Comprehensive Review of Machine Learning Approaches for Alzheimer's Disease Diagnosis and Prognosis

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Abstract

Alzheimer's disease (AD) represents one of the most pressing challenges in modern healthcare, owing to its progressive nature, lack of curative treatments, and increasing global prevalence. In recent years, machine learning (ML) has emerged as a powerful tool to aid in the early diagnosis and prognosis of AD, offering data-driven approaches capable of managing high-dimensional, heterogeneous, and multimodal data. This review provides a comprehensive synthesis of ML techniques applied to AD, including supervised, unsupervised, and reinforcement learning algorithms. Particular emphasis is placed on models such as Convolutional Neural Networks (CNNs), Support Vector Machines (SVMs), and Recurrent Neural Networks (RNNs), which demonstrate strong performance in classifying disease stages and predicting cognitive decline.

The review systematically analyzes studies published between 2014 and 2024, outlining prevailing approaches in feature selection, data preprocessing, and model evaluation. Major datasets—including ADNI, NACC, and OASIS—are discussed in terms of accessibility, modality, and clinical relevance. The paper also highlights challenges related to data imbalance, interpretability, and generalizability across clinical settings. Despite promising advances, the integration of explainable AI (XAI) frameworks remains limited. Future work must prioritize the development of balanced models that combine predictive accuracy with clinical interpretability to foster real-world deployment and personalized healthcare in AD management.

Keywords

Alzheimer's Disease, Machine Learning, Deep Learning, Supervised Learning, Neuroimaging, Clinical Diagnosis, ADNI, Explainable AI, CNN, SVM, Cognitive Decline Prediction, Biomarkers, Feature Selection, Model Interpretability, Multimodal Data

1. Introduction

Early diagnosis of Alzheimer's disease (AD) is crucial because it enables individuals to receive timely treatment, plan for the future, and seek appropriate resources [1]. No effective cure currently exists, leaving early detection as a vital step in managing symptoms and improving well-being. Machine learning (ML) algorithms have demonstrated promise in enhancing AD diagnosis and prognosis [2]. These techniques, which generally involve classification, regression, clustering, or normative modelling, can handle complex, nonlinear, and high-dimensional data—qualities well suited to analysing heterogeneous neuroimaging and clinical datasets relevant to AD [3]. ML methods fall into supervised, unsupervised, and semi-supervised categories, and have been applied extensively across demographic, clinical, and biomarker domains. Numerous studies have evaluated models that include CNN, SVM, and RNN frameworks; each show particular efficacy in detecting AD, predicting cognitive decline, and estimating individual disease trajectories.

Advances in data acquisition now allow research into a wider spectrum of input features and outcomes. Many recent ML approaches are data-driven: they determine key information from unstructured inputs alone and subsequently provide diagnosis and prognostic estimates. Reliance on anatomical and functional neuroimaging—large, several gigabytes per scan—has limited the variety of datasets used.

Moreover, high data dimensionality and limited patient numbers necessitate compression techniques ranging from manual region-of-interest selection to advanced dimensionality-reduction methods. Supplementary information such as demographics and clinical results ('metadata') can be considered to facilitate predictive tasks, but is often overlooked. Existing techniques do not completely exploit available data, and diagnostic precision remains inadequate for clinical deployment.

2. Background on Alzheimer's Disease

Alzheimer's disease manifests as a progressive deterioration in cognitive, behavioral, and functional abilities. Its clinical course typically begins with subtle memory difficulties**,** followed by impairments in reasoning, orientation, language, and the ability to perform daily tasks. As the disease advances, patients may experience personality changes, disorientation, mood disturbances**,** and, in later stages, severe dependency and loss of self-care capacity**.** Clinically,

Alzheimer's is assessed through a combination of cognitive tests, medical history, and neurological examinations. Standard tools include the Mini-Mental State Examination (MMSE)**,** Clinical Dementia Rating (CDR)**,** and the Neuropsychiatric Inventory (NPI)**,** which measure memory, executive function, mood, and behavior. These tools provide structured input for machine learning models, especially in early detection and staging tasks [3]. Moreover, some patients exhibit mild cognitive impairment (MCI) before developing full dementia. Not all MCI cases progress to Alzheimer's, which underscores the importance of accurate prediction tools. Genetic markers, such as those identified in the IGAP study, further enhance risk stratification and prediction capabilities when integrated into ML frameworks.

3. Review Strategy and Methodology

The growth of this assessment pursued a systematic and careful methodology intended to ensure comprehensive coverage of the most pertinent and recent literature in the field of Alzheimer's disease (AD) prognosis and diagnosis using machine learning techniques. The process combined organized literature search approaches with qualitative thematic synthesis, permitting a holistic grasp of the present research landscape and emerging directions.

The primary step involved pinpointing fitting academic databases to source applicable publications. Priority was assigned to well-established and widely used repositories for example PubMed, IEEE Xplore, ScienceDirect, SpringerLink, and Google Scholar. These platforms were opted considering their extensive indexing of peer-reviewed journals and conference proceedings in both the medical and computer science domains. The time span for the literature search was configured from 2014 to 2024, encompassing a decade of rapid advancement in machine learning and artificial intelligence applications in healthcare. Several longer papers examined novel ML techniques for improved modeling of disease progression while shorter reports evaluated specific biomarker combinations. Overall, the review uncovered a variety of approaches with varying levels of complexity and performance [4].

A combination of keyword searches and Boolean operators was employed to identify studies of interest. Search terms included variations and combinations of keywords such as: *"Alzheimer's disease"*, *"machine learning"*, *"deep learning"*, *"diagnosis"*, *"prognosis"*, *"MRI classification"*, *"ADNI dataset"*, and *"explainable AI"*. These terms were refined iteratively to balance the specificity and breadth of the search results. Additional filters were applied to include only articles published in English and accessible in full-text form.

Once the initial pool of studies was gathered, a rigorous screening process was conducted to determine eligibility. The inclusion criteria focused on studies that directly addressed the use of machine learning algorithms for the diagnosis, prediction, or classification of Alzheimer's disease. Studies involving the application of ML to neuroimaging data (such as MRI or PET), genomic biomarkers, clinical assessments, or multimodal datasets were prioritized. Conversely, articles were excluded if they lacked methodological clarity, did not report on any implementation or experimental validation, or were editorial commentaries, theses, or non-peer-reviewed opinions.

For the analytical phase of the review, a qualitative thematic synthesis approach was employed. Rather than using a meta-analytical framework focused on statistical aggregation, this method allowed for in-depth comparison of methodological trends, challenges, and innovations. The selected studies were grouped according to their primary methodological orientation, type of data used, and application focus [4].

Each study was examined for the types of algorithms applied—such as Support Vector Machines (SVM), Convolutional Neural Networks (CNN), Recurrent Neural Networks (RNN), Decision Trees, and ensemble methods—and for the performance metrics reported, including accuracy, sensitivity, specificity, precision, recall, F1-score, and AUC. Where possible, additional emphasis was placed on the interpretability of the models, especially when explainable AI frameworks like SHAP or LIME were utilized.

This structured approach enabled not only the identification of prevailing techniques and best practices but also a critical evaluation of current limitations, such as data scarcity, overfitting, bias, and lack of generalizability. Furthermore, the synthesis facilitated the recognition of significant gaps in the literature—particularly concerning the integration of multi-modal data and the need for clinically deployable, interpretable ML models.

In sum, this review methodology ensured a high level of academic rigor and relevance, while also establishing a coherent framework for the critical analysis of machine learning applications in the context of Alzheimer's disease.

4. Machine Learning Fundamentals

Machine learning is one of the most effective and promising artificial intelligence techniques in data science, providing inferences from complex data [2]. These algorithms analyze and reveal data patterns and exhibit capabilities in classification, regression, clustering, or normative modeling tasks. Supervised models work on labeled data, unsupervised algorithms separate unlabeled data into related groups, and semi-supervised frameworks learn from both labeled and unlabeled datasets. The objective is to identify the best model among alternatives that harmonize with a set of observations, with a machine learning algorithm encapsulating this selection procedure. Various classical techniques have been developed for automatic diagnosis, such as the nearest-neighbor method, self-organizing maps, and linear support vector machines. Advances in computing empower machines to process extensive raw data and extract meaningful features, determining the optimal way to process information and choose appropriate model parameters.

Broadly, learning methods divide into three groups: supervised, semi-supervised, and unsupervised learning, differing in the presence or absence of labeled data. In supervised learning, the algorithm receives a collection of labeled training samples and infers a general rule that maps inputs to outputs, then predicting labels of new data points following a similar distribution. Unsupervised learning processes data points without associated labels or class information, discerning the inherent structure in the data, with the main task often being to identify groups of similar samples, termed clustering. Semi-supervised learning introduces an intermediate scenario with access to a limited family of samples that precede their labels, combining elements of both preceding approaches.

A general machine learning system supporting these paradigms requires five principal modules: - Data acquisition captures information relevant to the task, converting it into structured data. - Feature extraction reduces raw data to a compact and descriptive signature. - Feature selection identifies the most important features in the training dataset. - Classification uses the selected features and trained models to classify new samples. - Evaluation assesses the overall performance of the system and individual components.

Alzheimer's disease (AD) is a progressive neurodegenerative disorder affecting memory, thinking, and behavior, characterized by abnormal protein deposition and brain cell death. Symptoms begin with mild memory loss and worsen over time, significantly impacting daily functioning [5]. Accurate identification of early AD and its precursors is crucial to delay disease progression and design effective therapies. Machine learning techniques automatically analyze patterns in genetic, physiological, and biochemical data, enabling timely detection and intervention [1].

4.1 Types of Machine Learning

The three major types of machine learning are supervised, unsupervised, and semi-supervised. In supervised learning, labeled data guide the prediction of output values with algorithms such as artificial neural networks (ANN), support vector machines (SVM), naive Bayes (NB), k-nearest neighbors (KNN), decision trees, and random forests. Unsupervised learning extracts structural information from unlabeled data and includes algorithms such as K-means clustering, principal component analysis (PCA), independent component analysis (ICA), autoencoders, and restricted Boltzmann machines (RBM). Semi-supervised learning combines elements of the first two types. Machine learning algorithms train on a data subset and select the model that best fits the available information, contrasting with deductive modeling that constructs functions from known facts or hypotheses. Advantages include the ability to model nonlinearity, fault tolerance, and real-time application suitability [6].

Model types are chosen based on the nature of the data to analyze. When the desired outcome is a qualitative assessment, a classification model is appropriate. Algorithms include SVM, NB, ANN, decision trees, and random forests. For example, a classification model might label Lewy bodies, a hallmark of neurodegenerative diseases, as present or absent. Given a quantitative response variable, a regression approach is used. Regression models anticipate a constant outcome, such as MMSE score or cholesterol level. They use past information to forecast future trends.

Machine learning strategies in Alzheimer's research are typically split into three primary classifications: supervised learning, unsupervised learning, and reinforcement learning, which sees less use. Every type has unique benefits depending on the nature of the information and the planned prediction or grouping task.

In supervised learning, models are trained on datasets that link features such as MRI scans, genetic markers, or clinical ratings to known outcomes like what stage of diagnosis or conversion from mild cognitive impairment to Alzheimer's disease. Algorithms such as Support Vector Machines, Random Forests, and Artificial Neural Networks fall under this category. These models are widely applied in AD classification and early diagnosis due to their high accuracy and ability to organize structured information [7].

Unlike supervised learning, unsupervised learning does not rely on results that are classified. Instead, its goal is to uncover hidden patterns or groupings in the information. This approach has proven valuable in categorizing types of Alzheimer's, determining abnormal progression routes, or classifying patients according to imaging or cognitive qualities. Clustering algorithms like K-means, Principal Component Analysis, and Independent Component Analysis are commonly used here.

Both learning types serve complementary purposes: while supervised models aid clinical decision making through precise sorting, unsupervised models offer understandings into the heterogeneity of the disease and help generate fresh theories about its progression over time, which can vary widely between individuals. Some have slow cognitive decline over decades, while others experience relatively sudden changes.

4.2 Evaluation Metrics

Key metrics vital for machine learning forecasting fashions are correctness, sensitivity, and specificity. Usually measured because the realm under the receiver operating characteristic curve (AUC), accuracy gauges the percentage of proper classifications throughout all consequence classes, whereas sensitivity steps the proper prediction of constructive outcome instances and specificity assesses the proper prediction of detrimental outcome circumstances. High values throughout all these metrics are coveted as a result of a model that solely favors one classification will have disproportionate sensitivity and specificity that restrict its usefulness [8].

Integrating these three metrics permits a extra full evaluation of mannequin efficiency in numerous conditions, offering a richer understanding of predictive talents. This is significantly vital for duties with class imbalance and purposes the place the penalties of false constructive and false damaging errors range vastly. Ultimately, correctness, sensitivity, and specificity are crucial to assessing the potency of classification fashions throughout a wide array of domains, serving as very important metrics for evaluating predictive efficiency in each analysis and utility settings.

5. Machine Learning Techniques in Alzheimer's Research

Machine learning (ML)—a subfield of artificial intelligence that enables computers to learn from data without explicit programming—has made significant strides in medicine, particularly in the diagnosis and prognosis of Alzheimer's disease (AD) [2]. ML algorithms broadly fall into three categories: supervised, unsupervised, and reinforcement learning. Supervised learning aims to model the relationship between input and output variables to predict unseen data and is typically employed in AD diagnosis and prognosis. Unsupervised learning seeks to identify latent structures in datasets without predefined labels and has been used for patient stratification based on cognitive features. Reinforcement learning involves sequential decision-making and can optimize treatment strategies. Appropriate performance metrics for ML models in clinical applications include accuracy, sensitivity, specificity, precision, recall, F1-score, and the area under the Receiver Operating Characteristic curve. Most studies report high accuracy (>75%) in classification and prediction tasks relevant to AD. ML techniques thus represent a valuable tool for supporting the clinical management of AD, facilitating early diagnosis and disease monitoring.

6. Reinforcement Learning

Reinforcement learning (RL) is a paradigm involving an agent learning to make sequential decisions in an environment through trial and error interactions and delayed reward feedback. The agent attempts to maximize cumulative reward by exploring and exploiting the environment via a sequence of actions taken in particular states. The environment responds with a state transition and a (possibly delayed) reinforcement signal indicating the goodness of the action (change leading to the new state). These signals can be binary, reflecting success/failure, discrete indicating degrees of success, or continuous to represent magnitude of success [9]. RL algorithms typically utilize value function methods from dynamic programming or value function approximations through either Monte Carlo methods or temporal difference learning. The methods estimate expected future reward and use these approximations to select actions based on a learned policy; the policy thereby maps states to actions to maximize expected future reward.

Classification and regression techniques serve as the foundation for numerous artificial intelligence (AI) algorithms widely applied to address various problems. Classification involves dividing a dataset into known classes, while the goal of regression is to predict a continuous variable value. Clustering aims to group data points based on similarity; semi-supervised learning combines both labeled and unlabeled data during the training stage; and then RL enables the AI algorithm to decide the best action in a given state to maximize total reward [6]. Numerous AI algorithms are used to implement these techniques, including support vector machine, logistic regression, artificial neural networks, decision trees, Bayes, and many others.

Recent advances in machine learning have led to the emergence of diverse algorithmic approaches for diagnosing and predicting Alzheimer's disease (AD). Each algorithm offers unique strengths depending on the nature of the input data, the complexity of the clinical task, and the desired level of interpretability or generalization. In particular, models such as Convolutional Neural Networks (CNNs) and Recurrent Neural Networks (RNNs) have demonstrated superior performance when applied to high-dimensional imaging and time-series data, respectively. Meanwhile, classical methods like Support Vector Machines (SVMs), Random Forests, and Naive Bayes classifiers continue to be utilized in scenarios where interpretability and low computational demand are essential.

To better illustrate the comparative performance and application domains of these commonly used machine learning techniques, Table 1 summarizes the key characteristics of six widely studied algorithms. The table highlights the type of data each algorithm is best suited for, the primary task it addresses (such as diagnosis or disease progression prediction), and the typical performance metrics reported in recent literature.

Table 1. Comparative performance of machine learning algorithms used in Alzheimer's disease diagnosis and prognosis.

Algorithm	Data Type	Primary Task
SVM	MRI, Clinical	Diagnosis
CNN	MRI, PET	Diagnosis
RNN	EEG, Time-Series	Progression Prediction
Random Forest	Clinical, Genetic	Diagnosis
Naive Bayes	Clinical	Classification
ANN	Multimodal	Diagnosis, Prediction

This table highlights the comparative effectiveness of different machine learning algorithms based on the type of input data, their primary clinical task, and reported performance metrics. CNNs and RNNs consistently outperform others in image-based diagnosis and temporal progression modeling, respectively. As illustrated in Figure 1, the machine

learning pipeline for Alzheimer's disease classification comprises key phases including data acquisition, preprocessing, feature selection, model training, and prediction.

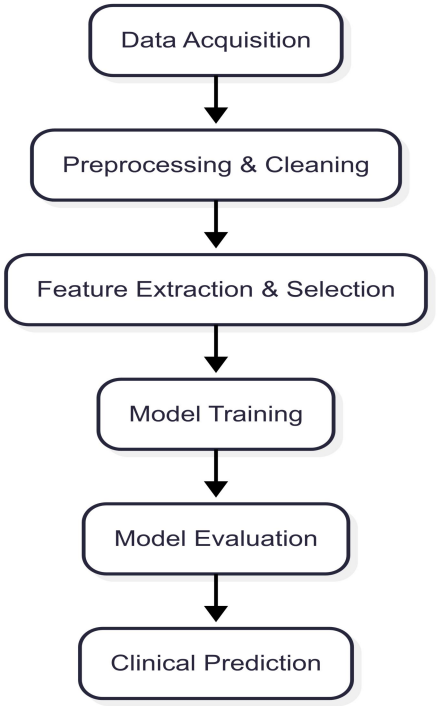

Figure 1. Workflow Diagram: Machine Learning Pipeline for Alzheimer's Disease Classification

The flowchart of using machine learning methods for Alzheimer disease (AD) classification is illustrated as a multi-step pipeline that consists of data-centric tasks and model-centric tasks. We used raw inputs from standardized datasets, including ADNI, NACC, and OASIS, which were prepared by cleaning noise, removing missing values, and addressing inconsistencies in the raw input data. This was instrumental for improving data quality and allowing learning. Biomarkers that were found to be relevant and structural indicators were manually culled (for example, step-wise criteria) or through automated dimensionality reduction techniques (for example, principal component analysis and mutual information ranking to derive features).

These prepared features and machine learning algorithms were then trained with models such as support vector machines random forests ensemble methods and convolutional neural networks, specific to the data type and classification task. All these models were strictly tested using different metrics including accuracy, precision, recall, area under curve, and F1-score. The last step was the clinical prediction in which the trained model was used for new unseen cases to assist in diagnosis, assess disease severity, or predict progression. The outputs from this stage should ideally be interpretable, e.g. when models will be deployed to real-world clinical environments.

This formalized procedure illustrates the noted relationship and dependence between data preparation, algorithm design, and evaluation strategy to help build more robust, reliable and clinically meaningful machine-learning-based systems for the diagnosis of Alzheimer disease.

7. Data Sources for Machine Learning in Alzheimer's Disease

Data Sources for Machine Learning in Alzheimer's Disease Numerous research projects and funding sources support the quest for effective machine learning approaches that detect Alzheimer's disease (AD), including the National Institute of Health Research (NIHR) Maudsley Biomedical Research Centre, the European Union Joint Programme—Neurodegenerative Disease Research (EU JPND), and Horizon 2020 initiatives. Several major studies have contributed to developing approaches that analyze neuroimaging, in-home sensors, and clinical data for early detection and tracking of disease progression. Reviews have examined machine learning methods—including neural networks, support vector machines, and random forest models—for predicting the development of dementia and AD from mild cognitive impairment [10].

Dementia risk indices and data mining techniques have been explored for their ability to identify individuals at high risk of the disease [11]. Available data sets favor supervised-learning approaches, but the burgeoning availability of data from the EVOTION project and SmartAging infrastructure will facilitate new investigations of unsupervised algorithms. Lack of representative and balanced data remains a major limitation, especially among samples drawn from clinical populations. Harmonization of multi-site data and unified analysis pipelines could alleviate such limitations. All analyses invariably rest on assumptions about the future that are framed during training, which challenges forecasting the highest-risk individuals for focused healthcare planning down the road.

7.1 Clinical Datasets

Clinical datasets are a crucial resource for developing and benchmarking machine learning models for the diagnosis and prognosis of Alzheimer's disease (AD). The National Alzheimer's Coordinating Center (NACC) dataset is a notable example, containing 169,408 records with 1,024 features. Support vector machine models trained on the selected features produced high performance on an external dataset. In particular, an accuracy of 71% was achieved for multiclass classification. To bring human perspective and extract factors from both a data-driven and model-driven way, we employed two rule-extraction methods, class rule mining and a stable model-independent interpretable rule set that provide human-explainable rules useful for the domain expert to decipher the most critical factors leading to AD. SHAP and LIME models validated our rules and found that memory, judgment, communication, and orientation are strong determinants of AD risk. The Clinical Dementia Rating (CDR), which was developed for the prediction of AD, was also highlighted [12].

Clinical features like clinical survey data, neuroimaging, genetics, and cerebrospinal fluid are employed in the classification of Alzheimer's disease [13]. Among the most useful resources regarding clinical features are the ADNI project and the NACC datasets [14].

Over 1,000 subjects aged 55 years to 90 years old from the Alzheimers Disease Neuroimaging Initiative (ADNI) dataset. The Alzheimer's Disease Neuroimaging Initiative (ADNI) data consist of magnetic resonance images (MRI), positron emission tomography (PET), daily clinical and neurocognitive assessment ratings and cerebrospinal fluid and blood bio-markers. These measurements are obtained from the longitudinal study of MCI and AD progression [2].

Many prior studies using machine learning for research in Alzheimer disease define their methods but rely on access to a well-organized repository of annotated clinical, imaging, genomic, and demographic features. In the last two decades, there have been several large-scale efforts for making the provision of open or semi–open access to these data to enable reproducible experiments and benchmarking. We highlight differences with regard to content, data access limitation and tasks these datasets are best able to support. Table 2 outlines this comparison for the most commonly used datasets in this domain (ADNI, NACC, OASIS, AIBL, and MIRIAD). The following table summarizes all the possible data types, access modalities, and machine learning-based AD research scenarios for each dataset.

Table 2. Overview of Major Datasets for Alzheimer's Disease Research and Machine Learning Applications

Dataset	Data Types	Access Type	Typical Usage
ADNI	MRI, PET, CSF, Clinical	Public (upon request)	Diagnosis, Progression
NACC	Clinical, Cognitive	Public	Risk Factors, Severity
OASIS	MRI, Demographics	Public	Early Detection
AIBL	MRI, Clinical, Biomarkers	Restricted	Prognosis Validation
MIRIAD	MRI	Restricted	Longitudinal Studies

Table 2 provides a summary of the relative benefits of various datasets depending on the goals and methodology of consideration. For instance, the ADNI (Alzheimer's Disease Neuroimaging Initiative) cohort is multimodal in combination of structural MRI, PET, CSF biomarkers, neuropsychological testing, and genotyping. This feature richness makes ADNI probably the most extensive resource available for training and validating predictive and progression models, especially those involving deep learning architectures and multimodal fusion strategies.

In contrast, a dataset such as the NACC (National Alzheimer's Coordinating Center) brings a more clinically focused profile with many records and variables based on multiple cognitive and behavioral measures. In its breadth and availability, it offers a particularly compelling incentive for research around explainable machine learning, where the interpretability of appropriate input features are paramount.

Due to its specific prep-symptomatic stage annotations including cognitively normal, MCI, and AD subjects, OASIS is often a more preferred option than other datasets, especially for demographic studies and early detection models. Longitudinal Data (Disease Progression, Treatment Response): MIRIAD, and to a lesser extent AIBL, although more limited in availability, provides longitudinal data,so that these data can be used to investigate disease progression and response to treatment over time, for example [15].

The decision of a dataset in model development has to consider Read more data completeness, balance across disease stages fundamental to patient cohort data selection: a systematic review; frequency of follow-up visit; and the presence of interpretable clinical features. For example, NACC and OASIS datasets may be more suitable for explainable AI (XAI) framework developments, whereas ADNI and AIBL offer a vast source for assessing high-dimensional imaging deep learning applications.

In summary, the diversity of datasets currently available allows researchers to align their methodological strategies with the specific clinical questions they aim to address. However, the challenge remains in **harmonizing cross-dataset**

variability, especially when attempting to generalize findings or build unified models. Future efforts should focus on integrating these datasets through common data models and federated learning frameworks, while ensuring patient privacy and data consistency across sites.

7.2 Neuroimaging Data

Alzheimer's disease poses unprecedented challenges to current healthcare systems. Reliable diagnosis and accurate prognosis of AD are important for early intervention and treatment. Development of neuroimaging techniques provides an opportunity to estimate the underlying pathology related to clinical progression of AD. However, the overwhelming amount of data from neuroimaging studies requires new data analysis algorithms.

Machine learning approaches have been widely used to analyze imaging data in AD. Classification methods based on machine learning have generally been more successful when high-quality data are available [16].

Multiple imaging modalities can be used to predict AD risk and progression. Multimodal brain MRI contains complementary information of neurodegenerative processes ones available brain mortometry and connecto-sphere methods for training predictive models on multimodal MRI-derived brain morphometry and white matter structural connectomes images may thus improve accuracy of classification for AD, mild cognitive impairment (MCI) and subjective memory complaints (SMC) compared with benchmark models trained on cerebrospinal fluid (CSF) biomarkers [17]. Pattern classification of obtained images enables identification of diagnostic or prognostic markers for early AD from large neuroimaging data.

Traditional computer-aided diagnosis approaches in neuroimaging have generally involved linear classifiers such as support vector machines (SVM) applied to biologically relevant features at voxel or regional level. Whole-brain approaches generally achieve higher classification accuracy than region-based methods, and the use of data pre-processing methods such as the DARTEL registration package can also have a significant impact on results. Transition towards non-linear methods, especially artificial neural networks (ANNs), for Alzheimer's dementia diagnosis: the learning ability of an ANN can be combined with investigations carried out using linear classification methods to achieve high accuracy diagnosing AD [18].

7.3 Genomic Data

Genomic data have also been leveraged for machine-learning-based AD diagnostics. Support Vector Machines are the most widely utilized technique for predicting AD from genomic data, while Neural Networks and Natural Language Processing have recently attracted attention as well [9,10] examine multi-dimensional imaging genomics data—including genetic single-nucleotide polymorphism (SNP) features—for AD prediction. They find that adding genetic SNP features to other modalities improves classification and that some features are shared across feature-selection methods and may have high correlation with the disease. The integration of genetics with other data sources thus represents a promising direction for future research.

8. Preprocessing and Feature Selection

Conventional feature selection remains a critical stage for Alzheimer's disease (AD) diagnosis and prognosis, especially because of the high dimensionality that arises when handling multi-modality data. The extracted features for AD characterization typically contain redundant or irrelevant elements that can be discarded to enhance performance. Dimensionality reduction, therefore, aims to identify a subset of data, adhere to the original feature's geometry, and preserve identical information [10]. Various methods address this task, including sparse regression, forward and backward recursion, graph-based selection, and clustering techniques [11].

Feature selection for AD prediction has recently attracted more attention. An evaluation of three state-of-the-art techniques using the ADNI database reveals that the HGM-FS method achieves superior classification accuracy, sensitivity, and specificity with linear support vector machines (SVMs). The applied approaches identify both distinctive and shared features for AD and Mild Cognitive Impairment (MCI) classification. A fusion of multi-dimensional imaging and genomics data further enhances prediction, with PET modality yielding the highest accuracy. Although individual SNP data exhibit weaker discrimination, their integration nonetheless improves classification performance.

An alternative classification framework incorporates preprocessing, feature extraction, selection, and recognition. Preprocessing includes an averaging filter that removes irrelevant details. A combined technique involving principal component analysis (PCA), stepwise linear discriminant analysis (SWLDA), and an artificial neural network subsequently extracts and identifies the most salient features, thereby simplifying disease classification. The SWLDA component employs both forward and backward recursion: the former selects the most interconnected features based on partial Z-test coefficients, while the latter eliminates the least correlated ones. After feature selection, an optimized neural network performs classification. Experimental results demonstrate that this selection method substantially contributes to elevated recognition rates, outperforming state-of-the-art systems.

9. Case Studies of Machine Learning Applications

Numerous studies apply multiple algorithms, investigating various disease stages and aspects while addressing technical challenges. The diversity of data modalities, acquisition and preprocessing methods, and algorithms lead to methods with unique strengths, influencing their applicability in Alzheimer's disease (AD) diagnosis. Some algorithms require features derived from medical images, while others process raw volumetric images. Approaches employing hand-crafted features construct distinct features, often reducing dimensionality compared to image size. For instance, features extracted from a 2D image (192×192 pixels) possess a dimensionality of 36,864, whereas 3D volumes (182×218×182) reach 7,208,712. Extracted features can include volumetric or shape properties of brain tissues or regions, signal intensity of MRI voxels, and brain connectivity measure. A directory of model implementations spanning several studies offers ready-to-run code that facilitates further development [3].

A methodology using 3D convolutional layers identifies individuals with AD based on brain MRIs without requiring derived features. Employing a debate network, two models predict AD presence to ensure predictions match MRI patterns. Spectral features can calculate cerebral blood flow and peak time from arterial-spin-labeling images. Analysis of spatial patterns using t-distributed stochastic neighbor embedding enables cluster-based classification of AD facing challenges of high dimensionality and small dataset size [2].

9.1 Early Diagnosis

Early diagnosis of Alzheimer's disease (AD) remains a challenge because changes in biomarkers are subtle and often overlooked. Machine learning (ML) models, however, hold promise for identifying at-risk individuals. Many studies prioritise accuracy over explainability. Using data from the National Alzheimer's Coordinating Center, researchers trained support vector machine models on 1024 features derived from 169,408 records. Rule-extraction methods—class rule mining and stable rule sets—produced human-interpretable rules that aid experts in uncovering key factors in AD development. Explanation tools such as SHAP and LIME highlighted memory, judgment, communication and orientation as significant indicators. AD is a neurodegenerative disorder affecting memory and behaviour, characterised by abnormal protein accumulations that cause brain cell death. Symptoms start with mild memory loss and difficulty in routine tasks, progressing into disorientation, behavioural changes and impaired self-care [5]. Machine learning techniques applied to neuroimaging data also show potential for early diagnosis. Several approaches focus on deep learning algorithms. Datasets like the Alzheimer's Disease Neuroimaging Initiative (ADNI) and the Open Access Series of Imaging Studies (OASIS) support these investigations. Deep learning architectures, including convolutional neural networks, have been evaluated for AD detection using magnetic resonance imaging (MRI) [1]. These ML approaches provide additional valuable tools for identifying AD at early stages. Machine learning is implemented in different modes—including classification, regression, clustering and normative modelling—to address disease progression. Various algorithms—supervised, unsupervised and semi-supervised—are selected for their non-linearity, fault tolerance and real-time operation abilities, making them suitable for such complex applications [2].

9.2 Progression Prediction

Prediction of progression is of increasing importance to help prioritize patients in urgent need of further examination and early treatment [14]. Multiple markers can enhance projection of decline, but the contribution of individual features to performance improvements varies widely [15]. Model performance can be improved by considering temporal trajectories in multimodal data [16].

Because therapeutic interventions would be most effective in early stages of the disease, prior to extensive neuronal damage, predicting progression from MCI to AD enables the application of preventative treatments for slowing or halting decline. Many MCI patients progress to AD; however there is heterogeneity in the timelines of decline and various studies characterizing subtypes are emerging.

In this context, the prediction of progression for AD subjects with mild cognitive impairment (MCI) is relevant for enabling early interventions at stages when therapeutic treatments might exert larger effects. To describe the heterogeneity in AD patients undergoing progression, a probabilistic model was developed that recovers distinct atrophy and cognitive decline patterns from longitudinal clinical and MRI data. An EM clustering procedure estimates the model's parameters and associates each subject to a corresponding pattern.

10. Challenges and Limitations

Despite significant progress in previous years, obstacles remain. These are discussed in further detail below.

One of the primary challenges is the limited availability of high-quality, standardized, and annotated datasets for AD research. This paucity restricts algorithm development and impedes widespread adoption. Model generalizability also remains an open issue, as performance often declines substantially when models trained on one dataset are tested on external datasets [3]. AD pathology is highly heterogeneous and influenced by multiple factors such as genetics, lifestyle, environment, and co-morbidities, necessitating techniques capable of managing such variability and complexity. Interpretability is likewise a critical concern; transparent models and recommendations enable more informed clinical decisions and bolster trust among users.

10.1 Data Quality Issues

Data set structure: The data set has 1024 features that were reduced to a subset for modelling. Representation learning techniques were used to automatically select and construct representations for input data, resulting in 71 representations. Initially, eight crucial features relevant to Alzheimer's dementia were selected before applying representation learning. Feature selection prior to representation learning is recommended to mitigate potential negative impacts on data quality. Sample size and class balance are important for determining the applicability of representation learning. A sample of approximately 1200 with balanced classes allowed for effective representation learning and sufficient data space for model training [5].

Data quality: The data set contained approximately 20% missing values, evenly distributed across classes. Missing data were treated as invalid values, following guidelines that imputation can adversely affect data quality.

10.2 Interpretability of Models

The adoption of complex ML models often involves a trade-off between accuracy and explainability. Identifying crucial features and enabling domain-experts' understanding of the main reasons behind the model's decision is still challenging [17]. Nonetheless, enhancing model explainability is paramount. Two rule-extraction approaches—class rule mining and stable and interpretable rule set for classification—yielded human-understandable rules and pinpointed the Clinical Dementia Rating tool as a key predictor. Alzheimer's disease (AD) entails abnormal amyloid beta and tau protein accumulation with progressive symptoms such as memory loss, disorientation, and mood changes. ML methods have analyzed multi-modal datasets for early diagnosis and risk prediction, potentially facilitating timely intervention and mitigation of progression.

11. Conclusion

This review provided a comprehensive synthesis of recent advances in the application of machine learning techniques to Alzheimer's disease (AD) diagnosis, prognosis, and progression modeling. The reviewed literature covered a broad spectrum of methods, ranging from classical supervised algorithms like Support Vector Machines and Random Forests to more sophisticated deep learning architectures such as Convolutional and Recurrent Neural Networks. Supervised and hybrid models showed good predictive performance in multi-study early stage detection, disease classification and cognitive decline trajectory prediction.

We focused on the multiple modalities that may affect the accuracy and generalizability of a model: MRI, PET, genetic profiles, and clinical measures. The incorporation of multimodal data was a recurrent best practice for enhancing robustness and clinical utility. In addition, the vital problem of high-dimensional data was addressed, and by employing methods such as feature extraction (e.g. PCA) and feature selection (e.g. SWLDA) l outside the existing features, and ensemble selection strategies, predictive performance was enhanced.

Study characteristics on performance varied greatly due to differences in datasets, preprocessing, and reporting. Even though common metrics such as accuracy, AUC and f1 score can be useful at an early-stage point, a higher emphasis on cross-cohort validation and model interpretability is required. Although multiple higher-quality datasets exist like a large ADNI and NACC, but will still face the limitation of data imbalance, data heterogeneity and data limitation accessing for better generalization of the models.

One of the most showcased topics within the review is the low level of incorporation of XAI frameworks in a clinical machine learning pipeline scenario. Methods like SHAP and LIME are available in the literature, but rarely used in research related to Alzheimer´s disease. Improving clinical adoption will only be realized when balanced models are created in which predictive performance is maximized, but not at the expense of the transparency and interpretability that clinical adoption requires, and this represents an important future avenue of work.

Despite the apparent groundbreaking potential of using machine learning for the prediction of Alzheimer disease, this potential will only be realized when the spirit of shared databasing, high emphasis on explainable systems, and rigorous evaluation in terms of clinical validity with respect to its complexity are prioritized.

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