Integrating Brain Networks and Multi-Modal Data for Early Detection of Alzheimer's Disease

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Abstract

Early diagnosis of Alzheimer's disease (AD) is crucial for providing timely treatment and care to patients. However, current diagnostic methods rely on clinical symptoms and biomarkers, which are often unreliable and invasive. Brain networks model the brain's structure and function in AD and other brain diseases. To fully capture their complexity, we need multi-modal models that combine different types of data, such as structural and functional connectivity, clinical and genetic information. This gives us a holistic view of the disease's many aspects. In this paper, we argue that brain networks and multi-modal data fusion can improve early diagnosis of AD by capturing the complex and heterogeneous nature of the disease. Using brain network modeling and multi-modal data fusion, we envisage a novel framework for detecting AD and its prodromal stages. The framework can simultaneously capture network properties from multi-modal as well as longitudinal datasets, which provide complementary information.

Keywords

Alzheimer's Disease, Brain Networks, Multi-modal data fusion, Artificial Intelligence, Prediction, Progression

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that affects millions of people worldwide. It is characterized by cognitive impairment, memory loss, and behavioral changes. AD is the most common cause of dementia and the sixth leading cause of death among adults. Early diagnosis of AD is crucial for providing timely treatment and care to the patients, as well as for reducing the social and economic burden of the disease.

The development of AD typically occurs in three primary phases. In the initial stage, known as pre-clinical AD, changes in the brain may initiate without observable symptoms, making detection of the disease challenging. Subsequently, in the second phase, referred to as mild cognitive impairment (MCI), individuals and their families may start noticing symptoms related to cognitive abilities, although these may not significantly affect daily functioning. Notably, not all individuals diagnosed with MCI progress to AD.

Research on Alzheimer's primarily focuses on identifying biomarkers capable of diagnosing

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the disease and predicting its progression. Various measurements have been developed and assessed for detecting AD, typically encompassing physical health examinations, neuropsychological assessments, and brain imaging techniques. Biomarkers are usually categorized into physiological, cognitive, behavioral, and psychological domains. Among the non-cognitive tests, neuroimaging techniques are commonly utilized, while the Mini Mental State Examination (MMSE) [1, 2] stands out as one of the most widely recognized cognitive assessments.

However, current diagnostic methods rely on clinical symptoms and biomarkers, which are often unreliable and invasive. Clinical symptoms are subjective and vary across individuals and stages of the disease. Biomarkers, such as cerebrospinal fluid (CSF) and amyloid-beta (Aβ), require invasive procedures and expensive equipment. Moreover, both clinical symptoms and biomarkers are not sensitive enough to detect the early and prodromal stages of AD, such as mild cognitive impairment (MCI) and subjective cognitive decline (SCD).

To capture the various symptoms of AD, including subtle changes that occur throughout the progression of the disease, there's widespread agreement that a reliable method for detecting early-stage Alzheimer's disease cannot rely solely on measurements from one source. Instead, it should employ a multi-modal approach by combining different types of biomarkers. Each type of data reveals unique aspects of the condition, and integrating them all provides a more comprehensive understanding, ultimately improving diagnostic accuracy.

Over the past few years, the progress in Artificial Intelligence-based methods for analyzing multi-modal data has fueled research seeking new approaches for early disease detection. In Comito et al. [3], an overview of the most recent approaches leveraging machine learning and deep learning techniques for the prediction of Alzheimer's disease by exploiting the huge amount of multi-modal data now made available from the public repositories mentioned above to researchers has been presented. However, current research does not consider an important modality that recently has attracted the interest of many researchers: the *brain connectome* introduced by Sporns et al. [4] in 2005. In particular, in the last ten years, the investigation of AD progression and early detection has shown promise through the concurrent utilization of advanced neuroimaging methods and complex network theory. By creating a brain network from imaging data and representing it using network graphs allows to capture the complex and dynamic interactions among brain regions, and reflect the changes in the brain structure and function due to AD. Several studies have shown that brain network analysis can provide useful insights into the pathophysiology and progression of AD, and can discriminate between AD and normal aging. Analyzing the complex network of the human brain provides valuable insights into its structural organization. This allows for the identification of abnormal interaction patterns or irregularities in the modular structure of brains affected by AD.

The objective of this paper is to explore new avenues and methods to integrate brain networks within multi-modal learning architecture to improve early diagnosis of Alzheimer's disease. To this purpose, the paper proposes a novel framework for detecting AD and its prodromal stages using brain network modeling and multi-modal data fusion. Unlike existing methods, our framework can simultaneously capture network properties from multi-modal as well as longitudinal datasets, which provide complementary information. We use network models to represent the structural and functional connectivity of the brain regions, and integrate multiple types of data, such as images, text, audio, etc., to capture the complex and heterogeneous nature of AD.

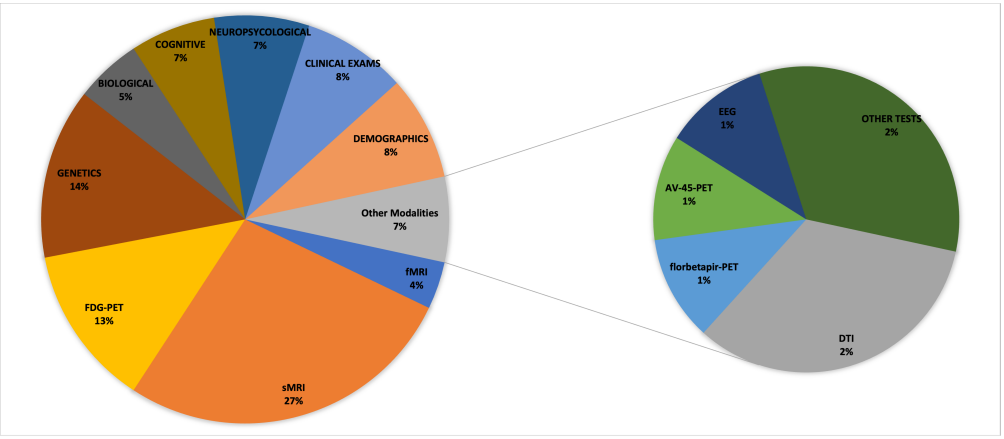

Figure 1: Data modalities used by the AI methods reviewed in the paper.

The paper is organized as follows. In Section 2, a summary of the current state-of-the-art multi-modal approaches for AD prediction overviewed in [3] is reported. Section 3 discusses brain networks, highlighting the most relevant trends of the network-based models. Section 4 presents the proposed framework integrating brain networks within multi-modal learning architectures. Finally, Section 5 concludes the paper.

2. Multi-modal Approaches for AD Prediction

This section summarizes the main data modalities and AI methods utilized in Alzheimer's disease research reviewed in [3].

As far as data modalities are concerned (see Figure 1), neuroimaging (i.e. different tipology of MRI and PET scans) stands out as the most prevalent data modality due to its non-invasive nature, the availability of large datasets, the advancement of robust AI tools capable of extracting significant features and classifying images, and the possibility of analyzing both structural and functional brain anomalies and changes in AD patients.

Following neuroimaging, biological and genetic markers (APOE-e4, SNPs, CSF) are predominantly used to identify individuals likely to develop AD. Actually, certain genes and CSF markers have been linked to an increased risk of the disease. Neuropsychological and cognitive assessment tests are the third most common, primarily serving as screening tools to pinpoint those requiring further evaluation. Lastly, demographic and clinical data, including blood markers, are less frequently employed in the classification and progression tracking of AD.

The complexity and diversity of the data involved in AD research are, in turn, reflected in the use of various AI techniques to classify the stages of the disease and predict its progression.

Traditional ML classifiers like SVM, DT, GB, RF, and LOR are widely used (see Figure 2), particularly when clinical, demographic, and cognitive data are adopted. On the other hand, DL methods, including NN, CNN, and RNN, show promise in medical image analysis, which is crucial for AD diagnosis and monitoring. However, there is a remarkable number of AI methods (referenced in Figure 2 as "OTHERS") that are used only in one or two approaches. This

highlights that the application of AI in AD prediction and progression is indeed a multifaceted field.

The mixed outcomes of the research in this field suggest that there is no one-size-fits-all solution, and the choice of technique may depend on the specific dataset and task at hand. Moreover, the need for careful parameter tuning, data selection, and experimental settings cannot be overstated, especially when dealing with limited data availability, which is a common challenge in AD research. The exploration of ensemble neural networks and the comparison of various ML models underscore the ongoing efforts to refine predictive models for AD.

Overall, the continuous evolution of AI methods in AD prediction and progression demonstrates the dynamic nature of the field and the potential for AI to contribute to our understanding and management of this complex disease.

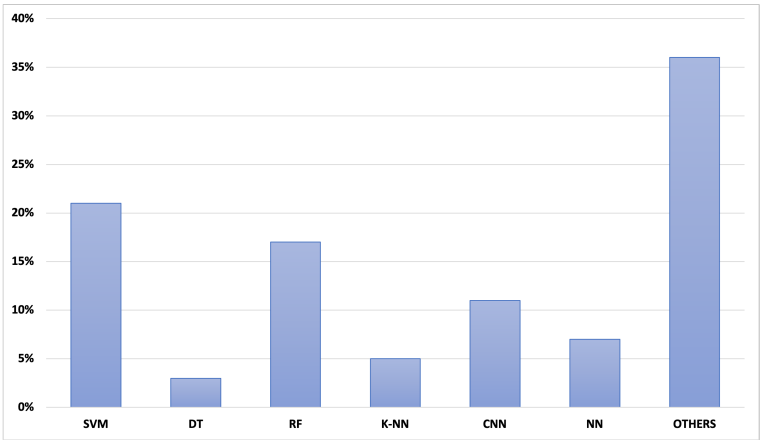

Figure 2: AI Methods used for Alzheimer's Disease Prediction and Progression.

3. Brain networks

In the last decade, the study of the progression of Alzheimer's disease and its early detection has provided promising results from the joint use of advanced neuroimaging techniques and complex network theory [5]. The construction of a *brain network* from an imaging model through the formalism of *network graphs* has significantly improved the understanding of how the brain of an AD patient behaves. The complex networks-based analysis of the human brain provides better insights into the network structure, thus uncovering abnormal patterns of interactions or randomness in the modular structure of an AD-infected brain.

Graphs are a mathematical model widely used for studying complex systems. In the literature on brain networks and neurodegenerative diseases in general, there are different ways to formalize and model the brain through a graph. More formally, the entities of a brain and their relationships can be represented with a brain network BN modeled as a graph $G = (V, E, W)$ where V is a set of n objects, called nodes or vertices, $E \subseteq V \times V$ is a set of links, called edges, that connect two elements of V, and $W : V \times V \to R$ is a function which assigns a weight to a couple (i, j) of nodes i and j, if there exists an edge connecting i and j, and 0 if an edge between i

and j does not exist. In almost all the AD-related studies, the nodes of the graph are usually brain regions, while the edges may capture different relationships between regions [6, 7]. We therefore classify brain networks and study their connectivity accordingly, as follows.

- **Anatomical/structural brain networks**: constructed from structural magnetic resonance imaging (MRI), the edges represent physical connections between regions (e.g., the estimated white matter connection strength in terms of number of fibers between any pair of brain regions [7], interregional similarity [8] [9], etc.).
- **Functional brain networks**: the edges capture the functional interaction (magnetic, electrical, or hemodynamic/metabolic) between brain regions that are not necessarily adjacent or physically connected. These networks are usually constructed from imaging models like functional magnetic resonance imaging (fMRI), electroencephalography (EEG), and magnetoencephalography (MEG). In recent studies, resting-state functional magnetic resonance imaging (rs-fMRI) has also been used in AD progression studies. This imaging technique evaluates the BOLD (Blood oxygenation level-dependent) signal in various regions of the brain. Its fluctuations, together with other functional connectivity alterations, are used as AD biomarkers.
- **Cortical thickness networks**: these are hybrid networks based on structural data with functional-like edges representing correlations between regions.
- **Directed progression networks** (DPNets): closely related to cortical thickness networks, they attempt to capture the temporal progression of the disease, more than the correlations between regions, similar to the epidemic network models where an edge represents the spreading of the disease. In this network formalism, the edges are directed and capture the degree to which one brain region thinning precedes the second region thinning.

To characterize network topology, thresholding sparsification techniques are usually applied to structural or functional connectivity matrices to remove edges with noisy weights [10].

Even if these types of networks are clearly related, the comparison between them and their joint analysis with the goal of having a systemic and multi-layer view of the disease progression is not straightforward [7].

An important aspect that the study of brain networks has highlighted in recent years is the detection of building blocks, i.e. the presence of overabundant small subgraphs sharing patterns of interconnections, called *network motifs*, occurring with a frequency higher than that in a random network [11]. Network motifs have been recognized as fundamental building blocks of networks [11] giving insights into the functional mechanisms of the analyzed system, and revealing different organization models of the same network.

A *motif* of a graph G is defined as an unordered subset $M = \{v_1, \dots, v_r\}$ of nodes of G presenting a particular pattern of interconnections. Fig. 3 shows five types of motifs among three and four nodes (Fig. 3(a)-Fig. 3(e)). Their labeling follows the same convention adopted in [12]. The bi-fan motif, for example, is over-expressed in neuronal networks.

Motifs have been largely analyzed in brain networks, especially in structural and functional networks. In [13], Meier et al. exploit motifs for clustering the functional brain network built on MEG data. This type of network, called *effective connectivity network*, is composed by ROIs linked by their *effective connectivity*, a measure describing the causal effect of one brain region

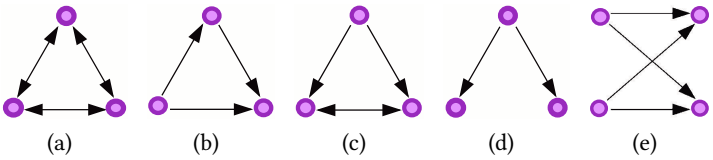

Figure 3: (a) M_4, (b) M_5 (feed-forward loop), (c) M_6, (d) M_8, (e) M_{bifan} motifs.

on another region. To calculate this pairwise value between brain regions, the measure of Phase Transfer Entropy (PTE) is applied. Here, some 3 and 4 nodes motifs are over-expressed, moreover, motif-based clustering reveals a strong symmetry between the two hemispheres, supporting the idea of a higher-order organization of the effective connectivity brain network.

Battiston et al. [7] analyze the presence of motifs spanning over a two-layer brain network of healthy subjects composed of a structural and a functional layer. The multiplex two-layer network is built by forming a first structural network layer with DW-RMI data (Diffusion Magnetic RMI) and a second functional layer with rs-fMRI data. The motifs analyzed are multiplex, which is statistically overabundant small subgraphs spanning over the two layers and jointly considered. Results show that motifs in which links between brain regions at the structural layer also have a functional activity are frequent, but there are also frequent multiplex motifs having distant regions with strong functional dynamics. Finally, the analysis shows the existence of a reinforcement mechanism between the structural and the functional layers for which the probability of having a link is related to the intensity of the connection in the other layer.

Recent studies have highlighted that network motif analysis can provide new markers for the diagnosis and progression of Alzheimer's disease. Friedman et al. [14] were able to distinguish AD from HC patients with directed motif analysis of their DPNets. In addition, the entropy of the motif distribution provides a new imaging marker for MCI.

In the next section, a review of the most recent proposals studying brain networks for the diagnosis of Alzheimer's disease is reported.

3.1. Network-based approaches

As part of the Network Medicine approaches, the network-based methods are able to reveal the network disruptions or the structural changes initiated by the disease through the application of methodologies proper of Network Science and Graph Theory, offering practical techniques able to tackle the limitations of the consolidated biomarkers [5]. These methods are increasingly attracting interest due to their ability to simplify the understanding of the modeling of the disease at multiple biological levels [15]. In the following, we review the most relevant works in this area by reporting in Table 1 the type of brain network modeling.

- Dragomir and Vrahatis [16] review the current state-of-the-art in network-based biomarkers for preclinical AD diagnosis by subdividing the current trends into two research lines: AD biomarkers focusing on the modular substructures at a (1) *molecular level* (i.e. blood omics-biomarkers in molecular networks) and at a (2) *brain level* (i.e. volumetric

approaches and connectivity from MRI data on connectivity networks). In this context, the benefits of monitoring the early stages of the disease by jointly considering genotype and brain phenotype information as noninvasive biomarkers are discussed. Particular emphasis is placed on methods that analyze the network substructure through methods of complex network analysis since disruptions usually occur locally, in different brain regions and molecular pathways, and at different rates. Finally, a framework integrating knowledge from the two information levels, molecular omics-based data collected from blood samples and brain connectivity obtained from neuroimaging techniques, is proposed, showing that this multi-level solution can further improve diagnosis.

- In [8], Tijms et al. analyze the structural brain network of gray matter extracted from MRI images, and the clinical progression in nondemented subjects who have abnormal amyloid markers in the cerebrospinal fluid (CSF), that is a marker of predementia AD. The study investigates if network structural measures like size, connectivity density, degree, clustering coefficient, path length, betweenness centrality, and the small-world property are somehow associated with the rate of progression to MCI or dementia, using Cox proportional hazard models to assess associations between the structural measures and time to clinical progression. Results indicate that when these measures have low values there is an increased risk of fast progression to MCI. In particular, lower clustering values, indicative of a more randomly organized network, in specific anatomical areas are associated with clinical outcomes and fast clinical progression.
- In recent work, [9] Ding et al. investigate the relationship between topological features of gray matter morphological networks and the clinical cognitive performance of healthy control subjects (HCs) and patients with SCD or MCI. Analyzing local graph measures, the networks of SCD and MCI show a significant decrease of degree centrality in the caudate neucleus and of nodal efficiency in the caudate neucleus, right insula, lenticular nucleus and putamen. In terms of global topological measures, SCD and MCI patients show lower values of path length, normalized path length, and global efficiency in their brain networks. The study concludes that the topological features of the structural gray matter network can be considered biomarkers that can improve AD prognosis and interventions in its early stage.
- Friedman et al. [6] define and analyze the DPNets in AD, particularly directed brain networks where an edge between two regions represents nor the physical connectivity nor a functional connectivity but the temporal spreading of the pathology. The DPNets are constructed by evaluating the change in cortical thickness measurements: when a node A is thinning over time, it is considered infected with a certain probability and may spread its infection to other nodes. A directed edge connects node A to a node B if in a late period B shows a higher thinning rate (i.e. B has been ”infected” by A), with a weight representing an infectious similarity (ISIM). By using several local and global measures (degree, indegree, outdegree, size of the giant component, path length, global efficiency, clustering coefficient, modularity and small world properties), the results show that DPNets are able to classify AD patients looking at clustering (low) and small-world property (low) values.
- Lama and Kwon [17] design an AD diagnosis approach able to classify subjects into AD, MCI, or HC, modeling the brains as functional graphs and exploiting graph theory-based

Table 1
Type of brain networks graphs in the reviewed works of AD brain network analysis (GM= gray matter).

Study	Brain network type	Data	# of nodes	Node type	Edge type
[8]	structural	MRI	62 SCD, 160 MCI	GM 3x3x3 voxels	interregional similarity
[9]	structural	MRI	39 SCD, 39 MCI. 26 HC	GM 2x2x2 anatomical regions	interregional similarity
[6]	DPNet	MRI	39 AD, 97 NC	GM ROI with 0.94 x 0.94 x 1.2 voxels	infectious similarity
[17]	functional	rs-fMRI	31 AD, 31 MCI, 31 HC	GM ROI with 3.3 thickness voxels	ROI correlation
[14]	DPNet	MRI	39 AD, 65 MCI, 54 CONV, 97 HC	GM ROI with 0.94 x 0.94 x 1.2 voxels	infectious similarity

features. The functional brain network is built by setting on each edge the Pearson's correlation functional connectivity between ROIs. Then, graph embedding (node2vec) is used to transform graphs into a vector and applying machine learning techniques. To classify the subjects into classes, different classification techniques including linear support vector machines (LVSM) and regularized extreme machine learning (RELM) are explored. The highest accuracy is obtained by combining LASSO with LSVM.

4. Fusing Brain Networks and Multi-modal data: Proposed Learning Model

Brain networks are complex and intricate systems that reflect the brain's structure and function in various brain diseases, such as AD. Multi-modal data is essential to capture their complexity. Multi-modal data integrates different types of data, such as structural and functional, connectivity, clinical, and genetic information, to form a holistic understanding of the disease's multifaceted nature. Previous research has tried to fuse various modalities.

However, studies investigating the combination and the relationship of the brain connectome with biomarkers and genetics are very few. Only recently, Yu et al. [10] pointed out the link between the changes in structural and functional network organization in Alzheimer's disease brain and the accumulation of amyloid-β and tau in particular parts of the brain. Moreover, Badhwar et al. [18] proposed a roadmap to fusing multiomics measurement for the diagnosis of Alzheimer's disease.

To bridge this gap we propose a novel multi-modal architecture that integrates brain network with biomarkers and genetics data. Integrating brain networks and multi-modal data within a learning framework for Alzheimer's prediction is a promising approach that leverages diverse sources of information to improve the accuracy and reliability of predictive models. Brain networks provide a comprehensive representation of the brain's structural and functional connectivity patterns, offering valuable insights into the underlying neurobiology of Alzheimer's disease. Multi-modal data, on the other hand, encompasses various types of information such as neuroimaging scans (e.g., MRI, PET), clinical assessments, genetic markers, and cognitive scores, each providing unique perspectives on the disease.

Figure 4 shows the proposed learning framework. The model is crafted for a multi-modal multitask objective, aiming to grasp Alzheimer's disease progression and cognitive scores based on a variety of data. As illustrated in Figure 4, the model initially processes data from five modalities: neuroimaging, biomarkers, genomics, clinical, and demographics. Specifically,

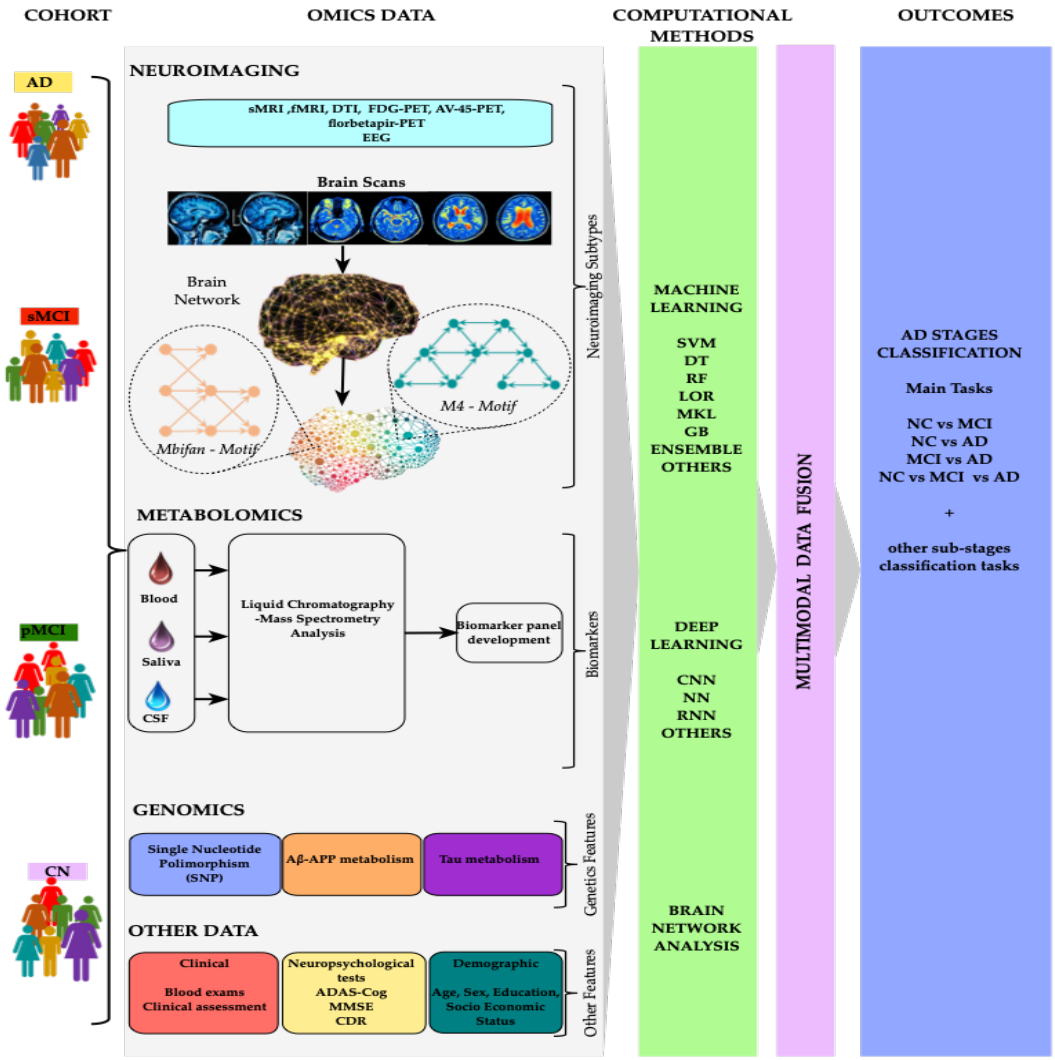

Figure 4: Multi-modal Learning Framework

multimodal data including MRI scans, demographics, medical history, functional assessments, and neuropsychological test results, are used to develop learning models on various classification tasks. Local and temporal feature learning in the model is facilitated by exploiting machine and deep learning cutting-edge methods. The features from various modalities (cognitive scores, neuropsychological battery, MRI, PET, and assessment modalities) undergo preprocessing to enhance data quality. AI techniques are utilized for feature reduction, extracting principal components from high-dimensional MRI and PET data. For example, neuroimaging features from MRI and PET modalities can be extracted using FreeSurfer. Subsequently, deep features are independently learned from each modality using both ML and DL approaches like stacked

CNN-BiLSTM models. Abstract deep features obtained from the previous step are then fused to extract common features from all modalities using a series of dense layers within a deep neural network. As the final stage of the learning framework, a classification is produced.

By combining brain networks with multi-modal data in a learning framework, we can capitalize on the complementary nature of these sources to enhance prediction accuracy and understand the complex progression of AD. Here are some key points to consider:

- Feature Fusion. Integrating information from brain networks and multi-modal data involves fusing features extracted from different sources into a unified representation. This can be achieved through techniques such as feature concatenation, attention mechanisms, or graph-based fusion methods.
- Learning Architecture. The learning framework should incorporate neural network architectures capable of processing multi-modal inputs and capturing complex relationships within the data. This may involve the use of deep learning models such as convolutional neural networks (CNNs), recurrent neural networks (RNNs), or graph neural networks (GNNs) tailored to handle multi-modal data.
- Regularization and Adaptation. Given the high-dimensional and heterogeneous nature of multi-modal data, regularization techniques such as dropout, and batch normalization, can help prevent overfitting and improve generalization performance. Additionally, model adaptation strategies may be employed to adapt the learning process to different data modalities and patient cohorts.
- Evaluation and Validation. Robust evaluation metrics and validation procedures are essential for assessing the performance of the learning framework. Cross-validation, hold-out validation, and external validation on independent datasets can help validate the generalizability of the predictive models.
- Clinical Interpretability. Interpretable models are crucial for translating predictive insights into actionable clinical decisions. Techniques such as attention mechanisms, feature importance analysis, and visualization methods can provide insights into the contribution of different modalities to the prediction task and aid in clinical interpretation.
- The rapid growth of new AI approaches in the last decade has largely overlooked the importance of computational efficiency in algorithm design and data generation. This has led to the widespread adoption of complex AI techniques with high computational costs and energy consumption. This is true also in medical applications, such as AD detection, where improvements in accuracy come at the cost of increased data availability. The development of novel algorithms able to deal with limited resources while maximizing the quality of the results obtained is a main objective of the emerging so-called *Green AI* methods. Considering the large volumes of multimodal data nowadays available for AD, the design and development of new energy-aware AI techniques with low computational needs and reduced data while reaching high predictive accuracy is a desirable objective in the near future of AD research.

Overall, integrating brain networks and multi-modal data within a learning framework holds great potential for advancing Alzheimer's prediction research, leading to more accurate and reliable predictive models that can aid in early diagnosis and personalized treatment planning for patients.

5. Conclusion

In conclusion, early detection of Alzheimer's disease is paramount for effective intervention and patient management. However, existing diagnostic methods often fall short, relying heavily on clinical symptoms and biomarkers that may not provide accurate or timely results. Brain networks offer a promising avenue for understanding the complex structural and functional changes associated with AD. To fully grasp this complexity, a multi-modal approach is necessary, incorporating various data types such as structural and functional connectivity, clinical assessments, and genetic information.

In this paper, we advocate for the integration of brain networks and multi-modal data fusion to advance early AD diagnosis. By combining these approaches, we can better capture the diverse and nuanced characteristics of the disease. Our proposed framework seeks to leverage brain network modeling and multi-modal data fusion to develop a comprehensive understanding of AD and identify prodromal stages. This innovative approach aims to extract network features from diverse datasets, including longitudinal data, to enhance diagnostic accuracy and inform timely interventions for individuals at risk of AD.

Acknowledgments

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