRI and PET have the highest similar information for classification.

							Ensemble Method for Data Fusion: Multiple SVM models are trained on multiple kernel matrices from different modalities. For any particular test sample, each model will make a prediction and the final output is decided using majority voting. **Prominent Evaluation Metrics:** The method discussed in the paper, achieved a high accuracy (93.2%) for AD classification, a relatively high sensitivity (81.8%) for MCI classification, and especially a high sensitivity (91.5%) for classification of MCI converters.		
4	Multi-modal Classification of Alzheimer's Disease using Nonlinear Graph Fusion	Pattern Recognition	2017	Nonlinear Graph Fusion	Alzheimer's Disease Neuroimaging Initiative (ADNI)	AD: 37 MCI: 75 NC: 35	**Non -Linear Fusion Method for Combining Multiple Modalities: S**tate-of-the-art studies use linear methods to fuse the information from multiple modalities, which is not optimal for exploiting the complimentary information across	**Lack of Demographic Data:** The data used in the paper lacks demographic information about the subjects. However, the demographic information could potentially provide complementary information to boost	Multi-modality biomarkers were used for the classification of AD. Nonlinear graph fusion was used to investigate the multi-modal complementary information.

							modalities. The complementary information from multi-modal data is not necessarily linearly related. The authors presented a novel framework for multi-modality classification of AD using a nonlinear graph fusion method. **Data Imputation to Expand Sample Size:** The imputation approaches can fill the missing data of the excluded subjects so that it is likely to use as many samples as possible in the evaluation.	the classification performance. For example, it is reported that older subjects are more likely to develop AD than younger subjects. This means that age is an important predictor for classification of AD. Therefore, the classification performance could potentially be improved by adding age as an additional feature. **Dataset Limitations:** A subset of 147 subjects from ADNI were included in this study. The sample size is limited by the fact that four modalities were used in the work, which requires that data from four modalities were available for each subject. Many subjects were excluded due to the missing of their data from one modality or more. However, the excluded subjects could be potentially useful and	Validations were performed in different classification scenarios. Achieved superior results than the state-of-the-art linear combination approaches. The proposed method provides an effective way to integrate multiple heterogeneous data for the classification of AD.

								provide additional information for classifier training. **Lack of focus on Longitudinal Data:** This paper only focuses on cross-sectional data. Interesting insights can be found on using longitudinal data with graph fusion.	
5	Early Diagnosis of Alzheimer's Disease with Deep Learning	IEEE Journal of Bio-Medical and Health Informatics	2015	Stacked Sparse Auto-Encoders, Softmax Regression	Alzheimer's Disease Neuroimaging Initiative (ADNI)	AD: 65 MCI: 169 NC: 77	**Semi Supervised Non-Linear Model:** SVM Based Classification reduces Alzheimer's prediction to binary classification problem. Similarly, some methods embed prior knowledge into the data but the dependence of prior knowledge may be also sensitive to the changes of the dataset and hard to configure. Targeting at the constraints in previous studies, we believe the existing workflows can be efficiently optimized. This paper proposed a novel early diagnosis method for AD based on a deep learning architecture, consisting of stacked sparse auto-	**Longitudinal Analysis:** Alzheimer's disease is a progressive condition, and the paper does not discuss whether the deep learning model can effectively track disease progression over time. **Data Variability:** Deep learning models are highly data-dependent, and the effectiveness of the approach may vary depending on the diversity and quality of the dataset. The paper does not discuss how the model performs on different datasets or the impact of data variability.	This study has proven that multi-layered parametric learning model can be applied on biomedical datasets with smaller size to extract high-level biomarkers. The proposed method conducts AD diagnosis as a multi-class classification task, with minimal prior knowledge dependency in the model optimization.

							encoders and a soft-max regression layer. The proposed method has a multi-class nature and could reduce the reliance on prior knowledge about the data. Furthermore, this method is semi-supervised that can be extended to use unlabelled training samples, which are easier and cheaper to obtain. **Lucky Trail Avoidance:** To maximally avoid the 'lucky trails', the training and testing instances from each class, were randomly sampled to ensure they have similar distributions as the original dataset. For all methods in each fold of cross validation, about 90% subjects were used for training (including the pre-training of the deep neural nets) and the rest subjects were used for testing.		

							Reservation of Synergies between different Modalities: The proposed method performs dimensionality reduction and data fusion at the same time to reserve the synergy between data modalities.		
6	Fully Convolutional Networks for Semantic Segmentation	Proceedings of the IEEE conference on Computer Vision and Pattern Recognition (CVPR)	2015	Fully Convolutional Networks (FCNs)	PASCAL VOC 2011, 2012	Not Specified	**FCNs enable pixel-wise semantic segmentation:** Unlike traditional methods that classify images into pre-defined categories, FCNs provide the ability to assign a label to each pixel in the image. This capability allows for detailed understanding and analysis of the image content, leading to more precise segmentation results. **End-to-end learning for dense prediction tasks:** FCNs facilitate end-to-end learning, enabling the network to directly optimize the segmentation task. This streamlined learning process avoids the need for separate feature	**Memory-intensive; may require substantial GPU resources:** FCNs can be computationally demanding and memory-intensive, particularly when processing high-resolution images. This characteristic necessitates significant computational resources, particularly high-end GPUs, which can increase the cost and hardware requirements for implementing FCNs in real-world applications. **Limited context for large objects in early layers:** FCNs may encounter	The introduction of FCNs has significantly influenced the field of computer vision and image analysis. Their ability to perform pixel-wise semantic segmentation and streamline the learning process for dense prediction tasks has revolutionized the way researchers approach image understanding and analysis. Despite their computational complexity and limitations in capturing fine-grained details,

							extraction and classification steps, leading to more efficient and accurate predictions. **Utilizes deconvolutional layers for Upsampling:** FCNs incorporate deconvolutional layers that allow the network to learn to increase the spatial resolution of the feature maps. By using these layers, FCNs can efficiently produce segmentation maps with pixel-level accuracy, enabling better visualization and understanding of the intricate details within the image.	challenges in capturing the complete context of large objects, particularly in the early layers of the network. As a result, the segmentation of such objects may not be as accurate or detailed as desired, potentially leading to misclassifications or incomplete segmentation results. **Fine-grained details may still be challenging:** Although FCNs excel at capturing the overall semantic information in an image, they may encounter difficulties in accurately capturing fine-grained details within the image. This limitation can impact the precise delineation of intricate structures or objects with subtle visual variations, potentially leading to inaccuracies or loss of important information during the segmentation process.	FCNs remain a foundational framework for various segmentation tasks and continue to be a key area of research for improving the accuracy and efficiency of semantic segmentation models.

7	Prediction of Alzheimer's Disease in Subjects with Mild Cognitive Impairment from the ADNI Cohort Using Patterns of Cortical Thinning	NeuroImage	2013	Cortical Thickness Measurement, Machine Learning	Alzheimer's Disease Neuroimaging Initiative (ADNI)	AD: 194 CN: 226	**Utilization of cortical thinning patterns for Alzheimer's disease prediction in individuals with mild cognitive impairment:** The study leverages cortical thickness measurements as potential biomarkers for predicting the progression from mild cognitive impairment (MCI) to Alzheimer's disease. By focusing on changes in cortical thickness, the research highlights the potential of structural neuroimaging as an effective tool for early detection and prediction of Alzheimer's disease. **Leave-One-Out Validation Technique to prevent bias:** A leave-one-out (LOO) validation strategy was employed, wherein, for each comparison, all subjects, with the exception of one, were employed to select features and construct	**Possible confounding factors not fully addressed:** While the study focuses on cortical thinning patterns, it may not fully address all potential confounding factors that could influence cortical thickness measurements. Factors such as age-related cortical changes or comorbid conditions could potentially impact the accuracy of the predictions, highlighting the need for comprehensive consideration of various contributing factors in the analysis.	**Highlights the potential of structural neuroimaging for early diagnosis of Alzheimer's disease:** The research underscores the significance of utilizing structural neuroimaging techniques, specifically the analysis of cortical thinning patterns, for the early detection and prediction of Alzheimer's disease in individuals with mild cognitive impairment. This emphasis on leveraging neuroimaging data to identify potential biomarkers aids in understanding the underlying structural changes associated with disease progression, ultimately contributing to

							a classification model. Subsequently, the excluded subject was utilized for testing. This process was iterated for every subject within the two compared groups, thereby validating the method across all subjects. By excluding the test subject from feature selection and classifier construction, any potential bias or "double dipping" in predictive efforts for converters was effectively avoided.		the development of early intervention and management strategies for Alzheimer's disease.
8	Early Detection of Alzheimer's Disease Using Magnetic Resonance Imaging: A Novel Approach Combining Convolutional Neural Networks and Ensemble Learning	Frontiers in Neuroscience	2020	Convolutional Neural Networks, Ensemble Learning	Alzheimer's Disease Neuroimaging Initiative (ADNI)	509 subjects AD: 137 NC: 162	**Application of Data Augmentation Techniques to Enhance the Dataset:** To address the potential over-fitting issue in training resilient CNN models and to integrate potential image disparities, augmented images were created from the original slices using six operations: rotation, translation, gamma correction, random noise addition, scaling, and random affine transformation. These augmented data were then incorporated	**Lack of detailed information on the specific architecture and parameters of the utilized Convolutional Neural Networks:** While the study integrates Convolutional Neural Networks, it does not provide comprehensive insights into the specific architecture, hyperparameters, or training procedures employed. This limitation may hinder the reproducibility	

							into the initial training dataset to ensure an adequately large sample size. The utilization of data augmentation also served to alleviate the initially imbalanced dataset (for instance, there were more subjects with MCInc than those with MCIc). The predefined number of augmented slices to be generated varied from class to class based on the specific dataset imbalance. **Integration of Convolutional Neural Networks and Ensemble Learning for early detection of Alzheimer's disease using MRI data:** The study's innovative approach combines the strengths of Convolutional Neural Networks (CNNs) and Ensemble Learning techniques to enhance the accuracy and efficacy of early detection of Alzheimer's disease based on Magnetic	and further optimization of the proposed methodology by other researchers, potentially limiting the broader application of the approach in different research settings.	

							Resonance Imaging (MRI) data. This integrated methodology allows for more comprehensive analysis and identification of complex patterns associated with the disease, potentially leading to improved diagnostic accuracy and earlier intervention. **Automatic Selection of ROIs:** The discussed method does not require manual selection of ROIs, but automatically extracts the discriminable features from the MR images using a CNN-based adaptive representation learning method in a data-driven way. The proposed method also employs a two-stage EL scheme to improve generalization and robustness. **Ability to Detect Other Neurological Problems:** The advocated method may be useful for identifying additional candidate neuroimaging		

							biomarkers for AD as well as for other brain diseases such as Parkinson's disease, autism, schizophrenia and severe depression, especially for identifying candidate neuroimaging biomarkers for other little-known brain disorders, in a data-driven way.		
9	Hippocampus and Amygdala Volume Estimation in Magnetic Resonance Images Using Deep Learning	Alzheimer's & Dementia	2018	Deep Learning	Alzheimer's Disease Neuroimaging Initiative (ADNI)	Not specified	Accurate estimation of hippocampus and amygdala volumes through deep learning techniques. Efficient analysis of large-scale MRI datasets for automated hippocampus and amygdala volume measurement.	Lack of information regarding specific deep learning architecture and training procedures.	The study emphasizes the potential of deep learning for precise volumetric estimation of critical brain structures.
10	Resting-state Multi-spectrum Functional Connectivity Networks for Identification of MCI Patients	PloS One	2012	Resting-state Multi-spectrum Functional Connectivity Networks	Data was generated by studying subjects recruited by the Duke-UNC Brain Imaging and Analysis Center (BIAC), Durham, North Carolina, USA.	MCI: 12 NC: 25	**Utilization of multi-spectrum functional connectivity networks for identification of MCI patients:** The study leverages the power of multi-spectrum functional connectivity networks, allowing for a comprehensive analysis of various functional connectivity patterns	**Possible challenges in generalizing the results to diverse datasets:** As the dataset is developed solely for the particular paper, the generalizability of the findings to different populations or settings may be limited. Addressing these potential variations and	The paper's emphasis on multi-spectrum functional connectivity networks for the identification of MCI patients highlights the potential of resting-state functional connectivity analysis as a

							within the brain. By incorporating multiple spectra, the research can potentially capture more nuanced and comprehensive information about the functional connectivity changes associated with mild cognitive impairment (MCI), aiding in the early identification and diagnosis of at-risk individuals. **Provides insights into the use of resting-state functional connectivity for early detection of cognitive impairment:** By focusing on resting-state functional connectivity networks, the research offers valuable insights into the potential use of intrinsic brain activity patterns as biomarkers for the early detection of cognitive impairment. This approach enables the identification of specific functional connectivity alterations that may	ensuring the robustness of the findings across diverse datasets is essential for establishing the broader applicability of the proposed methodology in identifying individuals with MCI.	valuable tool for early detection and intervention in cognitive impairment. However, addressing the limitations related to dataset characteristics and reproducibility is crucial for ensuring the reliability and broader applicability of the research findings in diverse research settings.

							serve as early indicators of cognitive decline, facilitating timely intervention and management strategies for individuals at risk of developing MCI.		
11	Detection of Subjects and Brain Regions Related to Alzheimer's Disease Using 3D MRI Scans Based on Eigenbrain and Machine Learning	Frontiers in Computational Neuroscience	2015	Eigenbrain Analysis, Machine Learning	Open Access Series of Imaging Studies (OASIS)	126 subjects (98 NCs and 28 ADs)	**Utilization of Eigenbrain and machine learning for the detection of subjects and brain regions associated with Alzheimer's disease:** The study leverages the potential of Eigenbrain analysis and machine learning techniques to identify specific subjects and brain regions that may be indicative of Alzheimer's disease. By employing advanced analytical methodologies, the research can potentially detect subtle patterns and variations in the brain's structural characteristics, aiding in the early identification and diagnosis of individuals at risk of developing Alzheimer's disease. **Provides insights into the application**	**Two-Dimensional Behaviour of Eigenbrain:** Eigenbrain is essentially two-dimensional, which does not reduce the redundancy along the slice direction. **Computationally Intensive:** There is a need of preprocessing for spatial registration, which costs large amount of computation resources.	The paper presented an automated and accurate classification method that was based on eigenbrains and machine learning, in order to detect AD subjects and AD-related brain regions using 3D MR images. The results showed the proposed POL-KSVM method achieved 92.36% accuracy, which was competitive with state-of-the-art methods.

							of 3D MRI scans and advanced analytical techniques for early identification of Alzheimer's disease: By emphasizing the use of 3D MRI scans in conjunction with advanced analytical techniques, the research offers valuable insights into the potential application of sophisticated imaging modalities for the early detection of Alzheimer's disease. This approach facilitates a more comprehensive and detailed analysis of the brain's structural features, enabling the identification of specific biomarkers and patterns associated with the onset and progression of Alzheimer's disease. **Advantages of Eigenbrains:** The advantages of eigenbrain are three-fold: (i) it reaches very high classification accuracy, which was better than or competitive with state-		

							of-the-art methods; (ii) it can directly find discriminant voxels/regions within the whole brain; (iii) it can be combined with other features, in order to increase the classification performance.		
12	DeepAD: Alzheimer's Disease Classification via Deep Convolutional Neural Networks Using MRI and fMRI	BioRxiv	2016	Deep Convolutional Neural Networks, MRI, fMRI	Alzheimer's Disease Neuroimaging Initiative (ADNI)	AD: 263 NC: 183	**Robust Pipelines:** The method involves the development of robust pipelines that incorporate extensive preprocessing modules and deep learning-based classifiers. **Structural and Functional MRI Data Integration:** The approach utilizes both structural and functional MRI data, allowing for a comprehensive analysis of brain abnormalities associated with Alzheimer's disease. **Scale and Shift Invariant Features:** The method employs a convolutional neural network architecture to extract scale and shift invariant low- to high-level features from a	**Practical Implementation Challenges:** Implementing deep learning models, especially those involving complex neuroimaging data like MRI and fMRI, in clinical settings can present practical challenges. The computational requirements for training and deploying deep learning models can be significant, necessitating powerful computing resources. The hardware and infrastructure demands could potentially limit the widespread adoption of the proposed methodology in real-world clinical environments with	In this study, functional MRI data were used for the first time in deep learning applications for the purposes of medical image analysis and Alzheimer's disease prediction. These proposed and implemented pipelines, which demonstrate a significant improvement in classification output when compared to other studies, resulted in high and reproducible accuracy rates of 99.9% and 98.84% for the fMRI and MRI pipelines, respectively.

							substantial volume of whole-brain data, enhancing the model's robustness. **Highly Accurate Predictive Model:** The extracted features contribute to the creation of a highly accurate and reproducible predictive model for distinguishing Alzheimer's-affected brains from normal healthy brains in older adults. **Superior Performance:** The accuracy rates achieved for both MRI and fMRI modalities, as well as the use of state-of-the-art architectures like LeNet and GoogleNet, surpass the performance of all previous methods used for the same purpose. **Incorporation of fMRI Data:** The study pioneers the use of fMRI data to train a deep learning-based pipeline, extending the applicability of the	limited computational resources. **High Computation Requirements:** The pipelines used to process the modal data were executed on a GPU-based high performance computing platform.	

							method to new and valuable sources of information. **Characterization of Multimodal MRI Biomarkers:** The study showcases that the developed pipelines serve as effective algorithms for characterizing multimodal MRI biomarkers, contributing to a more comprehensive understanding of brain conditions. **Potential for Disease Progression Prediction:** The proposed methods exhibit strong potential for predicting the stages of Alzheimer's disease progression, offering valuable insights into the temporal evolution of the condition. **Classification of Aging Effects:** The methods also show promise in classifying the effects of aging in the normal brain, contributing to a better		

							understanding of age-related changes in brain structure and function.		
13	Deep Sparse Multi-Task Learning for Feature Selection in Alzheimer's Disease Diagnosis	Brain Structure and Function	2013	Deep Sparse Multi-Task Learning, Feature Selection	Alzheimer's Disease Neuroimaging Initiative (ADNI)	AD: 198 pMCI: 167 sMCI: 236 NC: 229	**Addressing 'High-Dimension and Small Sample' Problem:** The method tackles the challenging issue of 'high-dimension and small sample' in neuroimaging-based Alzheimer's Disease/Mild Cognitive Impairment (AD/MCI) diagnosis, a common problem in this field. **Sparse Multi-Task Learning for Feature Selection:** The proposed method employs sparse multi-task learning for feature selection, effectively reducing dimensionality and addressing the challenge of noise interference with informative features during optimization. **Incorporation of Subclass Labeling Scheme:** The method incorporates a subclass labeling scheme,	**Sensitivity to Hyperparameters:** Deep sparse multi-task learning methods often rely on the selection of appropriate hyperparameters to achieve optimal performance. The sensitivity of these methods to the choice of hyperparameters can pose a significant challenge, as the effectiveness of the feature selection process and the overall diagnostic accuracy may heavily depend on the specific settings of these parameters. Inaccurate or suboptimal hyperparameter choices may lead to subpar feature selection results and affect the overall diagnostic performance, highlighting the importance of careful	

							reflecting the complex distributional characteristics in each class, which contributes to a more nuanced and accurate representation in AD/MCI diagnosis. **Iterative Filtering in Hierarchical Fashion:** Instead of selecting informative features in a single hierarchy, the method iteratively filters out uninformative features in a hierarchical fashion, preventing the underestimation of informative features and overestimation of uninformative features. **Utilization of Regression Coefficients as Context Information**: At different hierarchies, the method utilizes regression coefficients optimized in the lower hierarchy as context information, enhancing the determination of informative features for classification.	parameter tuning and optimization. **Interpretability of Feature Selection Results:** While deep learning-based feature selection methods can effectively identify relevant biomarkers and imaging features, interpreting the specific rationale behind the selection of these features can be challenging. The lack of interpretability in the feature selection process may hinder the understanding of the underlying biological or pathological significance of the selected features. Interpreting the selected features in the context of Alzheimer's disease pathology is crucial for gaining insights into the disease mechanisms and improving the clinical interpretability and translational value of the feature selection results.	

							Equal Consideration of Feature Importance from Different Modalities: While acknowledging the potential impact of different modalities, the method treats features from different modalities equally. However, it suggests the possibility of adapting to modality-specific importance through the use of multi-kernel SVM, as demonstrated by prior studies. **Consideration of Subjective Cognitive Complaints as a Genetic Risk Factor:** The method recognizes the significance of subjective cognitive complaints as an important genetic risk factor, contributing to the identification of individuals in the 'pre-MCI' stage, an aspect often underestimated in the field.	**Data Dependency and Generalizability:** The performance of deep sparse multi-task learning methods for feature selection can be heavily influenced by the characteristics of the specific datasets used for training and evaluation. Variations in data distributions, imaging protocols, and patient demographics across different datasets can impact the effectiveness and generalizability of the feature selection results. Ensuring the robustness and generalizability of the feature selection methodology across diverse datasets is essential for establishing the broader applicability and reliability of the proposed approach in different research and clinical settings.	
14	Integrating Different Data Modalities for the	SN Computer Science	2023	ML-based omics imaging approach	ANMerge	AD: 42 MCI: 428 NC: 250	**Improved Performance through Integration:** The	**Potential Bias from Clinical Features:** The utilization of clinical features,	The authors proposed an extensive evaluation of a

	Classification of Alzheimer's Disease Stages						method demonstrates enhanced performance by integrating omics and imaging features, surpassing the individual contributions of these features when considered separately. **Consistent Performance Across AD Classification Problems**: The observed improvement holds true for various binary AD classification problems, indicating the robustness and generalizability of the approach. **Superior Performance in Challenging MCI vs. CN Patient Distinction:** The method excels in the challenging task of distinguishing Mild Cognitive Impairment (MCI) vs. Cognitively Normal (CN) patients, showcasing its efficacy even in complex diagnostic scenarios.	particularly cognitive test scores, is identified as a potential limitation. These features, being part of the clinician diagnosis process, may introduce a positive bias in the results, hindering a fair evaluation of the method. **Dependency on Specific Dataset (ANMerge):** The method's applicability and performance are contingent on the characteristics of the ANMerge dataset. The generalizability to other datasets or real-world scenarios may need further validation. **Limited Comparison with Existing Methods:** As the ANMerge dataset is relatively new, there is a limitation in the ability to compare the method with existing approaches, potentially limiting the contextual	machine learning procedure for classifying Alzheimer's patients using data from the ANMerge dataset. They considered data from different modalities, including imaging, omics, and clinical features, taken alone or combined together.

								understanding of its performance.	
15	Inter-modality Relationship Constrained Multi-modality Multi-task Feature Selection for Alzheimer's Disease and Mild Cognitive Impairment Identification	NeuroImage	2014	Multi-modality Multi-task Feature Selection, Inter-modality Relationship Constraint	Alzheimer's Disease Neuroimaging Initiative (ADNI)	AD: 51 MCI: 99 NC: 52	**Preservation of Inter-Modality Relationships:** The method introduces a novel multi-task feature selection approach that considers feature selection from each modality as a separate task. Importantly, it imposes a constraint to preserve the inter-modality relationship, ensuring that different yet complementary information from various modalities is not overlooked. This enables the model to capture a more comprehensive and synergistic representation of the data. **Enhanced Classification Performance:** The proposed method achieves superior performance compared to state-of-the-art classification methods. The accuracy rates of 94.37% and 78.80% for AD and MCI identification,	**Requirement for Equal Feature Numbers Across Modalities:** The proposed feature selection method necessitates that each modality provides the same number of features. This poses a limitation, particularly when dealing with modalities, such as CSF and genetic data, in the ADNI database, which may have different feature counts. This limitation restricts the method's immediate applicability to datasets with varying feature dimensions. **Potential Inclusion of Additional Modalities in Future Work:** The study acknowledges the absence of certain modalities, such as CSF and genetic data, in the current method. While the intention is to extend the method to include more modalities in future	The proposed method addresses a critical gap in Alzheimer's Disease diagnosis by innovatively preserving inter-modality relationships during feature selection.

							respectively, along with high area under the ROC curve (AUC) values, highlight the effectiveness of the approach in accurately classifying Alzheimer's Disease and mild cognitive impairment. **Applicability to MCI Conversion Prediction:** The method extends its utility to predicting the conversion of Mild Cognitive Impairment (MCI) to Alzheimer's Disease. With an accuracy of 67.83% and an AUC of 0.6957 for distinguishing between MCI converters and non-converters, the proposed method addresses a clinically significant aspect, showcasing its versatility in handling different diagnostic tasks related to AD.	work, the current limitation may result in an incomplete representation of pathological information available in these additional data sources. **Need for Testing on Completely Independent Datasets:** Despite using cross-validation to evaluate generalizability, the study acknowledges the importance of testing on a completely independent dataset. The lack of such testing introduces a potential limitation in establishing the method's performance and reliability across diverse datasets and real-world applications.	
16	Preclinical Detection of Alzheimer's Disease Using FDG-PET, with or without	Journal of Alzheimer's Disease	2020	FDG-PET, with or without Amyloid Imaging	Review Paper	-	**High Sensitivity for Disease Discrimination:** FDG-PET exhibits high sensitivity in distinguishing Alzheimer's Disease (AD) from both healthy	**Absence of Postmortem Data:** A major limitation lies in the absence of postmortem data in most FDG-PET studies. This hinders the confirmation of	This paper reviews reports of clinical and preclinical CMRglc reductions observed in

	Amyloid Imaging						controls and other neurodegenerative diseases. It serves as a valuable tool for identifying individuals at higher risk for AD. **Quantitative and Topographical Correlation:** The method offers good quantitative and topographical correlation with clinical progression. This strength enhances its utility in tracking disease-related changes and understanding the spatial distribution of metabolic abnormalities. **Potential for Risk Stratification:** FDG-PET's ability to differentiate individuals at higher versus lower AD risk enhances its role in stratifying risk levels, aiding in early identification and intervention.	clinical symptoms and reductions in cerebral metabolic rate of glucose (CMRglc) as solely attributable to AD pathology, raising uncertainties about the specificity of findings. **Reliance on Clinical Diagnosis:** The use of clinical diagnosis as the gold standard introduces a potential limitation, as it may result in the inclusion of patients with a dementia other than AD in the AD group and vice versa. This reliance on clinical diagnosis raises the risk of misclassification. **Hypometabolism Not Exclusive to AD:** In asymptomatic subjects with hypometabolism, CMRglc deficits may arise from causes other than AD pathology. Additionally, not all individuals with hypometabolism may necessarily progress to	association with genetic and non-genetic risk factors for AD.

								AD, introducing ambiguity in the interpretation of FDG-PET findings. **Need for Imaging of AD Pathology:** The authors emphasize the essential role of imaging AD pathology in resolving uncertainties. This indicates a dependence on complementary imaging modalities to provide a more definitive understanding of the underlying pathology contributing to hypometabolism observed in FDG-PET studies.	
17	Multimodal Neuroimaging Feature Learning With Multimodal Stacked Deep Polynomial Networks for Diagnosis of Alzheimer's Disease	IEEE Journal of Biomedical and Health Informatics	2018	Multimodal Stacked Deep Polynomial Networks (MMSDPN)	Alzheimer's Disease Neuroimaging Initiative (ADNI)	AD: 51 MCI: 99 NC: 52	**Effectiveness for Small Datasets:** The proposed MM-SDPN algorithm demonstrates effectiveness, particularly for small datasets. This suggests potential utility in scenarios where limited data is available, showcasing adaptability to situations common	**Limited Theoretical Foundation:** DPN is a new DL algorithm with limited theoretical foundation and algorithmic development. This raises concerns about its robustness and generalizability, emphasizing the need for further theoretical advancements to	A novel MM-SDPN algorithm has been introduced, featuring a two-stage SDPN. It demonstrates the capability to effectively learn and integrate multimodal data for the diagnosis of Alzheimer's disease. MM-

							in medical imaging studies. **Fast Processing for Large-Scale Data:** Due to the absence of forward and backward feedbacks between successive basic DPNs, SDPN, and MM-SDPN, these algorithms are relatively simple and fast. This simplicity positions them as promising candidates for handling large-scale data, ensuring efficiency in processing. Versatility in Learning Feature Representation: The planned application of MM-SDPN to learn feature representation directly from local patches of MRI and PET demonstrates the versatility of the algorithm. This adaptability to diverse data sources signifies its potential in handling multimodal neuroimaging information. **Future Exploration of Semi-Supervised**	establish its credibility. **Effectiveness Primarily Demonstrated for Small Datasets:** While MM-SDPN exhibits effectiveness for small datasets, its performance on larger datasets is assumed based on the simplicity and speed of the algorithm. This assumption requires empirical validation to ensure consistent efficacy across different data scales. **Dependency on Future Algorithmic Improvements:** The mention of future work to improve the DPN algorithm implies a dependency on algorithmic advancements for the method's overall efficacy. The success of the MM-SDPN and related frameworks is contingent on continuous improvements in the underlying DPN algorithm.	SDPN attains state-of-the-art performance in classifying both two stages and four stages of AD progression.

							Learning: The intention to explore semi-supervised MM-SDPN acknowledges the practicality of acquiring unlabeled medical images, offering a pathway to enhance representation learning. This strategic approach aligns with the recognition that unlabeled data can contribute to performance improvement. **Integration with MKL for Enhanced Classification:** The proposed integration of Multiple Kernel Learning (MKL) with MM-SDPN for Alzheimer's Disease (AD) classification represents a sophisticated strategy. Leveraging the learned features from SDPN and individual features from MRI and PET enhances the classification framework, with the potential to further improve performance.		
18	Automated Detection of	NeuroImage	2018	Combined Spatial Atrophy	A total of 1037 participants were	79 patients with a	**Innovative Multimodal**	**Sample Selection Bias:** The method's	The present study evaluated an

	Amnestic Mild Cognitive Impairment in Community-Dwelling Elderly Adults: A Combined Spatial Atrophy and White Matter Alteration Approach			and White Matter Alteration Approach	drawn from the Sydney Memory and Aging Study (MAS), a longitudinal study of non-demented, community dwelling individuals aged 70–90 years old at baseline	clinical diagnosis of aMCI and 204 who were cognitively normal	**Approach:** The method introduces a novel approach by incorporating measures of both spatial atrophy from T1-weighted images and white matter alterations assessed through Diffusion Tensor Imaging (DTI) tract-based spatial statistics (TBSS). This multimodal strategy enhances the comprehensiveness of the neuroimaging analysis. **Advanced Feature Extraction Techniques:** Subcortical volumetric features are extracted using a sophisticated FreeSurfer-initialized Large Deformation Diffeomorphic Metric Mapping (FS+LDDMM) segmentation approach. Additionally, fractional anisotropy (FA) values are obtained for white matter regions of interest. These advanced techniques contribute to a more	reliance on participants from the Sydney Memory and Aging Study (MAS) introduces a potential selection bias. The study population consists of non-demented, community-dwelling individuals aged 70–90 years at baseline, recruited randomly from specific areas in Eastern Sydney. This may limit the generalizability of findings to broader demographics. **Limited Generalization to Non-Scanner Subgroup:** The subgroup with both T1-weighted and DTI scans (283 individuals) may not fully represent the entire cohort (1037 MAS participants). Findings from the neuroimaging analysis may not be directly generalizable to the larger group without imaging data, potentially limiting the broader	automated, data-driven method for identifying individuals with aMCI in a community-based elderly sample, and was the first to do so using a combination of T1-weighted-derived volumetrics and DTI-derived measures of WM alterations

							nuanced and detailed representation of brain structure. **Optimized Feature Selection with SVM:** The method employs a Support Vector Machine (SVM) for feature selection, identifying an optimal subset of features ranked by their discriminative ability between individuals with amnestic Mild Cognitive Impairment (aMCI) and those with normal cognition. This ensures an efficient and focused feature set for training SVM classifiers, enhancing classification accuracy. **Consideration of Potentially Confounding Factors:** The study goes beyond neuroimaging features and identifies various sociodemographic, lifestyle, health, and other factors that may impact the classification of individuals. This comprehensive	applicability of the method's outcomes. **Statistical Testing Challenges:** Conducting multiple tests (ANOVA or chi-square) simultaneously for numerous factors raises concerns about inflated Type I error rates. The liberal significance level (pb0.10) for pair-wise comparisons may increase the risk of identifying statistically significant results by chance, impacting the reliability of the findings. **Backward Stepwise Logistic Regression:** The use of backward stepwise logistic regression introduces the risk of overfitting and may result in a model that fits the specific dataset too closely. This could limit the generalizability of the model to broader populations or datasets.	

							consideration adds a layer of contextual understanding to the classification schema, addressing potential confounding variables.		
19	Statistical Analysis of Longitudinal Neuroimage Data with Linear Mixed Effects Models	NeuroImage	2013	Linear Mixed Effects Models	Alzheimer's Disease Neuroimaging Initiative (ADNI)	AD: 188 cMCI: 166 sMCI: 227 HC: 210	**Powerful and Versatile Framework:** Linear Mixed Effects (LME) models offer a powerful and versatile framework for analyzing longitudinal data, particularly suitable for handling unbalanced data with variable missing rates across timepoints and imperfect timing. **Effective Handling of Unbalanced Data:** LME models elegantly handle unbalanced data, accommodating subjects with a single time-point to characterize inter-subject variation, providing a robust representation of group mean trajectories and covariance structures between serial measurements. **Enhanced Sensitivity in**	**Complexity of Analysis:** The comprehensive nature of LME models, while advantageous, introduces complexity in managing and interpreting large datasets. This complexity may pose challenges, especially for researchers unfamiliar with the intricacies of LME models. **Focused on Univariate Analysis:** The study primarily focuses on univariate analysis, where the correction for "multiple comparisons" is not addressed. Future work is suggested to extend the LME framework to the mass-univariate setting, acknowledging the need for more complex analyses	The study provides a quantitative empirical evaluation of the performance of LME and competing alternatives popularly used in prior longitudinal structural MRI studies, like repeated measures ANOVA.

							Realistic Settings: The study demonstrates that LME models provide enhanced sensitivity in realistic LNI settings compared to alternative methods like repeated measures ANOVA or the analysis of summary metrics. This is crucial for accurately detecting effects in complex datasets.	involving a large number of pixels/voxels. **Subject to Model Fit Improvement:** While the study highlights the potential improvement in model fit afforded by including subjects with a single time-point, this may introduce biases or assumptions that need to be carefully considered. The generalizability of this improvement to other datasets should be explored in future research.	
20	View-Centralized Multi-Atlas Classification for Alzheimer's Disease Diagnosis	Human Brain Mapping	2014	View-Centralized Multi-Atlas Classification	Alzheimer's Disease Neuroimaging Initiative (ADNI)	AD: 97 pMCI: 117 sMCI: 117 NC: 128	**Ensemble Classification Strategy:** The study proposes an ensemble classification method by combining results from multiple classifiers corresponding to multiple atlases. This ensemble strategy, including PC, Lasso, and the proposed VCMA method, consistently performs better than other	**High Computational Cost:** The use of multiple atlases for image registration contributes to a high computational cost in the VCMA method. This limitation should be considered, especially in scenarios where computational efficiency is crucial. **Limited Feature Representation:**	

							methods, highlighting the effectiveness of ensemble approaches in boosting classification results based on multiatlas data. **Robustness to Parameter Variations:** The VCMA method demonstrates robustness to parameter variations, indicating that its performance is not highly sensitive to the selection of parameter values. This enhances its applicability and ease of use. **Effective Feature Selection:** The VCMA method introduces a feature selection approach that focuses on one atlas at a time, addressing redundancy in features extracted from multiple atlases. This effective feature selection contributes to improved diagnostic power, surpassing the performance of compared methods.	The study only extracts regional features for feature representation, neglecting other morphometric features such as Jacobian determinants. Incorporating a broader set of features could enhance the method's capability. **Single-Modality Data:** The VCMA method relies solely on MRI data for learning the classification model, overlooking the potential benefits of incorporating other biomarkers such as FDG-PET. The inclusion of multiple biomarkers could potentially enhance the overall learning performance. **Baseline Data Only:** The experiments utilize only the MRI baseline data from the ADNI dataset. Future work could involve incorporating both	

								baseline and longitudinal data to capture spatiotemporal development patterns of brain atrophy, improving the diagnosis and prediction of brain diseases.	
21	Multi-modal Multi-task Learning for Joint Prediction of Multiple Regression and Classification Variables in Alzheimer's Disease	NeuroImage	2012	Multi-modal Multi-task Learning	Alzheimer's Disease Neuroimaging Initiative (ADNI)	186 ADNI subjects with all MRI, PET and CSF data AD: 45 MCI: 91 NC: 50	**Innovative Multi-Modal Multi-Task Learning:** The proposed M3T learning method introduces a novel approach by combining two successive steps: multi-task feature selection and multi-modal support vector machine. This innovative method aims to jointly predict multiple regression and classification variables from multimodal data. **Recognition of Complementary Information from Different Modalities:** Acknowledging the complementary information from various modalities, the M3T method effectively combines MRI, PET,	**Dependency on Availability of Multi-Modal Data:** The M3T method relies on the availability of multi-modal data, specifically MRI, PET, and CSF. The requirement for each subject to have corresponding modality data limits the size of the subject pool for study. **Exclusion of Other Modalities (e.g., APOE):** Despite the existence of other modalities such as APOE data, the study does not consider them due to data limitations. The exclusion of certain modalities may impact the	This paper is one of the first investigations on jointly predicting multiple regression and classification variables from the baseline multi-modal data.

							and CSF data for joint regression and classification tasks. It outperforms individual-modality-based methods, showcasing the advantage of leveraging multi-modal information. **Robustness to Feature Selection Variability:** The M3T method incorporates feature selection techniques like MTFS and Lasso, ensuring adaptability to different subsets of selected features in cross-validation trials. Crucial features, such as hippocampal regions, consistently contribute to the model. **Consideration of Multi-Modal Regression:** In contrast to existing works that focus on multi-modal classification, the M3T method extends its application to multi-modal regression. It demonstrates that	comprehensiveness of the analysis. **Limited Sample Size for Comprehensive Study:** The study acknowledges limitations in sample size, especially concerning subjects with all baseline MRI, PET, and CSF data. This limitation may affect the generalizability of the findings. **Exclusion of Some Clinical Variables:** Due to data availability constraints, the study does not investigate certain clinical variables present in the ADNI database. While including more clinical variables could enhance performance, this was not explored in the current study.	

							combining MRI, PET, and CSF data enhances the performance of regression models. **Use of Multi-Modal SVM for Both Regression and Classification:** The current model employs multi-modal SVM for both regression and classification tasks. The linear kernel, with normalized feature vectors, proves effective and requires no additional parameter tuning.		
22	Sparse Learning and Stability Selection for Predicting MCI to AD Conversion Using Baseline ADNI Data	BMC Neurology	2012	Sparse Learning and Stability Selection	Alzheimer's Disease Neuroimaging Initiative (ADNI)	MCI: 319	**Large and Unbiased MCI Cohort:** The study benefits from a large cohort of Mild Cognitive Impairment (MCI) samples, ensuring statistical robustness. The crucial aspect of this advantage is that the cohort is unbiased concerning age or education status, minimizing confounding variables that could affect the results. **Integration of Various Baseline Data:** Unlike some	**Cerebellar Atrophy Association:** The study notes a surprising correlation between cerebellar atrophy and AD. While this association has been detected in other studies, the specific role of the cerebellum in AD remains unclear. This unexpected finding highlights the need for further investigation to understand the significance of cerebellar atrophy in the context of MCI-to-AD conversion.	The results demonstrate the effectiveness of stability selection for feature selection in the context of sparse logistic regression

							other studies, this research integrates and tests a diverse range of baseline data available in the Alzheimer's Disease Neuroimaging Initiative (ADNI). This comprehensive approach includes data from MRI scans, demographic information, genetic factors (APOE genotyping), and cognitive measures. The inclusion of multiple types of data enhances the depth and richness of the analysis. **Application of Sparse Logistic Regression with Stability Selection:** The study employs advanced statistical techniques by applying sparse logistic regression with stability selection to ADNI data. This methodology ensures robust feature selection, enabling the identification of the most relevant variables for predicting the outcome. Sparse logistic regression helps prevent overfitting and	**Cingulate Cortex Atrophy:** The study identifies the atrophy of the rostral anterior cingulate cortex as predictive of conversion to AD. While this aligns with previous studies, the specific implications and functional consequences of cingulate cortex atrophy in early AD stages warrant further exploration. **CSF Biomarkers Lack Specificity:** The results suggest that cerebrospinal fluid (CSF) biomarkers, while showing an aberrant signature in MCI Converters, lack the specificity to discriminate between MCI to AD Converters and Non-converters. This limitation emphasizes the need for additional and more specific biomarkers for accurate predictions.	

							enhances the interpretability of the selected features. **Four-Year Follow-Up Period:** The evaluation considers a 4-year follow-up period, providing a longitudinal perspective on the progression of MCI. This extended timeframe allows for a more comprehensive understanding of the factors influencing the conversion from MCI to other conditions.	**Feature Interpretation and Redundancy:** While the study effectively identifies a set of 15 features (Biosignature-15) with high predictive power, some of these features are known to be important in characterizing Alzheimer's Disease (AD). This raises a challenge in distinguishing whether the identified features genuinely contribute to prediction or if they are redundant with existing knowledge. The reliance on features closely associated with AD may limit the novelty of the findings.	
23	Association of Elevated Amyloid Levels with Cognition in Preclinical Alzheimer's Disease	JAMA Neurology	2017	Exploratory Analysis	Alzheimer's Disease Neuroimaging Initiative (ADNI)		Identification of Preclinical AD: The study successfully **Identification of Preclinical AD:** The study successfully identifies a larger proportion of cognitively normal individuals with elevated brain amyloid at baseline who later	**Infrequent Use of Antidementia Medications:** The study acknowledges the infrequent but greater use of antidementia medications in the group with elevated amyloid during follow-up. This introduces a potential	The study provides valuable insights into the identification and progression of preclinical AD, leveraging long-term follow-up, comprehensive cognitive assessments, and analysis of

							developed cognitive symptoms. Dichotomizing participants into elevated vs. normal amyloid groups effectively separates those with progressive cognitive decline from those without, suggesting that preclinical Alzheimer's Disease (AD) may manifest in clinically normal individuals with elevated brain amyloid. **Longitudinal Assessment:** The study benefits from a long-term follow-up (up to 10 years) of the ADNI cohort, providing insights into the natural history of cognitive decline in relation to amyloid status. This extended follow-up allows for the observation of changes over an extended period and enhances the understanding of the trajectory of cognitive decline. **Use of Composite Cognitive Measures:** The study utilizes a	confounding factor, as these medications may have influenced the progression of cognitive decline, potentially impacting the observed differences between groups. **Uncertain Clinical Importance of Group Differences:** The study notes that group differences and changes on continuous measures are of uncertain clinical importance. While statistical significance may be observed, the clinical relevance of these differences remains unclear. This limitation highlights the need for additional studies to establish the practical implications of the findings. **Limited Number of Observations and High Loss to Follow-up:** The study expresses concern about the limited number of observations at the	biomarker data, including genetic factors. These findings have important implications for future therapeutic interventions and regulatory considerations in the field of Alzheimer's Disease research.

							modified version of the Preclinical Alzheimer Cognitive Composite (PACC), a cognitive composite designed for preclinical AD trials. The inclusion of PACC, MMSE, and Logical Memory tests contributes to a comprehensive assessment of cognitive function, enhancing the reliability of the findings. **Biomarker Data Analysis:** The study analyzes biomarker data, including CSF tau, pTau, and Aβ42, providing a comprehensive understanding of their associations with elevated brain amyloid. The longitudinal analysis of biomarkers reveals their sensitivity to elevated amyloid but suggests that they may not reflect cognitive and clinical decline once amyloidosis is established. **Association with Genetic Risk (APOE Genotype):** The study	latest time points and a high rate of loss to follow-up. This raises questions about the reliability of conclusions drawn from these latest time points and the possibility of unsupported extrapolations from earlier trends. However, sensitivity analyses with models imposing no assumptions about mean trajectory shape yielded similar conclusions. **Need for Randomized Trials:** The study recognizes that randomized trials would be necessary to assess whether interventions based on the findings affect the course of the disease. This limitation highlights the observational nature of the study, and the need for interventional studies to establish causal relationships.	

							explores the association between APOE genotype, amyloid accumulation, and cognitive decline. The presence of an APOEε4 allele is found to be associated with substantially increased cognitive decline, emphasizing the importance of genetic risk factors in preclinical AD. **Support for Amyloid as a Critical Factor:** The results support previous findings pointing to the critical role of amyloid in the neurobiology of AD. The study strengthens the link between elevated amyloid and primary manifestations of AD-related cognitive dysfunction.	**Lack of Tau PET Imaging and Limited CSF Tau Data:** The absence of tau PET imaging and limited collection of cerebrospinal fluid (CSF) tau data are acknowledged as limitations. Only 83% of participants had lumbar punctures at baseline, limiting the utility of CSF tau in the analysis. While ventricular volume was used as a covariate, the absence of direct tau measurements is a constraint in understanding the full spectrum of neurodegeneration. **Absence of Baseline Cognition as a Covariate:** The study notes that baseline cognition was not included as a covariate in the models. Instead, it was modelled as an outcome variable to illustrate the degree of separation at baseline. This approach may introduce complexities	

								in fully accounting for baseline cognitive differences between groups. **Exploratory Nature of Analyses:** The study emphasizes the exploratory nature of analyses, highlighting that the analyses were not specified prior to data collection and the large number of comparisons carried out. This underscores the need for cautious interpretation of results and encourages further confirmatory studies.	
24	Prediction of Alzheimer's Disease in Subjects with Mild Cognitive Impairment Using Patterns of Cortical Thinning	NeuroImage	2013	Cortical Thickness Measurement, Machine Learning	Alzheimer's Disease Neuroimaging Initiative (ADNI)	AD: 194 CN: 226	**Utilization of cortical thinning patterns for Alzheimer's disease prediction in individuals with mild cognitive impairment:** The study leverages cortical thickness measurements as potential biomarkers for predicting the progression from mild cognitive impairment (MCI) to Alzheimer's disease. By focusing on changes in cortical	**Possible confounding factors not fully addressed:** While the study focuses on cortical thinning patterns, it may not fully address all potential confounding factors that could influence cortical thickness measurements. Factors such as age-related cortical changes or comorbid conditions could potentially impact the	**Highlights the potential of structural neuroimaging for early diagnosis of Alzheimer's disease:** The research underscores the significance of utilizing structural neuroimaging techniques, specifically the analysis of cortical thinning patterns, for the early

							thickness, the research highlights the potential of structural neuroimaging as an effective tool for early detection and prediction of Alzheimer's disease. **Leave-One-Out Validation Technique to prevent bias:** A leave-one-out (LOO) validation strategy was employed, wherein, for each comparison, all subjects, with the exception of one, were employed to select features and construct a classification model. Subsequently, the excluded subject was utilized for testing. This process was iterated for every subject within the two compared groups, thereby validating the method across all subjects. By excluding the test subject from feature selection and classifier construction, any potential bias or "double dipping" in predictive efforts for converters was effectively avoided.	accuracy of the predictions, highlighting the need for comprehensive consideration of various contributing factors in the analysis. **Potential Overestimation of Prediction Accuracies:** The study highlights the risk of artificially inflating prediction accuracies by including the subject under analysis in the generation of discriminant features. This emphasizes the importance of avoiding "double dipping" in the estimation of classifications and predictions based on cortical thickness statistical maps. **Trade-off Between Sensitivity and Specificity:** While the specificity of predicting MCI to AD conversion within 3 years is relatively high (84%), the sensitivity is relatively low (64%).	detection and prediction of Alzheimer's disease in individuals with mild cognitive impairment. This emphasis on leveraging neuroimaging data to identify potential biomarkers aids in understanding the underlying structural changes associated with disease progression, ultimately contributing to the development of early intervention and management strategies for Alzheimer's disease.

								This trade-off suggests challenges in achieving both high sensitivity and specificity, which are essential for clinically applicable predictions.	
25	Multivariate and Univariate Neuroimaging Markers of Alzheimer's Disease	NeuroImage	2012	Univariate and Multivariate Discriminant Analysis of FDG–PET	Self Built Dataset using Patients from University of Michigan and Technical University of Munich	*Michigan* AD: 17 HC: 33 *Munich* AD:102 HC: 20	**Multivariate Analysis Sensitivity:** The multivariate analytic method shows higher sensitivity (range [0.85,1]) compared to the univariate method, making it potentially more effective in identifying early Alzheimer's disease. **Robustness of Multivariate Marker:** The multivariate marker appears to be more robust, as demonstrated by the unchanged ROC characteristics even when specific brain regions are removed. This suggests that multivariate analysis, using the entire spatial covariance structure of the data, may capture more comprehensive information.	**Non-Random Recruitment Bias:** The study acknowledges potential biases in non-random recruitment that may limit the generalization of findings to the broader population. This raises concerns about the representativeness of the study sample. **Small Sample Size Concerns:** The study recognizes the limitations of small sample sizes, especially when trying to map the neural correlates of AD progression. The regional composition of disease markers varied substantially based on the selected AD sample, suggesting the need for larger	The study strongly suggests that multivariate analysis might be more sensitive than univariate analysis for early diagnosis of Alzheimer's disease. The ability of multivariate techniques to utilize the entire spatial covariance structure of data is highlighted as a key factor contributing to this sensitivity.

							Prospective Validation: The study includes a prospective validation approach, applying identified patterns to new data samples. This enhances the credibility of the findings and supports the potential generalizability of the identified markers. **Realistic Context:** The data is divided into derivation and replication samples, providing a more realistic context for evaluating the effectiveness of the analytic methods. This helps in understanding how well the findings generalize to different datasets. **Systems-Level Biomarker Potential:** The study suggests that FDG–PET imaging combined with multivariate analysis has promise as a systems-level biomarker for Alzheimer's disease. This could enable early detection before clear	subject numbers for more reliable insights. **Specificity Confirmation Pending:** The study doesn't claim confirmation of the specificity of the AD-related covariance pattern to Alzheimer's disease. Further research is needed to validate the specificity of the identified patterns with respect to other neurodegenerative diseases. **Lack of Mechanistic Insight:** The study emphasizes that the identified FDG–PET patterns are downstream effects of the disease and do not provide mechanistic insight into the etiology of Alzheimer's disease. The focus is on diagnostic efficacy rather than understanding the underlying mechanisms.	

							clinical symptoms manifest.	**Trade-off in Biomarker Development:** The study discusses the trade-off between reductionist strategies targeting specific diseases with molecular compounds and a more widely applicable approach using standard imaging and analytic technology. While the latter is cost-effective, specificity to Alzheimer's disease needs further confirmation.	
26	Classifying MCI Subtypes in Community-Dwelling Elderly Using Cross-Sectional and Longitudinal MRI-Based Biomarkers	Frontiers in Aging Neuroscience	2017	Ensemble Voting Classifier made of SVM (rbf kernel), Logistic Regression and Random Forest.	Self Built Dataset using Patients from Sydney Memory and Aging Study	HC: 56 aMCI: 28 naMCI: 7	**Classification Framework:** The study employs a comprehensive classification framework for Mild Cognitive Impairment (MCI) subtypes using both cross-sectional and longitudinal MRI measurements. This approach allows for a more nuanced understanding of the dynamics of brain changes associated with MCI. **Data-Resampling:** The study addresses the	**Limited Sample Size:** The study acknowledges a limitation related to the sample size, particularly in the context of longitudinal data requirements. The restricted availability of subjects with MRI scans at both time points might impact the generalizability of findings. **Population-Based Sample:** The study is conducted on a population-based	The study's focus on accurately classifying MCI into meaningful subtypes, specifically distinguishing between amnestic (aMCI) and non-amnestic (naMCI) types, is commendable. Recognizing the differences in etiology and outcomes between these subtypes is crucial for facilitating early interventions with

							challenge of class-imbalance through a data-resampling step in the classification framework. This enhances the reliability of the classification results, particularly when dealing with varying sample sizes across different cognitive states. **Effective Differentiation:** The study successfully demonstrates that individuals with amnestic MCI (aMCI) can be differentiated from cognitively normal (CN) and non-amnestic MCI (naMCI) using MRI-based biomarkers. The achieved classification accuracy, sensitivity, specificity, and AUC are reported to be superior to previous studies.	sample, which may introduce biases as it consists of more cognitively normal individuals than those with MCI. The difference in sample sizes between aMCI and naMCI is also noted as a potential limitation. **Potential Double-Dipping Risk:** The study acknowledges the risk of "double-dipping" when using the same dataset for both feature selection and classification. Careful separation of training and test datasets through cross-validation is implemented to mitigate this risk.	targeted treatments.
27	Alzheimer's Disease Pattern Of Brain Atrophy Predicts Cognitive Decline In Parkinson's Disease	Brain	2012	Voxel-Based Morphometry Analysis	University of Pennsylvania Center of Excellence for Research on Neurodegenerative Diseases (CERND)	84 participants	**Validation of Neurodegeneration Patterns:** By applying a validated Alzheimer's disease-pattern of brain atrophy to MRI scans, the study offers a robust foundation for the examination of	**Lack of Formal Diagnostic Criteria:** The absence of formal diagnostic criteria for Mild Cognitive Impairment (MCI) and dementia is a limitation. The use of standardized	Integrated findings indicate that the Alzheimer's disease spatial pattern predicts cognitive decline, emphasizing hippocampal

							neurodegenerative patterns in Parkinson's disease. This validation enhances the reliability and interpretability of the findings. **Prediction of Cognitive Decline in Non-Demented Patients:** Notably, the Alzheimer's disease pattern of atrophy predicts cognitive decline even in non-demented patients with Parkinson's disease. This finding suggests the potential utility of neurodegeneration patterns as preclinical biomarkers for cognitive decline, providing an opportunity for early intervention.	criteria would enhance the precision of cognitive status classification and contribute to the validity of the findings. **Sample Characteristics:** The study primarily includes patients with mild to moderate stage Parkinson's disease. This sample characteristic might limit the generalizability of the findings to individuals with more advanced stages of the disease. Enrolling a broader range of disease stages would provide a more comprehensive understanding. **Limited Follow-up Period:** The 2-year follow-up period may be relatively short, especially considering the progressive nature of neurodegenerative diseases. Longer follow-up durations would offer a more thorough exploration	involvement in Parkinson's cognitive impairment.

								of cognitive decline trajectories. **Psychotic Symptom Assessment:** Lack of a validated rating scale for assessing psychotic symptoms is acknowledged as a limitation. The sensitivity of the assessment tool used may impact the detection of psychotic symptoms, potentially influencing the study's findings. **Need for Larger Samples:** The study acknowledges the need for larger sample sizes to enhance statistical power and generalizability. Enrolling larger cohorts would strengthen the robustness of the results and allow for more reliable conclusions. **Cautions in Extrapolation:** While the study suggests an overlap in neurodegenerative	

								regions between Alzheimer's disease and Parkinson's disease, caution is warranted in extrapolating these findings without direct clinicopathological correlation. The specific contributions of each pathology to cognitive decline need further investigation.	
28	Alzheimer's Disease Diagnostics by a Deeply Supervised Adaptable 3D Convolutional Network	arXiv Preprint	2016	Feature Extraction: 3D Convolutional Autoencoder Task Specific Classification: Deeply supervised target-domain-adaptable 3D-CNN	CADDementia Dataset	Not Specified	**Domain Adaptability:** The deep 3DCNN is designed to learn generic and transferable features across different domains. It effectively detects and extracts characteristic AD biomarkers in one domain (source) and performs task-specific classification in another domain (target). **Combination of Networks:** The network combines a generic feature-extracting stacked 3D-CAE, pre-trained in the source domain, with upper task-specific fully-connected layers. The lower layers	**Single Imaging Modality:** The proposed DSA-3D-CNN relies solely on a single imaging modality, namely structural Magnetic Resonance Imaging (sMRI). Limiting the method to a single modality might result in a lack of comprehensive information that could be obtained from the integration of multiple modalities, such as functional MRI (fMRI), Positron Emission Tomography (PET), or other imaging techniques. **Omission of Skull-Stripping:**	

							capture generic features, while the upper layers are fine-tuned for domain-specific tasks in the target domain. **Feature Extraction Capability:** The 3D-CAE addresses feature extraction limitations of conventional approaches by automatically learning and extracting discriminative AD features that capture anatomical variations associated with AD. **Adaptation to Different Datasets:** Pre-trained convolutional filters of the 3D-CAE are adapted to another domain dataset, such as the Alzheimer's Disease Neuroimaging Initiative (ADNI), after initial pre-training on a different dataset (CADDementia). This adaptation allows the network to leverage pre-learned generic features for improved performance in specific	The method does not perform skull-stripping as a preprocessing step. Skull-stripping is a common step in neuroimaging to remove non-brain tissues and artifacts, and its omission may lead to the inclusion of irrelevant information or noise in the input data.	

							tasks in the target domain. **Deep Supervision for Adaptability:** The incorporation of deep supervision allows for the effective adaptation of pre-learned generic features to specific tasks.		
29	Variationally Regularized Graph-based Representation Learning for Electronic Health Records	arXiv	2021	Encoder-Decoder Graph Neural Network	eICU Cohort, MIMIC-III Cohort, AD-EHR (Alzheimer's Disease Prediction) Cohort obtained from inpatient and outpatient EHR data from NYU Langone Health.	Not Specified	**Variational Regularization:** Introduction of variational regularization for node representation learning addresses limitations of self-attention in graph-based models. This addresses challenges in constructing knowledge graphs manually from real-world noisy data, enhancing the model's adaptability. **Improved Predictive Performance:** The method's innovative design, incorporating variational regularization on node representations in Graph Neural Networks (GNN), leads to superior performance compared to previous graph representation	**Potential Overfitting:** The use of adaptive learning of connections and variational regularization may lead to a risk of overfitting to the specific characteristics of the training data. The method's performance on unseen data or different populations is not discussed. **Exploration of Self-Supervised Learning:** The text indicates that future studies will explore self-supervised learning to improve generalization. This implies that the current method might	The proposed variational regularization encoder-decoder graph network adaptively learns informative medical graph structures, achieving robust representation learning. The model outperforms existing methods in EHR predictive tasks and offers insights through singular value analysis.

							learning methods in health predictive tasks. This is demonstrated through evaluations on clinical EHR data and two public EHR datasets.	have limitations in terms of generalization, and additional techniques are being considered to address this.	
30	Residual And Plain Convolutional Neural Networks For 3D Brain MRI Classification	arXiv	2017	Residual And Plain 3D Convolutional Neural Network	Alzheimer's Disease Neuroimaging Initiative (ADNI)	AD: 50 LMCI: 43 EMCI: 77 HC: 61	**End-to-End Models:** The proposed deep learning algorithms for brain MRI classification offer end-to-end models, eliminating the need for complex multistep pipelines and handcrafted feature generation. **Small Dataset Handling:** Neuroimaging datasets are often small, posing a challenge for traditional neural network training. The convolutional neural networks (CNNs) introduced in this study can learn features efficiently even with limited data. **Advanced Techniques:** Leveraging modern advancements in deep learning, such as batch normalization and	**Limited Exploration of Augmentation Techniques:** Although suggesting data augmentation as a future research avenue, the study does not experiment with or provide details on specific augmentation techniques to enhance model robustness. **Scalability Concerns:** The study mentions a potential future goal of achieving similar or better results for unprocessed images. However, the scalability and computational efficiency of such models for large-scale deployment are not extensively discussed.	Deep 3D CNNs offer simplicity and efficacy in Alzheimer's MRI classification. Their potential for rapid, one-step analysis presents a promising shift from multistep pipelines in neuroimaging research.

							residual network architectures, mitigates issues associated with small training datasets while facilitating automatic feature generation. **Applicability to 3D MRI Images:** The proposed models can be directly applied to 3D MRI images without the need for intermediate handcrafted feature extraction.		
31	Sparse Learning and Stability Selection for Predicting MCI to AD Conversion Using Baseline ADNI Data	BMC Neurology	2012	Sparse Learning and Stability Selection	Alzheimer's Disease Neuroimaging Initiative (ADNI)	MCI: 319	**Large and Unbiased MCI Cohort:** The study benefits from a large cohort of Mild Cognitive Impairment (MCI) samples, ensuring statistical robustness. The crucial aspect of this advantage is that the cohort is unbiased concerning age or education status, minimizing confounding variables that could affect the results. **Integration of Various Baseline Data:** Unlike some other studies, this research integrates and	**Cerebellar Atrophy Association:** The study notes a surprising correlation between cerebellar atrophy and AD. While this association has been detected in other studies, the specific role of the cerebellum in AD remains unclear. This unexpected finding highlights the need for further investigation to understand the significance of cerebellar atrophy in the context of MCI-to-AD conversion.	Sparse Learning and Stability Selection for Predicting MCI to AD Conversion Using Baseline ADNI Data

							tests a diverse range of baseline data available in the Alzheimer's Disease Neuroimaging Initiative (ADNI). This comprehensive approach includes data from MRI scans, demographic information, genetic factors (APOE genotyping), and cognitive measures. The inclusion of multiple types of data enhances the depth and richness of the analysis. **Application of Sparse Logistic Regression with Stability Selection:** The study employs advanced statistical techniques by applying sparse logistic regression with stability selection to ADNI data. This methodology ensures robust feature selection, enabling the identification of the most relevant variables for predicting the outcome. Sparse logistic regression helps prevent overfitting and enhances the	**Cingulate Cortex Atrophy:** The study identifies the atrophy of the rostral anterior cingulate cortex as predictive of conversion to AD. While this aligns with previous studies, the specific implications and functional consequences of cingulate cortex atrophy in early AD stages warrant further exploration. **CSF Biomarkers Lack Specificity:** The results suggest that cerebrospinal fluid (CSF) biomarkers, while showing an aberrant signature in MCI Converters, lack the specificity to discriminate between MCI to AD Converters and Non-converters. This limitation emphasizes the need for additional and more specific biomarkers for accurate predictions. **Feature Interpretation and**	

							interpretability of the selected features. **Four-Year Follow-Up Period:** The evaluation considers a 4-year follow-up period, providing a longitudinal perspective on the progression of MCI. This extended timeframe allows for a more comprehensive understanding of the factors influencing the conversion from MCI to other conditions.	**Redundancy:** While the study effectively identifies a set of 15 features (Biosignature-15) with high predictive power, some of these features are known to be important in characterizing Alzheimer's Disease (AD). This raises a challenge in distinguishing whether the identified features genuinely contribute to prediction or if they are redundant with existing knowledge. The reliance on features closely associated with AD may limit the novelty of the findings.	
32	Qualitative Estimates of Medial Temporal Atrophy as a Predictor of Progression From Mild Cognitive Impairment to Dementia	Arch Neurol	2007	Qualitative Study	769 participants were recruited from 69 Alzheimer's Disease Cooperative Studycenters in the United States and Canada.	190 images	**Blinded Prospective Design:** The study design's blinded and prospective nature enhances the reliability and objectivity of the findings, minimizing bias in the evaluation process. **Well-Defined Patient Cohort:** Inclusion of a well-defined patient cohort	Selective Study Cohort: The study cohort's select nature, including well-educated individuals with moderately severe memory impairments, may limit the generalizability of findings to broader populations. Effect of Experience: The study suggests	

							with detailed surveillance by experienced physicians provides robust and clinically relevant data for analysis. **Physician Expertise:** Physicians with dementia experience conducted detailed surveillance, ensuring a high level of expertise in evaluating patients, contributing to the study's credibility. **Simple and Translatable Method:** The simplicity and good reliability of the method used make it easily translatable into standard clinical practice, potentially facilitating widespread adoption.	that experience with the scale may modestly affect its predictive value, particularly with a cutoff score greater than 2.0, indicating potential limitations in generalizability. Small Number of Participants with High Scores: The study's small number (n = 15) of participants with mean MTA scores greater than 2.0 may contribute to differences among raters, emphasizing the need for larger sample sizes.	
33	Medial Temporal Lobe Atrophy Predicts Alzheimer's Disease in Patients with Minor Cognitive Impairment	J Neurol Neurosurg Psychiatry	2002	Volumetry of the Hippocampus, Volumetry of the Parahippocampal Gyrus, and Qualitative Rating of Medial Temporal Lobe Atrophy	31 Patients from the Maastricht Memory Clinic		**Prospective Follow-up:** The study features a prospective follow-up assessment conducted 1 to 3 years after the initial assessment, providing valuable longitudinal data on cognitive decline.	**Different MRI Scan Axes:** The study used different scan axes for measuring hippocampal volume and parahippocampal gyrus volumetry and MTA scoring. While the slice thickness was thin, potential bias due to the difference	The findings suggest that combining age, memory function, and measures of medial temporal lobe atrophy could enhance the ability to detect patients with minor cognitive

							MRI Methodology: The use of a three-dimensional volumetric scan and inversion recovery scan for MRI allows for detailed imaging of the hippocampus and parahippocampal gyrus, contributing to precise MTA score determination. **Neuropsychological Assessment:** The inclusion of a neuropsychological assessment involves standardized clinical tests, such as the AVLT and SCWT, enhancing the depth and reliability of cognitive evaluation. **Clinical Applicability:** The study suggests that volumetry of the hippocampus is a preferred predictor but acknowledges the time and resource limitations in clinical settings, making MTA scoring a practical alternative with good predictive accuracy.	in scan axis is acknowledged. **Long-Term Predictive Models:** The study acknowledges the need for further investigation to determine the simplest model for predicting long-term outcomes beyond the follow-up period. **Selective Age Group:** The mean age of the study sample is lower than in comparable studies, potentially impacting the positive predictive value of medial temporal lobe atrophy as the conversion rate to dementia is lower in younger patients. **Depression Consideration:** Patients with mild to moderate depression were not excluded, possibly introducing a confounding factor. However, analyses with correction for depression severity yielded similar results.	impairment at high risk for Alzheimer-type dementia. Assessment of medial temporal lobe atrophy is seen as a valuable supplement to the diagnostic investigation of patients with minor cognitive impairment.

35	Classification and prediction of cognitive performance differences in older age based on brain network patterns using a machine learning approach	Netw Neurosci	2023	Support vector machine (SVM), K-nearest while (KNN), decision tree (DT), naïve Bayes (NB) and linear discriminant analysis (LDA)	1000BRAINS project				
36	Baseline structural MRI and plasma biomarkers predict longitudinal structural atrophy and cognitive decline in early Alzheimer's disease	Alz Res Therapy	2023	Linear Mixed Effect Modeling	Alzheimer's Disease Neuroimaging Initiative (ADNI)	MCI: 439 CN: 286	**Comprehensive Analysis:** The study includes a thorough analysis involving both structural MRI and plasma measurements, providing a comprehensive understanding of potential biomarkers for disease progression. **Diagnostic Specificity:** By conducting analyses within specific diagnostic groups (CN and MCI) and Aβ+/Aβ− subgroups, the study recognizes the heterogeneity within the cohort and tailors the analysis to each subgroup's characteristics.	**Limited Plasma Measurements:** The study only incorporated two plasma measurements (plasma p-tau181 and NfL), potentially limiting the comprehensiveness of the identified biomarkers. The exclusion of other promising plasma measures, such as plasma p-tau217 and glial fibrillary acidic protein, might impact the overall predictive power of combined biomarkers. **Potential Plasma Biomarker Omissions:** The omission of potentially more sensitive plasma biomarkers, like	This study underscores the predictive potential of combining baseline plasma and structural MRI biomarkers for early Alzheimer's disease (AD) progression. Notably, the complementary information provided by these biomarkers enhances predictions of longitudinal atrophy and cognitive decline, especially in Mild Cognitive Impairment (MCI) cohorts. The findings

							Stepwise Modeling: The stepwise linear mixed effect modeling approach allows the systematic identification of the subset of baseline measurements that optimally predict longitudinal changes. The use of Akaike Information Criterion (AIC) for model selection adds rigor by favoring models that balance goodness of fit with simplicity. **Iterative Feature Selection:** The iterative process of adding baseline measurements to the model based on AIC improvement enhances the precision of the final models, ensuring that only the most informative variables are included. **Covariate Consideration:** The inclusion of relevant covariates such as age, sex, education, APOE ε4 status, and intracranial volume (ICV) in the initial	plasma p-tau217, which is suggested to be more sensitive to early Alzheimer's disease pathology than p-tau181, could impact the study's ability to capture early disease stages. **Variability in Predictive MRI Measures:** The structural MRI models demonstrated variability in the most predictive measures across different iterations (e.g., BA35 thickness, posterior hippocampal volume, anterior hippocampal volume, ERC thickness, BA36 thickness). This variability challenges the specificity of the identified effects in the medial temporal lobe (MTL), making it challenging to interpret the consistent impact of MTL subregions on disease progression. **Need for MTL Summary Measurement:**	support the feasibility of using non-invasive plasma biomarkers in clinical trials, addressing practicality concerns. The proposed combined biomarkers exhibit effectiveness in discriminating fast and slow progressors, crucial for enriching at-risk cohorts in AD research. The study also hints at the structural MRI biomarkers' potential in predicting normal aging-related decline, offering insights into both AD and age-related cognitive changes. However, the study acknowledges limitations, including the need for additional plasma measures

							model controls for potential confounding effects and strengthens the validity of the results. **Longitudinal Analysis:** The use of longitudinal measurements allows the examination of changes over time, providing insights into disease progression dynamics. **Subgroup Analysis for Progression Prediction:** The logistic regression analyses for discriminating fast and slow progressors add a predictive element to the study, enhancing its relevance for identifying markers associated with different rates of disease progression. **Model Comparisons:** Comparing different models, including base models with only covariates and models with selected baseline plasma or MRI	While structural MRI measurements were consistently included, the study suggests that using a summary value derived from all MTL subregional measurements through event-based modeling may offer a more consistent and sensitive measurement. This approach is proposed for future investigation to enhance the specificity and reliability of MTL effects. **Clinical Trial Stratification Focus:** The study highlights the potential utility of plasma and structural MRI biomarkers for clinical trial stratification and prognosis. However, the focus on these specific applications might limit the broader implications of the findings for other clinical contexts or research objectives.	and validation in independent datasets. Overall, this research advances the understanding of integrated biomarker approaches for AD prediction and highlights their utility in clinical trial stratification and prognosis.

							measures, enables a nuanced understanding of the contribution of each type of measurement to the predictive accuracy of the models. **Supplementary Analysis:** The inclusion of supplementary analyses, such as univariate analysis, provides additional insights into the predictive value of individual baseline measurements, contributing to a more comprehensive interpretation of the results.		
37	Combining MR Imaging, Positron-Emission Tomography, and CSF Biomarkers in the Diagnosis and Prognosis of Alzheimer Disease	American Journal of Neuroradiology	2010	Regression Analyses	Alzheimer's Disease Neuroimaging Initiative (ADNI)	AD: 38 MCI: 73 NC: 42	**Multimodal Approach:** The study employs a multimodal approach, integrating MR imaging morphometry, FDG-PET, and CSF biomarkers, providing a comprehensive view of neurodegenerative changes in Alzheimer's disease (AD). **Diagnostic Sensitivity:** The study demonstrates	**Limited Plasma Biomarkers**: The study focuses primarily on CSF biomarkers, neglecting potential contributions from plasma biomarkers. The inclusion of plasma biomarkers could enhance the understanding of peripheral indicators of AD.	

							sensitivity to diagnostic status across morphometry, metabolism, and CSF biomarkers, highlighting the potential of these measures in distinguishing between normal controls (NC) and AD. **Individual Prognostic Potential:** MR imaging morphometry measures, in particular, show promise for individual prognostic use, potentially aiding in the identification of patterns of atrophy predictive of conversion to AD. **Comparative Analysis:** The study compares the contributions of MR imaging morphometry, FDG-PET, and CSF biomarkers, providing insights into their unique and redundant aspects in both diagnostic accuracy and clinical prediction.	**Heterogeneous MCI Group:** The MCI group in the study might be more heterogeneous compared to previous CSF studies, impacting the predictive power of CSF biomarkers. The study acknowledges potential variability in the MCI population. **Discrepancies in CSF Predictions:** The study notes discrepancies in the predictive value of CSF measures for clinical decline, possibly influenced by the heterogeneity of the MCI group and the use of continuous behavioral measures rather than conversion. **Scatter in Individual Prognostic Measures:** While MR imaging morphometry measures show potential for individual prognostic use, there is considerable scatter in	

								regression plots, indicating uncertainty in individual predictions. **Sample Selection Bias:** Participants were selected based on their willingness and ability to undergo specific imaging and biomarker assessments, potentially introducing selection bias and limiting the generalizability of findings.	
38	Episodic Memory in Amnestic Mild Cognitive Impairment (aMCI) and Alzheimer's Disease Dementia (ADD): Using the "Doors and People" Tool to Differentiate between Early aMCI—Late aMCI—Mild ADD Diagnostic Groups	Diagnostics	2022	Doors and People	90 patients from Greek Association of Alzheimer's Disease and Related Disorders	-	**Multifaceted Evaluation:** The Doors and People tool used in the study evaluates both visual and verbal aspects of episodic memory, providing a comprehensive assessment and enhancing ecological validity. **Confirmation of Hypotheses:** The study confirms three hypotheses related to the discriminative power of episodic memory, particularly in distinguishing between	**Uncertainty in Individual Prognostication:** While episodic memory measures can provide individual prognostic information, the study acknowledges the considerable scatter in regression plots, indicating uncertainty in individual predictions. **Age Discrepancy:** Participants in each group have significantly different ages, which may introduce a	The Doors and People tool's detailed assessment of episodic memory offers valuable insights into distinguishing MCI stages and predicting AD progression. Age-related limitations and the need for biomarker integration warrant consideration in future research.

							early and late aMCI stages, and between early aMCI and mild Alzheimer's Disease (ADD) patients. **Support from Neuroimaging Studies:** Findings align with neuroimaging studies, such as MRI and Voxel-based morphometry, supporting the significance of episodic memory in predicting progression from MCI to ADD. **Longitudinal Predictive Validity:** The study contributes to the existing literature by demonstrating the longitudinal predictive validity of episodic memory measures, supporting their role in identifying individuals at risk of developing dementia up to 10 years prior to diagnosis.	confounding factor. A longitudinal study with reevaluation after several years is suggested to address this limitation. **Limited Use of Biomarkers:** The study does not incorporate neuroimaging methods, cortical thickness measurements, Voxel-based morphometry, or CSF biomarkers. Integrating these measures could enhance the robustness of the findings. **Task-Specific Findings**: The discriminant potential varies among different tasks within the Doors and People tool. While certain tasks show excellent discriminant potential, others exhibit only fair or poor potential, limiting the tool's uniform efficacy across all its components.	

								Generalizability: The sample selection based on participants willing to undergo specific assessments may limit the generalizability of the findings to a broader population.	
39	Dual-Model Radiomic Biomarkers Predict Development of Mild Cognitive Impairment Progression to Alzheimer's Disease	Frontiers in Neuroscience	2019	Dual-Model Radiomic Analysis with Multivariate Cox Proportional Hazards Regression Model	Alzheimer's Disease Neuroimaging Initiative (ADNI)	cMCI: 131 ncMCI: 132	**Prediction Enhancement:** Radiomic analysis, combined with Cox models, enhances the prediction of MCI (Mild Cognitive Impairment) conversion to AD (Alzheimer's Disease), offering valuable prognostic insights. **Comprehensive Topography:** Identification of MCI conversion-related regions, integrating structural atrophy and metabolic abnormalities, aligns with existing literature, providing a comprehensive topographical understanding. **APOE ε4 Gene as a Predictor:** The identification of APOE ε4 gene as a risk	**Short Follow-Up Period:** The study's relatively short 3-year follow-up for individuals with Mild Cognitive Impairment (MCI) may limit the ability to capture long-term changes and progression to Alzheimer's Disease (AD), potentially affecting the generalizability of findings. **Incomplete Baseline Data:** A subset of MCI images lacked baseline data for both MRI and FDG PET imaging, introducing potential biases and limiting the comprehensiveness of the multimodal analysis. Future studies with complete baseline data are warranted for	This study pioneers a dual-model radiomic analysis, merging structural MRI and FDG PET data, unveiling significant ROIs associated with MCI to AD conversion. The fused-modality Cox model excels, showcasing the potential of personalized prediction in clinical practice.

							predictor in the clinical Cox model adds genetic information, contributing to a more comprehensive understanding of MCI conversion risk. **Prognostic Stability:** The fusion-modality Cox model exhibits higher Harrell's C and more stable relative risk, indicating increased stability and reliability in predicting the risk of MCI progression. **Applicability to Single Cases:** Radiomics analysis's ability to be applied on a single-case basis enhances its clinical utility, allowing for personalized predictions and facilitating individualized patient care. **Quantitative Feature Set:** The study's extraction of 172 radiomic features, including intensity, texture, and wavelet features, provides a	improved model performance. **Smoothing Step Impact:** The preprocessing smoothing step may introduce variability in the calculation of features and the definition of ROIs. While common in Alzheimer's Disease (AD) studies, the impact of smoothing on the accuracy of features and ROIs should be considered, and future research may explore alternative, more accurate segmentation methods. **Target Region Extraction Method:** The study utilized a routine smoothing step in preprocessing, which may impact the extraction of target regions. Future research could benefit from more accurate methods, such as manual segmentation, especially in the context of oncological	

							robust quantitative foundation for analysis and prediction. **Texture Analysis Value:** The significance of top quantitative features, such as entropy, complexity, and coarseness, underscores the value of texture analysis in capturing complex brain structural alterations associated with MCI conversion.	radiomics studies, to enhance precision. **Impact of APOE ε4 Gene:** Although the study identifies the APOE ε4 gene as a risk predictor, the specific impact and interactions with other predictors are not thoroughly explored. Future research could delve into the nuanced relationships between genetic factors and radiomic features in the context of prediction models.	
40	Brain Age Estimation from MRI Images using 2D-CNN instead of 3D-CNN	Acta Infologica	2021	2D CNN	IXI Dataset	563 T1-Weighted NC	**Efficient Plane-Based Approach:** The study efficiently employs axial, coronal, and sagittal planes of brain scans, eliminating the need for complex 3D models and reducing computational demands. **Optimized Model Utilization:** Leveraging pre-trained DenseNet121 model weights mitigates the impact of a small dataset, enhancing model performance	**Limited Dataset Size:** The study acknowledges a constraint in dataset size, potentially affecting the model's generalization to diverse populations or specific demographic groups. **Dependency on Pre-trained Weights:** Utilizing pre-trained model weights may introduce biases from the original dataset, limiting adaptability to the unique features	This study employs DenseNet in Brain Age Estimation (BAE) using 2D-CNN, demonstrating a MAE of 6.3. The innovative use of specific brain slices and diverse optimizers enhances efficiency and accuracy.

							without intensive computational requirements. **Reduced Training Time:** Achieves a low Mean Absolute Error (MAE) of 6.3 in estimating brain age, with a notably short training time of 5.35 minutes, demonstrating efficiency in model training. **Applicability for Neurodegenerative Disease Detection:** The proposed method, focused on Brain Age Estimation (BAE), holds promise for detecting neurodegenerative diseases like Alzheimer's and Parkinson's. **Comparable Performance:** Despite its efficiency, the method yields results comparable to similar studies, emphasizing its effectiveness in Brain Age Estimation tasks.	of the brain scans in the current study. **Simplification of Brain Structure:** By focusing on specific planes, the study may overlook nuanced three-dimensional interactions in brain structures, potentially affecting the accuracy of age estimation. **Task-Specific Application:** While excelling in Brain Age Estimation, the method's applicability may be constrained to tasks directly related to estimating age from brain MR images. **Optimization Dependency:** The reported performance metrics are tied to specific configurations (sagittal planes, Adamax optimizer), and generalization to alternative setups requires validation.	

41	Preclinical Detection of Alzheimer's Disease Using FDG-PET, with or without Amyloid Imaging	Journal of Alzheimer's Disease	2020	FDG-PET, with or without Amyloid Imaging	Review Paper	-	**High Sensitivity for Disease Discrimination:** FDG-PET exhibits high sensitivity in distinguishing Alzheimer's Disease (AD) from both healthy controls and other neurodegenerative diseases. It serves as a valuable tool for identifying individuals at higher risk for AD. **Quantitative and Topographical Correlation:** The method offers good quantitative and topographical correlation with clinical progression. This strength enhances its utility in tracking disease-related changes and understanding the spatial distribution of metabolic abnormalities. **Potential for Risk Stratification:** FDG-PET's ability to differentiate individuals at higher versus lower AD risk enhances its role in stratifying risk levels,	**Absence of Postmortem Data:** A major limitation lies in the absence of postmortem data in most FDG-PET studies. This hinders the confirmation of clinical symptoms and reductions in cerebral metabolic rate of glucose (CMRglc) as solely attributable to AD pathology, raising uncertainties about the specificity of findings. **Reliance on Clinical Diagnosis:** The use of clinical diagnosis as the gold standard introduces a potential limitation, as it may result in the inclusion of patients with a dementia other than AD in the AD group and vice versa. This reliance on clinical diagnosis raises the risk of misclassification. **Hypometabolism Not Exclusive to AD:** In asymptomatic subjects with hypometabolism,	Preclinical Detection of Alzheimer's Disease Using FDG-PET, with or without Amyloid Imaging

							aiding in early identification and intervention.	CMRglc deficits may arise from causes other than AD pathology. Additionally, not all individuals with hypometabolism may necessarily progress to AD, introducing ambiguity in the interpretation of FDG-PET findings. **Need for Imaging of AD Pathology:** The authors emphasize the essential role of imaging AD pathology in resolving uncertainties. This indicates a dependence on complementary imaging modalities to provide a more definitive understanding of the underlying pathology contributing to hypometabolism observed in FDG-PET studies.	
42	An Optimized Deep Learning Model for Predicting Mild Cognitive Impairment	Sensors	2023	VGG16, Inception-V3, and ResNet50	Alzheimer's Disease Neuroimaging Initiative (ADNI)	MCI: 337 NC: 442	**Early Diagnosis Potential:** Utilizing the entorhinal cortex (EC) as a biomarker enables early detection of Mild Cognitive	**Data Scope Restriction:** The model relies solely on MRI data, neglecting other potentially valuable data types	

	Using Structural MRI						Impairment (MCI) since changes in this area precede those in the hippocampus. **Innovative Approach:** The study pioneers the use of EC, an often overlooked biomarker due to its size, in predicting MCI, providing a unique perspective. **Efficient Classification:** Through experiments on brain slices, feature extraction, and classifier optimization, the study achieves an efficient classification system for distinguishing between MCI and normal cognition (NC) samples.	such as clinical, genetic, and genomics, limiting the comprehensiveness of the predictions. **Small EC Size Challenge:** Detecting changes in the EC, being smaller compared to the hippocampus, poses a challenge, potentially limiting the precision of the predictions. **Parameter Dependency:** The performance improvement of the convolutional neural network (CNN) classifier is contingent on tuning parameters for specific pre-trained models, potentially limiting generalizability.	
43	Computer aided Alzheimer's disease diagnosis by an unsupervised deep learning technology	Neurocomputing	2020	PCANet	Alzheimer's Disease Neuroimaging Initiative (ADNI)	AD: 243 MCI: 525 NC: 307	**High Prediction Accuracy:** The proposed method achieves high prediction accuracy, particularly for AD vs. MCI (97.01%) and AD vs. NC (89.15%), demonstrating its effectiveness in	**Cluster Size Bias:** The k-means clustering tendency to produce equal-sized clusters might lead to suboptimal results, especially for the AD vs. NC group, where the distributions are ellipse-shaped, indicating a limitation	Their completely unsupervised approach, incorporating a PCANet-based CNN and k-means clustering, showcases strong Alzheimer's disease prediction exclusively from

							Alzheimer's disease (AD) classification. **Utilization of TOP Slices:** Incorporating the TOP slices of MRI images significantly enhances classification accuracy (92.5%) compared to using a single slice, emphasizing the importance of capturing anatomical structures for accurate predictions. **Effective Feature Extraction:** The use of PCANet for feature extraction contributes to the success of the method, showcasing its capability to learn discriminative features from different views of MRI images. **Comparative Performance:** Despite slight performance differences with some state-of-the-art methods, the proposed method demonstrates competitive accuracy on a larger dataset without data selection.	in handling certain data distributions. **Dependency on Specific Views:** The method's reliance on specific views (TOP slices) for improved accuracy might limit its generalizability to diverse datasets, potentially hindering its applicability to different imaging protocols or populations. **Comparison to Selective Databases:** While the method achieves competitive results on the ADNI database, direct comparisons with some state-of-the-art methods involve selected databases, potentially affecting the generalizability of performance comparisons. **Limited Modalities:** The method utilizes only one modality (MRI), neglecting potential benefits from	MRI images. Achieving an average accuracy of 92.5%, their method, tested on the ADNI dataset without data selection, stands out among advanced techniques, highlighting its suitability for CAD systems in effective AD diagnosis.

								combining multiple modalities, as seen in some state-of-the-art approaches, limiting the method's scope in capturing diverse information sources.	
44	A Computational Monte Carlo Simulation Strategy to Determine the Temporal Ordering of Abnormal Age Onset Among Biomarkers of Alzheimer's Disease	IEEE/ACM Trans Comput Biol Bioinform	2022	Computational Monte Carlo Simulation Strategy	Not Specified	MCI: 382	**Quantitative Temporal Ordering:** The computational Monte-Carlo simulation (CMCS) provides a quantitative approach to determine the temporal ordering of abnormal age onsets (AAO) for various Alzheimer's disease biomarkers. **Statistical Examination:** CMCS employs statistical simulations to assess the ordering of AAO pairs and overall AAO, contributing to a robust understanding of Alzheimer's disease progression. **Multimodal Biomarker Assessment:** The study incorporates diverse biomarkers, including hippocampus volume, glucose hypometabolic	**Data Specificity:** The findings are based on data from 382 mild cognitive impairment converters and non-converters, potentially limiting generalizability to broader populations or diverse cohorts. **Sensitivity to Biomarker Selection:** The observed type-I error differences are specific to the selected biomarkers (V_HC, AVLT_STM, AVLT_LTM, HCI, MMSE, CDR-SOB, NfL), and the results may vary with alternative biomarker combinations. **Simulation Assumptions:** The accuracy of CMCS depends on the assumptions made during the simulation	

							convergence index, plasma neurofilament light, and cognitive assessments, offering a comprehensive view of disease onset. **Identification of Significant Differences:** The CMCS identifies significant differences in the AAO of biomarkers, revealing insights into the sequence of abnormalities in Alzheimer's disease progression.	of longitudinal data, introducing inherent uncertainties. **Clinical Application:** While the CMCS provides statistical inferences, translating these findings into direct clinical applications may require further validation and integration into diagnostic frameworks.	
45	Early diagnosis of Alzheimer's disease using combined features from voxel-based morphometry and cortical, subcortical, and hippocampus regions of MRI T1 brain images	PLoS ONE	2019	Feature Extraction: Voxel-Based Morphometry; Classification: SVM, Random Forest, KNN	NRCD dataset (private dataset which was generated in Chosun University hospitals)	163 (sMRI)	**Improved Classification Performance:** Combining various structural MRI features enhanced the classification accuracy compared to using individual features. The method achieved good AUC and ACC values, indicating robust performance. **Powerful and Steady Classifier:** The combination of VBM, CSC, and HV features resulted in a more powerful and	**Preliminary Nature:** The study is acknowledged as a preliminary proof-of-concept, indicating that further replication and validation are needed to solidify its findings. **Single Modality:** The proposed method relies on structural MRI (sMRI) modality, and the effectiveness with other imaging modalities like PET and functional MRI remains unexplored.	

							steady classifier than using a single feature. **Optimized Hyperparameter Tuning:** The study employed a rigorous approach to hyperparameter tuning using a grid search and five-fold stratified cross-validation, ensuring unbiased estimates of performance. **High Agreement Levels:** The proposed model demonstrated high agreement levels between different classification groups, as indicated by Cohen's kappa values. **Novel Feature Fusion Technique:** The introduction of a novel feature fusion technique, combining morphometric features with cortical and hippocampal volume features, contributed to improved classification accuracy.		

47	A semi-quantitative method for correlating brain disease groups with normal controls using SPECT: Alzheimer's disease versus vascular dementia	Computerized Medical Imaging and Graphics	2012	Semi-Quantitative Circumferential-Profile Analysis of Regional Cerebral Blood Flow (RCBF) SPECT in Alzheimer's Disease (AD) Versus White Matter Vascular Dementia (WM-VAD)	Patients referred over a five-year period from the UAB Memory Clinic and Alzheimer's Disease Centers to the Division of Nuclear Medicine of University of Alabama at Birmingham Medical Center (UAB) for Tc99m HMPAO brain SPECT	MCI: 86 NC: 17	**Novel Approach to Dementia Differentiation:** The study proposes a novel approach to differentiate between dementia subtypes, particularly Alzheimer's Disease (AD) and White Matter Vascular Dementia (WM-VaD), by assessing regional cerebral blood flow (rCBF) patterns. **Clear Differentiation of rCBF Patterns:** The study demonstrates clear and significant differences in rCBF among controls, AD, and WM-VaD patients, offering a distinct visualization of the cerebral impairment pattern associated with each condition. **Clinical Relevance:** The findings have potential clinical relevance, suggesting that WM-VaD may play a more prominent role in dementia than previously suspected. This could impact	**Semi-Quantitative Scoring System:** The scoring system used for quantifying the severity of White Matter Hyperintensities (WMH) is relatively simple and involves four stages in volume. This simplicity may limit the precision of the regional analysis. **Referral Bias and Sample Composition:** The high incidence of WM-VaD patients in the dementia evaluation sample may reflect referral bias, potentially impacting the generalizability of the findings to broader populations. **Limited Regional and Volumetric Data:** The study acknowledges that further subdivision of the WM-VaD group based on more precise regional and volumetric data could offer additional insights. This limitation implies that	The study presents a valuable exploration of differentiating dementia subtypes based on rCBF patterns, specifically focusing on WM-VaD.

							diagnostic and treatment strategies. **Utilization of SPECT for Differential Diagnosis:** The study supports the clinical utility of Single Photon Emission Computed Tomography (SPECT) in diagnosing and differentiating between dementia types, providing additional evidence for the role of SPECT in dementia evaluation. **Focus on Frontal Cortical Involvement:** The identification of a primarily frontal cortical involvement in WM-VaD patients contributes to a better understanding of the neurobehavioral effects associated with this type of dementia.	the current study provides a broad overview. **Absence of Automated Computational Quantification:** The study suggests that a more complex automated computational quantification of WMH might help reduce inter-rater subjectivity. The absence of such an approach limits the study's objectivity. **Causality vs. Association:** The study acknowledges that the relationship between WMH and clinical symptoms is not necessarily causal. Understanding the precise relationship between WMH and dementia requires further investigation. Difficulty in Differential Diagnosis: The study notes that distinguishing between typical AD and typical WM-VaD	

								may be clinically challenging, especially in cases involving later stages of AD, frontal degenerative processes, and non-frontal VaD. **Limited Validation of SPECT Approach:** While the study supports the clinically feasible approach of analyzing brain SPECT for differentiating WM-VaD from AD, the validation of this approach needs further confirmation through larger studies and comparison with gold standard diagnostic methods.	
48	Association of Elevated Amyloid Levels with Cognition in Preclinical Alzheimer's Disease	JAMA Neurology	2017	Exploratory Analysis	Alzheimer's Disease Neuroimaging Initiative (ADNI)		Identification of Preclinical AD: The study successfully **Identification of Preclinical AD:** The study successfully identifies a larger proportion of cognitively normal individuals with elevated brain amyloid at baseline who later developed cognitive symptoms. Dichotomizing	**Infrequent Use of Antidementia Medications:** The study acknowledges the infrequent but greater use of antidementia medications in the group with elevated amyloid during follow-up. This introduces a potential confounding factor, as these medications may have influenced the	The study provides valuable insights into the identification and progression of preclinical AD, leveraging long-term follow-up, comprehensive cognitive assessments, and analysis of biomarker data, including genetic factors. These

							participants into elevated vs. normal amyloid groups effectively separates those with progressive cognitive decline from those without, suggesting that preclinical Alzheimer's Disease (AD) may manifest in clinically normal individuals with elevated brain amyloid. **Longitudinal Assessment:** The study benefits from a long-term follow-up (up to 10 years) of the ADNI cohort, providing insights into the natural history of cognitive decline in relation to amyloid status. This extended follow-up allows for the observation of changes over an extended period and enhances the understanding of the trajectory of cognitive decline. **Use of Composite Cognitive Measures:** The study utilizes a modified version of the Preclinical Alzheimer Cognitive Composite	progression of cognitive decline, potentially impacting the observed differences between groups. **Uncertain Clinical Importance of Group Differences:** The study notes that group differences and changes on continuous measures are of uncertain clinical importance. While statistical significance may be observed, the clinical relevance of these differences remains unclear. This limitation highlights the need for additional studies to establish the practical implications of the findings. **Limited Number of Observations and High Loss to Follow-up:** The study expresses concern about the limited number of observations at the latest time points and a high rate of loss to follow-up. This raises	findings have important implications for future therapeutic interventions and regulatory considerations in the field of Alzheimer's Disease research.

							(PACC), a cognitive composite designed for preclinical AD trials. The inclusion of PACC, MMSE, and Logical Memory tests contributes to a comprehensive assessment of cognitive function, enhancing the reliability of the findings. **Biomarker Data Analysis:** The study analyzes biomarker data, including CSF tau, pTau, and Aβ42, providing a comprehensive understanding of their associations with elevated brain amyloid. The longitudinal analysis of biomarkers reveals their sensitivity to elevated amyloid but suggests that they may not reflect cognitive and clinical decline once amyloidosis is established. **Association with Genetic Risk (APOE Genotype):** The study explores the association between APOE genotype, amyloid	questions about the reliability of conclusions drawn from these latest time points and the possibility of unsupported extrapolations from earlier trends. However, sensitivity analyses with models imposing no assumptions about mean trajectory shape yielded similar conclusions. **Need for Randomized Trials:** The study recognizes that randomized trials would be necessary to assess whether interventions based on the findings affect the course of the disease. This limitation highlights the observational nature of the study, and the need for interventional studies to establish causal relationships. **Lack of Tau PET Imaging and Limited CSF Tau**	

							accumulation, and cognitive decline. The presence of an APOEε4 allele is found to be associated with substantially increased cognitive decline, emphasizing the importance of genetic risk factors in preclinical AD. **Support for Amyloid as a Critical Factor:** The results support previous findings pointing to the critical role of amyloid in the neurobiology of AD. The study strengthens the link between elevated amyloid and primary manifestations of AD-related cognitive dysfunction.	**Data:** The absence of tau PET imaging and limited collection of cerebrospinal fluid (CSF) tau data are acknowledged as limitations. Only 83% of participants had lumbar punctures at baseline, limiting the utility of CSF tau in the analysis. While ventricular volume was used as a covariate, the absence of direct tau measurements is a constraint in understanding the full spectrum of neurodegeneration. **Absence of Baseline Cognition as a Covariate:** The study notes that baseline cognition was not included as a covariate in the models. Instead, it was modelled as an outcome variable to illustrate the degree of separation at baseline. This approach may introduce complexities in fully accounting for baseline cognitive	

								differences between groups. **Exploratory Nature of Analyses:** The study emphasizes the exploratory nature of analyses, highlighting that the analyses were not specified prior to data collection and the large number of comparisons carried out. This underscores the need for cautious interpretation of results and encourages further confirmatory studies.	
49	Classification of Alzheimer's disease and prediction of mild cognitive impairment-to-Alzheimer's conversion from structural magnetic resource imaging using feature ranking and a genetic algorithm	Computers in Biology and Medicine	2017	Feature Ranking and Genetic Alogorithm	Alzheimer's Disease Neuroimaging Initiative (ADNI)	AD: 60 MCI : 136 NC: 65	**Advanced Feature Selection Method:** The proposed method introduces an automatic feature-selection technique based on feature ranking and a Genetic Algorithm (GA), which aims to select the most discriminative features with minimal dimensionality. **Effective High-Dimensional Pattern Recognition:** The feature-selection approach is specifically	**Potential Algorithm Selection Bias:** The study employs a Genetic Algorithm for feature selection, and while this is shown to be effective, the choice of meta-heuristic optimization algorithms could introduce bias. Consideration of other algorithms such as simulated annealing, particle swarm optimization, or ant colony optimization is suggested for future studies.	

							designed for high-dimensional pattern analysis, making it suitable for complex neuroimaging studies with intricate spatial patterns in brain structure. **Utilization of Fisher Criterion:** The incorporation of the Fisher criterion in the Genetic Algorithm enhances the ability to find an optimal subset of features, ensuring maximum separation between different groups. **Integration of Voxel-Based Morphometry (VBM) Analysis**: The method incorporates VBM analysis to define a mask based on regions of gray matter (GM) atrophy from Alzheimer's Disease (AD) and Healthy Control (HC) subjects. This integration enriches feature extraction for Mild Cognitive Impairment (MCI) prediction.	**Semi-Quantitative GM Atrophy Pattern:** The study uses a semi-quantitative cortical circumferential system for GM atrophy pattern analysis, which may introduce subjectivity. More complex automated computational quantification methods could be explored to enhance objectivity. **Limited Exploration of Other Modalities:** The study primarily focuses on MRI data, and future studies could benefit from exploring the inclusion of other modalities such as positron emission tomography (PET), cerebrospinal fluid (CSF), and genetic information for a more comprehensive analysis. **Absence of Longitudinal Data:**	

							Consideration of Heterogeneity in MCI: Acknowledging the heterogeneity in Mild Cognitive Impairment (MCI), the study includes both progressive (pMCI) and stable (sMCI) MCI patients, recognizing the differences in health status between the two subgroups.	The study does not involve longitudinal data, limiting the ability to capture changes over time. Including longitudinal data in future studies could enhance understanding of disease progression. **Evaluation Only on Binary Classification:** The study mainly focuses on binary classification tasks (AD vs. HC and MCI conversion prediction), and the extension to multiclass classification scenarios could provide a more comprehensive assessment.	
50	Alzheimer's Disease Diagnosis Based on Cortical and Subcortical Features	J Healthc Eng	2019	Softmax Classifier, SVM, KNN, and naïve Bayes	NRCD Dataset and OASIS	326	**Use of Combined Features:** The combination of cortical thickness and subcortical volume features proved effective, showcasing the importance of using multiple features for robust classification.	**Limited Feature Set:** The study relied only on cortical thickness and subcortical volume features, potentially limiting the diversity and richness of information for classification.	The study aimed at establishing the enhancement in accuracy and constancy that can be attained by combining more than one MR-based feature

							Multiple Classifiers Tested: The study employed four different classifiers (softmax, SVM, KNN, naïve Bayes) for comprehensive evaluation, providing insights into the strengths of each in different classification scenarios. **Applicability to Tertiary Group Classification:** The proposed technique demonstrated success in classifying a tertiary group (AD vs HC vs mAD), showcasing its potential for handling more complex classification scenarios. **Effective on External Datasets:** The model's performance was not only validated on the NRCD dataset but also demonstrated effectiveness when applied to the OASIS dataset, suggesting potential generalizability.	**Need for Longitudinal Data:** The study's focus on cross-sectional data may limit its ability to capture temporal changes over time. Future work using longitudinal datasets could enhance understanding of disease progression. **Classifier Dependency:** While the RBF-SVM classifier performed well in several cases, the choice of classifier might be dataset-dependent, and the robustness across different datasets and scenarios should be explored. **No Exploration of Hyperparameter Tuning:** The study does not provide details on hyperparameter tuning for classifiers, and optimal parameter settings could significantly impact performance.	

								Assumption of Homogeneous Data: The study assumes homogeneity within each diagnostic group, which may not fully represent the heterogeneity present in real-world clinical populations.	
51	Partial Least Squares For Discrimination in fMRI Data	Magnetic Resonance Imaging	2012	Linear Discriminant Analysis (LDA), Principal Component Analysis (PCA), Partial Least Squares (PLS), Orthogonal Partial Least Squares (OrPLS)	13 women with high Alzheimer's disease (AD) risk and 11 with low risk based on family history and apolipoprotein-E4 status	Not Specified	**Focused Dimension Reduction with OrPLS:** The use of Orthogonal Partial Least Squares (OrPLS) is advocated as an alternative to PCA. OrPLS is suggested to be more effective for dimension reduction in the context of discrimination among groups of subjects. The study implies that OrPLS may provide a more suitable approach by incorporating information on class structure. **Preserving Discriminative Information:** The study suggests that methods like OrPLS may better preserve the discriminative information present in functional	**Parcellation Scheme Impact:** The use of a parcellation scheme fixed to the Talairach atlas is acknowledged to have potential drawbacks. It is noted that this method may dilute activation and reduce sensitivity and specificity. A suggestion is made to consider an intersection of parcellation-based and functionally defined ROI methods to mitigate this effect. **Dependency on Thresholds:** The proposed approach suggests including only those voxels with significant activation in the calculation of subject-specific ROI mean values. This	The text emphasizes the advantages of OrPLS over PCA for discrimination in functional neuroimaging data, it also highlights considerations and challenges related to the methodology, sample size, and computational aspects that warrant further investigation and validation

							neuroimaging data. It emphasizes the need for techniques that can capture relevant patterns in distributed brain networks for accurate group discrimination. **Superior Performance of OrPLS:** The text asserts the superior performance of OrPLS over PCA in the context of Linear Discriminant Analysis (LDA) for identifying brain functional networks. It indicates that OrPLS achieves a higher classification accuracy compared to PCA-based approaches. Stability in **Discriminant Patterns:** The study references Habeck et al.'s findings regarding the stability of the spatial pattern of weights in OrPLS. It suggests that the discriminant patterns obtained through OrPLS are more stable, which is crucial for	introduces a dependency on the choice of thresholds for defining significant activation, which could impact the results. **Small Sample Size for Longitudinal Data:** While the study employs longitudinal data, it mentions that further validation with an independent sample will be conducted in the future. The small sample size in longitudinal validation raises concerns about the generalizability of the findings. **Computational Challenges with Voxel-Wise Data:** The study recognizes the increased complexity of applying OrPLS to voxel-wise neuroimaging data. Computational approaches to deal with the inversion of very large covariance matrices will need to be developed, indicating potential	

							reliable discrimination among subjects. **Longitudinal Validation**: The study presents the use of follow-up fMRI test data from the same subjects acquired four years later. It claims that the OrPLS method demonstrated low misclassification rates in this longitudinal validation, supporting its potential for robust discrimination over time. **Identification of Relevant Brain Networks:** OrPLS is credited with identifying brain networks that include specific regions such as the ventral temporal lobe, Brodmann areas 19 and 37, the praecuneus, and cingulate gyrus. This suggests that OrPLS not only discriminates effectively but also provides insights into the neuroanatomical basis of the discrimination.	challenges in scalability. **Comparison with Other Discrimination Techniques:** The study primarily compares OrPLS with PCA-LDA approaches. However, a broader comparison with other state-of-the-art discrimination techniques commonly used in neuroimaging studies would enhance the understanding of the method's relative strengths and weaknesses.	

52	Multi-scale graph-based grading for Alzheimer's disease prediction	Medical Image Analysis	2021	Multi Scale Graph-Based Grading Framework	Alzheimer's Disease Neuroimaging Initiative (ADNI)	AD: 130 MCI: 216 NC: 213	**Efficient Combination of Variability and Similarity**: The proposed method excels in efficiently combining intra-subject variability and inter-subject similarity within a common model. This ability enhances the adaptability of the model across different anatomical scales. **Multi-Scale Graph-Based Grading:** The utilization of a multi-scale graph-based grading framework is a significant strength. This approach allows for a comprehensive analysis that considers variations at different anatomical scales, providing a more nuanced understanding.	**Dependency on Segmentation Quality:** The major limitation stems from the method's dependence on the quality of segmentation maps. The accuracy and reliability of the proposed approach are directly influenced by the precision of segmentation, and any inaccuracies in segmentation maps can compromise the results. **Sensitivity to Segmentation Errors:** In cases where segmentation maps contain errors or inaccuracies, the proposed framework is likely to be sensitive to these issues. This sensitivity could lead to misinterpretations or misgradings, impacting the overall robustness of the method. **Subject-Specific Variation:** The method's performance may be affected by	The method integrates inter-subject similarity and intra-subject variability across anatomical scales, achieving state-of-the-art performance. The joint analysis of hippocampal subfields and brain structure highlights their complementarity in AD assessment.

								subject-specific variations in segmentation quality. If there are considerable variations in the accuracy of segmentation across different subjects, it could introduce inconsistencies in the grading framework. **Applicability Across Diverse Populations:** The method's generalizability might be limited when applied to diverse populations with varying anatomical characteristics. Anatomical variations between different groups may challenge the universality of the proposed framework. **Complexity and Computational Demands:** Depending on the computational demands of the multi-scale graph-based grading framework, there might be challenges related to	

								computational resources. The complexity of the approach could limit its practical applicability, especially in resource-constrained environments. **Interpretability of Multi-Scale Results:** The interpretability of results obtained from a multi-scale analysis might be challenging. Understanding and extracting meaningful insights from variations at different anatomical scales could be complex and may require advanced expertise. **Need for High-Resolution Imaging:** The proposed method may necessitate high-resolution imaging for accurate segmentation. In scenarios where high-resolution data is not available, the effectiveness of the	

								method could be compromised.	
53	Consistent connectome landscape mining for cross-site brain disease identification using functional MRI	Medical Image Analysis	2022	Connectome Landscape Modeling Method, Alternating Direction Method of Multipliers	-	-	**Cross-Site Consistency:** Addresses the challenge of inconsistent findings in brain disorder studies across different sites by mining cross-site consistent connectome landscapes. **Data-Driven Representation:** Utilizes data-driven representation of functional connectivity networks, avoiding reliance on human-engineered features and potentially improving discriminative power. **Connectome Landscape Learning:** Learns a weight matrix for joint cross-site connectome landscape learning, network feature extraction, and disease identification, providing a comprehensive approach.	**Dependence on Functional Connectivity Networks:** The effectiveness of CLM is contingent on the accuracy and relevance of the functional connectivity networks used as input. Inaccuracies or biases in these networks may impact the reliability of the results. **Sensitivity to Parameter Choices:** The performance of CLM may be sensitive to the choice of parameters, such as the regularization parameters for norm penalties. Suboptimal parameter selection could affect the method's robustness and generalizability. **Complexity and Interpretability:** The complexity introduced by the joint learning of connectome	CLM introduces a novel approach to brain disorder identification by mining cross-site consistent connectome landscapes. Its potential is demonstrated, but sensitivity to parameters and interpretability challenges persist.

							Norm Penalties: Incorporates row–column overlap norm penalty for capturing consistent connectome landscapes across multiple sites, enhancing reliability. Also, introduces an -norm penalty for capturing site-specific patterns. **Efficient Algorithm:** Employs the Alternating Direction Method of Multipliers (ADMM) for efficient and effective solution to the proposed objective function.	landscapes and disease identification may make the model challenging to interpret. Understanding the specific contributions of different features or patterns may be non-trivial. **Applicability to Specific Disorders:** The method's suitability for different brain disorders may vary. Its generalizability across diverse neurological conditions and its ability to capture nuanced differences between disorders need careful consideration. **Computational Intensity:** The efficient algorithm used (ADMM) may still be computationally intensive, especially when dealing with large-scale datasets or high-dimensional connectome representations, limiting its scalability.	

								Validation and Generalization: While demonstrating potential in real-world datasets, the generalizability and validation of CLM across a broader range of datasets and disorders need further exploration to establish its robustness.	
54	Ambivert degree identifies crucial brain functional hubs and improves detection of Alzheimer's Disease and Autism Spectrum Disorder	NeuroImage: Clinical	2020	Using ambivert degree as input features, deep neural networks detect AD and ASD from healthy controls	Alzheimer's Disease Neuroimaging Initiative (ADNI) and Autism Brain Imaging Data Exchange (ABIDE)	ADNI AD: 29 NC: 49 ABIDE ASD: 73 NC: 88	**Innovative Measures:** Introduces novel measures like ambivert degree and gateway coefficient, accounting for the strength of connections and the uniqueness of inter-modular connections. **Preservation of Modular Structure:** Addresses the impact of sparsification on network modularity, utilizing a thresholding scheme to maintain the modular structure during network analysis. **Clinical Relevance:** Applies the method to investigate the	**Dependence on Segmentation Maps:** Acknowledges a dependence on the quality of segmentation maps for aggregating patch-based grading and estimating abnormality, which may introduce variability. **Complexity of Interpretation:** Introduces new measures, which, while innovative, might add complexity to the interpretation of results and require a thorough understanding of their implications.	The study introduces crucial innovations in hub detection, revealing the impact of weak connections and modular structure on neurological diseases. The proposed measure, ambivert degree, proves effective for detecting perturbed hubs in AD and ASD, offering promising biomarkers for diagnosis.

							disruption of brain hubs in Alzheimer's disease (AD) and Autism Spectrum Disorder (ASD), highlighting potential clinical applications. **Informative Features for Classification:** Demonstrates the effectiveness of hub scores as features for classifying AD and ASD subjects, offering insights into the diagnostic potential of hub disruptions.	**Generalization:** The study focuses on specific disorders (AD and ASD) and large datasets, and the generalizability of the proposed measures and methods to other disorders or smaller datasets remains to be explored. **Impact of Lesions:** While the study considers the effect of inducing artificial lesions in brain functional networks, the broader implications of this manipulation on the clinical relevance of hub disruptions need further exploration. **Algorithm Sensitivity:** The method's sensitivity to parameters and the potential need for optimization could impact its robustness across different datasets and experimental conditions.	
55	Decoding Brain Functional	Medical Image Computing	2019	Feed-Forward Deep Neural Network	Alzheimer's Disease Neuroimaging Initiative (ADNI)	Not Specified	**Efficient Feature Reduction:** The recursive elimination of	**Model Complexity:** The complexity of the 5-layer feedforward	The study introduces a feature

	Connectivity Implicated in AD and MCI	and Computer Assisted Intervention					low-relevance features effectively addresses the challenge of handling fMRI data with a high feature-to-instance ratio. **Leaner DNN Design:** The approach results in a leaner Deep Neural Network (DNN), optimizing the model for fMRI classification tasks. **State-of-the-Art Performance:** Achieving state-of-the-art classification accuracy for MCI/AD and CN/AD, and comparable accuracy for CN/MCI classification highlights the effectiveness of the proposed method. **Biological Interpretability:** The identified important brain regions align with previous studies, enhancing the biological interpretability of the results. **Potential for Biomarker**	DNN might limit interpretability and generalization, and alternative architectures could be explored. **Dependency on Feature Relevance Scores:** The effectiveness relies on the accuracy of feature relevance scores, which could be influenced by the choice of the reference-based decoder. **Clinical Validation:** While the method shows promise for biomarker detection, its clinical utility should be validated through further studies and real-world applications. **Interpretability Challenges:** The interpretability of DNNs remains a challenge, and understanding the clinical implications of identified features requires additional research.	elimination approach for efficient deep learning on fMRI data, improving classification accuracy for AD, MCI, and CN scans. The method provides potential biomarkers for neurological diseases.

							Detection: The method holds promise for biomarker detection in various neurological ailments, supporting computer-aided detection applications.		
56	Learning brain connectivity of Alzheimer's disease by sparse inverse covariance estimation	NeuroImage	2010	Sparse Inverse Covariance Estimation (SICE)	Alzheimer's Disease Neuroimaging Initiative (ADNI)	AD: 49 MCI: 116 NC: 67	**Connectivity Model Identification:** The proposed SICE method successfully identifies connectivity model structures from PET data, providing insights into the functional brain connectivity of different groups (AD, MCI, NC). **Order of Inter-Region Connections:** With the aid of a quasi-measure, SICE can determine the order of inter-region connections in terms of connection strength, contributing to a more detailed understanding of network characteristics. **Group Comparison Insights:** The application of SICE to ADNI FDG-PET data revealed significant findings, including	**Data Heterogeneity in MCI Group:** The MCI group used for brain connectivity modeling is heterogeneous, consisting of subjects with varying outcomes (e.g., conversion to AD, remaining as MCI, or reverting to normal). The reliability of connectivity models for MCI may be affected by this heterogeneity. **Lack of Longitudinal Diagnostic Results:** The diagnostic results of the MCI subjects at later checkups were not available during the development of the paper. Future work plans to address this limitation by splitting the MCI group based on later diagnostic results,	

							decreased connections in the temporal lobe in Alzheimer's disease (AD) and increased connections in the frontal lobe, suggesting compensatory effects. **Clinical Trial Application:** The methodology proposed in the paper holds potential for application in clinical trials. It can be used to assess drug efficacy by comparing connectivity patterns between groups receiving and not receiving a certain drug, with the advantage of producing reliable models with small sample sizes. **Potential for fMRI Modeling:** The approach may be extended for functional brain connectivity modeling based on fMRI data. Subject-level connectivity models could be identified, and connectivity-based biomarkers for AD and MCI may be explored, complementing	leading to more reliable models. **Linear Interaction Modeling:** SICE provides a model for linear interactions between brain regions based on the covariance matrix. Future research directions could explore nonlinear interactions by incorporating discretized measurements and building graphical models. **Preprocessing Procedure:** The paper acknowledges the use of the default SPM5 registration in the current preprocessing procedure. Future work aims to explore improved image registration algorithms in SPM5/8 (DARTEL).	

							existing region-based biomarkers.		
57	Topographical Information-Based High-Order Functional Connectivity and Its Application in Abnormality Detection for Mild Cognitive Impairment	Journal of Alzheimer's Disease	2016	High-Order Functional Connectivity (HOFC)	Independent Study	MCI: 80 NC: 90	**Increased Sensitivity to Group Differences:** HOFC demonstrated higher sensitivity to detect group differences compared to conventional FC, providing more biologically meaningful results. **Individual Variability:** HOFC better captured individual variability than FC, allowing for potential applications in individualized classification. **Enhanced Modular Structure:** HOFC-based network analysis revealed a more prominent modular structure compared to FC, aiding in better analysis of network organization. **Prominent Group Differences:** Group differences in modularity were more pronounced in the HOFC network,	**Dependency on Pearson's Correlation:** The use of Pearson's correlation in HOFC has inherent limitations, such as neglecting time-domain information (e.g., phase synchrony, dynamic properties) and the inability to measure complex inter-regional interactions (e.g., modulation effects, partial correlation, mutual information). Future extensions could explore more sophisticated metrics to address these drawbacks. **Two-Level Correlation Computation:** The study only implemented a two-level correlation computation for HOFC. Future enhancements could involve adding more levels within the computational framework,	HOFC presents a novel and promising approach for characterizing high-level brain functional organizations, with potential applications in disease biomarker detection and understanding individual variability.

							indicating its ability to detect subtle alterations in brain functional organization. **Correlation with Behavioral Data:** HOFC network properties showed correlations with behavioral data, suggesting its potential biological relevance. **Olfactory Cortex and Frontal Cortex Connectivity Changes:** HOFC revealed interesting connectivity changes between the olfactory cortex and the frontal cortex in MCI, indicating early pathology changes associated with neurodegeneration in AD. **Modularity Configuration:** MCI showed a higher diversity in modularity configuration, suggesting a more functionally segregated brain and potential compensatory effects in response to pathology.	incorporating time-varying, multi-frequency, and multimodal information for higher-order FC. **Limited to fMRI Information:** The HOFC analysis in this study solely relied on functional connectivity (FC) information extracted from fMRI. Future developments could naturally extend HOFC by integrating more features into the profile vector, allowing for the fusion of multi-channel information from various modalities, such as diffusion tensor imaging-based structural connectivity. **Coarse Brain Parcellation:** The study utilized a coarse brain parcellation atlas (AAL). Adopting a finer parcellation scheme could improve the accuracy of FC estimation and extend the FC profile,	

								enhancing the benefits of HOFC calculation. **Integration of Additional Features:** While the study focused on FC information, the integration of additional features into the profile vector for HOFC calculation was mentioned as a future consideration. This could involve incorporating information from diverse modalities, contributing to a more comprehensive understanding of high-level brain functional organization.	
58	Aberrant Connectivity in Mild Cognitive Impairment and Alzheimer Disease Revealed by Multimodal Neuroimaging Data	Neuro-degenerative Diseases	2018	Multimodal SICE	Alzheimer's Disease Neuroimaging Initiative (ADNI)	AD: 116 MCI: 116 NC: 116	**Identification of Neurobiological Changes:** The study effectively identified the neurobiological changes between MCI and NC based on multimodal SICE, providing crucial insights into the progression of cognitive decline. **Insight into Brain Network**	**Limited Neuroimaging Modalities:** The study only considered a subset of neuroimaging modalities, including sMRI, FDG-PET, and florbetapir PET. Other potentially relevant data sources for distinguishing Alzheimer's disease (AD) or Mild Cognitive Impairment	

							Connectivity: By analyzing connectivity patterns, the research highlighted the progressive weakening of connectivity in key brain regions, notably the temporal, temporal-parietal, and occipital-parietal lobes, contributing to a comprehensive understanding of the underlying mechanisms of MCI. **Detection of Impaired Cognitive Regions:** The study successfully detected significant declines in connectivity within the temporal lobe, highlighting the correlation between temporal lobe connectivity loss and cognitive decline, a key feature in the trajectory of MCI progression. **Evidence of Compensatory Mechanisms:** The research indicated potential compensatory mechanisms in MCI patients, particularly observed in the	(MCI), such as cerebrospinal fluid (CSF), cognitive measures, and genomics, were not included. This limits the comprehensiveness of the analysis. **Incomprehensive Multimodal Integration:** The approach used to integrate multimodal imaging data may not be optimal. The study acknowledges that the method employed for integrating these modalities may have limitations, and there is a recognition that alternative techniques, such as weighted combination methods, could be explored for more effective multimodal integration. **Lack of Intrasubject Linkage:** The study did not consider intrasubject linkage of the imaging data. This means that the connection or	

							increased connectivity between certain brain regions, offering valuable insights into the brain's adaptive processes in the face of cognitive challenges. **Enhanced Diagnostic Capabilities:** By integrating multiple neuroimaging modalities such as sMRI, FDG-PET, and florbetapir PET, the study provided more comprehensive and accurate imaging-based biomarkers, enabling improved differentiation between NC, MCI, and AD patients, leading to earlier and more accurate diagnoses.	relationship between different modalities within the same subject was not explicitly taken into account. In future studies, addressing this limitation and exploring methods to link intrasubject multimodal data could enhance the accuracy and reliability of classification. **Potential Modality Weighting Issues:** The weighted combination method used for multimodal integration may have its limitations. The study acknowledges that there may be alternative ways to combine multimodal data, and the chosen method may not be the most effective for the specific dataset. Exploring and comparing different weighting strategies could provide insights into the robustness of the results.	
59	Learning Brain Connectivity Sub-networks	Frontiers in Neuro-informatics	2018	Leave-one-out Cross Validation, SICE	Independent Study Conducted in Xuanwu Hospital,	AD: 30 NC: 32	**Enhanced Classification Accuracy:** The	**Parameter Sensitivity:** The study's reliance on a	The authors proposed a novel

	by Group-Constrained Sparse Inverse Covariance Estimation for Alzheimer's Disease Classification				Capital Medical University, Beijing, China		proposed classification framework using fMRI time series significantly improved the diagnosis accuracy for distinguishing AD patients from NC, indicating its superiority over other methods. It showcases an improvement of at least 7.27% in diagnosis accuracy, highlighting the effectiveness of the sparse-based method in constructing brain networks compared to traditional fully-connected correlation-based networks. **Effective Biomarker Identification:** The top 5 brain connections identified by the proposed method serve as promising connectivity-based biomarkers for the diagnosis of AD. These connections correspond to brain regions known to be significantly associated with AD pathology, such as the Cingulum_Post and regions within the Default Mode Network (DMN), aligning with	fixed SICE tuning parameter (λ) for different subjects may impact the classification performance due to varying optimal parameters across individuals. To address this, the study proposes subject-specific λ optimization using the BIC method, enabling the construction of optimal connectivity networks for each subject in future research. **Atlas Relevance:** Limitations arise from using a Chinese brain atlas for MRI analysis in a study involving Chinese participants, rather than the Caucasian atlas (SPM8). Incorporating a culturally specific brain atlas during image segmentation and registration is suggested to enhance the extraction of precise MRI features, improving the	sub-network based classification framework to construct brain functional subconnectivity and explore its diagnostic power in distinguishing AD patients from NC.

							existing research findings. This strengthens the potential applicability of the proposed method in the diagnosis of MCI patients, showcasing its robustness and versatility. **Improved Network Construction:** The method's integration of the Group-constrained topology structure detection algorithm with SICE aids in improving classification performance. By encouraging a consistent network topology across subjects, the method minimizes inter-subject variability issues, thereby enhancing the generalization performance of trained classifiers. This emphasizes the efficacy of the method in constructing efficient functional brain sub-networks, crucial for accurate classification. **Reinforcement of Disconnection Hypothesis:** The	accuracy of diagnosing AD patients.	

							findings support the disconnection hypothesis of AD, demonstrating the significance of the identified brain regions in DMN. The reported decline in synaptic numbers in regions such as the Cingulum_Post aligns with previous studies, reinforcing the proposed method's ability to detect both impairments and compensatory mechanisms within DMN. This not only adds to the existing body of knowledge but also establishes the potential of the method for diagnosing MCI patients in the future. **Robustness in Detecting Pathological Changes:** By highlighting the connectivity changes within DMN, the method proves its robustness in detecting pathological changes, even at the MCI stage of AD. This further underscores its		

							relevance and potential for early diagnosis and intervention, establishing it as a valuable tool in the assessment and management of cognitive impairments.		
60	Gaussian process classification of Alzheimer's disease and mild cognitive impairment from resting-state fMRI	NeuroImage	2015	Bayesian Gaussian Process Logistic Regression (GP-LR)	Independent Study	AD: 27 aMCI: 50 NC: 39	**Innovative Approach:** Introduces a fresh method for patient stratification from resting-state fMRI scans, targeting the early phases of Alzheimer's disease (AD). **Diverse Methodology:** Incorporates the Gaussian process logistic regression (GP-LR) model alongside support vector machines (SVMs), providing a comprehensive approach for neuroimaging studies. **Principled Predictions and Customizability:** Offers principled estimates of predicted class membership and customizable classification	**Sample Size and Data Balance:** Small sample size in relation to tested features increases the risk of overfitting. Non-uniform distribution of educational backgrounds and gender ratios among groups introduces potential confounding variables. **Motion Artifacts and Local Atrophy Effects:** Potential impact of motion artifacts and local gray matter loss on functional connectivity requires further investigation for improved preprocessing methods. **Diagnostic Challenges and Misclassifications:** Lack of post-mortem	

							thresholds, enhancing adaptability for clinical decision-making. **Insightful Analysis:** Provides valuable insights into the key data features crucial for understanding AD diagnosis.	confirmation and potential overlap with other conditions like major depression pose challenges in accurate differentiation between various neurodegenerative disorders.	

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