

# Prediction Of Mild Cognitive Impairment to Alzheimer's Disease Conversion Via Machine Learning

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**Abstract.** Alzheimer's Disease (AD) is a progressive neurodegenerative condition characterized by deterioration of cognitive functions. Although there does not exist a cure for AD, early diagnosis and intervention during stages of Mild Cognitive Impairment (MCI) can be incredibly beneficial in slowing its development. However, predicting the conversion from MCI to AD remains a challenging task. This paper aims to provide an overview of the current research on predicting MCI to AD conversion, with a focus on machine learning methodologies to aid feature extraction and classification. Through a literature review, we aim to offer insights into the latest state-of-the-art techniques to predict MCI to AD conversion as well as prevailing trends in this field including deep learning, transfer learning, contrastive learning, and graph neural networks. We conclude from our study that utilizing AD/HC classes for feature extraction is a promising approach for generating discriminative features for stable MCI and progressive MCI classification. In addition, employing multi-modality models is instrumental in attaining a robust validation framework for the early diagnosis of AD.

**Keywords:** Alzheimer's Disease, Mild Cognitive Impairment, Machine learning, Deep learning.

## 1. Introduction

Alzheimer's Disease (AD) is an incurable and irreversible neurodegenerative disease causing a gradual reduction in brain volume and resulting in memory and cognitive impairment. Currently, more than 55 million people have dementia worldwide in 2023 and it is expected to increase to 152.8 million by 2050 [1,2]. Therefore, accurate diagnosis of AD is crucial for patient treatment and societal well-being. Unfortunately, the majority of AD diagnoses nowadays occur during the moderate to late stages of the disease, while the optimal time for intervention occurs during the early stages, resulting in less effective treatment options.

Mild Cognitive Impairment (MCI) characterizes a state of cognitive decline that is more pronounced than what is considered cognitively normal (CN) for one's age but falls short of the severity seen in individuals with dementia. The study of MCI has been a key area of focus, as those with MCI have a significantly greater chance of converting to AD compared to those who are CN. Annually, 10-15% of MCI individuals convert to dementia, while the conversion rate among those classified as CN stands at 1-2% [3,4]. In addition, there are two subtypes of MCI patients: progressive MCI (pMCI) patients, who convert to AD, and stable MCI (sMCI) patients, who do not convert to AD. The accurate classification of pMCI and sMCI would enable earlier intervention and more appropriate treatment for both classes of patients.

Machine Learning techniques have rapidly emerged as pivotal methodologies for identifying AD patients in recent years, demonstrating remarkable success. Binary class classification for AD achieves notably high accuracy when classifying AD/CN, AD/MCI, as well as CN/MCI [5]. However, distinguishing pMCI from sMCI remains a key challenge due to overlapping characteristics, a lack of discernible biomarkers derived from unstructured data, and the challenge of generalizing characteristics from diverse data modalities persists. The main objective of this literature review will be to summarise current advances in this area.

There is no definitive test nor is there a defined set of biomarkers to detect AD. A number of biomarkers identified via various genetic, biological, and neuroimaging techniques are used to spot AD. Public datasets play an enormous role in the research of AD, which contains various types of biomarker information. Prominent datasets include ADNI, OASIS, AIBL, and CADDementia.

This literature review will be organized as follows: Section II will identify diagnostic tools of preclinical dementia, which are currently used to distinguish sMCI and pMCI from both structured and unstructured datasets. Section III will discuss common preprocessing techniques of neuroimaging data. Section IV will explore the common machine learning approaches employed for the classification of sMCI/pMCI. Section V will consolidate the current challenges and limitations of sMCI/pMCI classification. Section VI will explore predominant trends in this field and Section VII will conclude the paper and provide recommendations for advancing computer-aided diagnosis in AD.

## 2. Diagnostic Tools of MCI

MCI diagnostic research can be categorized into two main types: static models (based on a single time point), which focus on identifying biomarkers that can differentiate MCI from NC, and dynamic models (longitudinal studies), which aim to predict the conversion of MCI to AD [6]. While static models can also classify sMCI/pMCI based on baseline images, they could be sub-optimal as the changes along the disease trajectory are overlooked. Longitudinal studies have gained prominence in predicting the conversion from MCI to AD.

Neuropsychological tests are administered to assess specific cognitive functions in detail such as one's episodic and semantic memory, attention, concentration, and executive functions [7]. On the other hand, cognitive evaluations provide a broader assessment of neurological function. Neuroimaging techniques have found extensive application in characterizing AD pathology in clinical, and preclinical diagnoses. Structural and functional Magnetic Resonance Imaging (sMRI/fMRI), Diffusion Tensor Imaging (DTI), Positron Emission Tomography (PET), and Single-Photon Emission Computed Tomography (SPECT) scans can all be used as predictors of preclinical AD [8]. Among these, PET with amyloid-beta and tau radiotracers and MRI are among the most popular techniques for the diagnosis of pre-clinical AD. PET with amyloid-beta and tau radiotracers can quantify changes in the brain metabolism, notably the accumulation of amyloid-beta protein and neurofibrillary Tau tangles, which correlate well with neuronal death and cerebral atrophy. In addition, structural and functional MRI is widely used to assess brain structure, volume, and atrophy and can be used to classify sMCI/pMCI. Moreover, the establishment of blood-based biomarkers, along with cerebrospinal fluid (CSF) indicators like reduced amyloid and elevated Tau levels, may offer valuable clinical insights as potential AD biomarkers.

## 3. Neuroimaging Data Preprocessing

In studies of neuroimaging data, a series of crucial pre-processing steps are employed to ensure data consistency and enhance analytical capabilities. Several packages are available for this purpose, including FreeSurfer, Computational Anatomy Toolbox, FMRIB Software Library (FSL), ANTS, and Statistical Parametric Mapping (SPM).

Image registration is used to align images from different time points into a common anatomical space, facilitating comparisons and the integration of multi-modal data like MRI and PET for improved analysis. Bias Field Correction, or intensity normalization, is essential for eliminating non-uniform intensity variations caused by magnetic field fluctuations, sensor sensitivities, and acquisition imperfections in MRI scans. Skull stripping, or brain masking, further refines the data by removing extraneous non-brain tissues, such as the skull and meninges, minimizing segmentation errors. Tissue segmentation then categorizes the data into different regions representing grey matter, white matter, and cerebrospinal fluid, enabling precise analysis of structural changes associated with AD pathology. Lastly, data augmentation techniques artificially expand the training dataset by introducing deformations, noise, cropping, reflection, translation, rotation, gamma correction, scaling, and modalities fusion like MRI and PET, which helps generate diverse pathological features for more

robust analysis and modelling. These pre-processing steps collectively enhance the quality and interpretability of neuroimaging data in AD research.

## 4. Traditional Machine Learning Models

### 4.1. Support Vector Machines

Support Vector Machines (SVMs) are designed to optimize the margins between a hyperplane and data points. In this case, the hyperplane is a decision boundary separating sMCI from pMCI classes in the feature space. These SVMs leverage kernel functions to effectively transform the data into higher-dimensional feature spaces, enabling the classification of patterns that are not linearly separable.

SVMs have been used extensively in sMCI/pMCI classification problems. Reference [8] utilized voxel-based morphometry to pinpoint regions of gray matter atrophy in sMRI data from AD patients, comparing them to NCs. These identified regions served as the basis for extracting voxel values from individuals in AD, NC, sMCI, and pMCI groups to form feature vectors. The process involved ranking features through t-test scores and employing a genetic algorithm to identify the most optimal feature subset for classifying individuals with sMCI/pMCI. Using an SVM classifier, the model achieved 93.01% and 75% accuracy in distinguishing AD/NC and sMCI/pMCI individuals, respectively, up to 36 months before clinical diagnosis, demonstrating results comparable to alternative methods using baseline MRI data. Notably, this study highlights that AD/NC classes are useful for identifying regions of interest (ROIs) for sMCI/pMCI classification.

### 4.2. Random Forest

Random Forest (RF) is an ensemble of decision trees trained on different data subsets and features. The decision trees collectively vote to make the final prediction via bootstrapping and aggregation. RFs have been used widely for feature extraction and sMCI/pMCI classification tasks.

Reference [9] introduces a comprehensive approach utilizing the RF algorithm to forecast MCI to AD conversion. Using features of demographic (age, race), physical biomarkers (hippocampal and ventricular volume), cognitive testing variables (ADAS13, ADAS11, FAQ, MMSE), and genetic biomarkers (APOE4) of sMCI/pMCI patients from the ADNI, the model attained a maximum accuracy of 93.6%, outperforming SVM, XGBoost and Logistic Regression benchmark models in accuracy, precision and AUC score. This accomplishment is notable when compared to prior studies, enabling predictions 5-7 years before AD onset. This paper also highlights the superior performance of multi-model diagnostic models.

### 4.3. Deep Learning and Convolutional Neural Networks

Deep learning has received wide attention for its advancements in various domains, surpassing the performance of conventional machine learning approaches. In Convolutional Neural Networks (CNNs), Convolutional layers slide kernels across input data to extract features like edges and patterns. Neurons connect to local input regions, forming receptive fields, and enabling spatial feature hierarchies. Pooling layers downsample data, reducing computation, improving feature preservation and invariance to small translations. Dense layers are used to classify these relevant features.

CNNs have achieved outstanding performance in various applications [10,11,12]. Reference [13] proposes a 3D VGG-variant CNN to classify paired T1-MR and FDG-PET images of the hippocampal area from the ADNI dataset, obtaining accuracies of 90.10%, 87.46%, and 76.9% for the classification tasks AD/CN, CN/pMCI, sMCI/pMCI respectively and state-of-the-art performance. Reference [13] extended their investigation by applying the CN/AD model to the sMCI and pMCI datasets. Surprisingly, this transfer of the CN/AD model yielded improved results in distinguishing sMCI/pMCI when compared to models trained solely on sMCI and pMCI data. The rationale behind this enhancement lies in the fact that the features distinguishing CN from AD exhibit greater distinctiveness and separability, thereby enhancing the discriminative power for sMCI/pMCI

classification. This finding underscores the potential utility of leveraging different stages of the disease spectrum, even when they are not the primary focus of classification, to aid in more effective feature extraction and classification tasks.

## 5. Challenges and Discussion

sMCI/pMCI classification problems present several challenges and limitations, both in terms of diagnosis and prediction. Many studies in this field suffer from a lack of data due to the privacy of medical data. In particular, access to large-scale longitudinal data, including neuropsychological assessments, neuroimaging, and genetic information can be limited [14]. This presents a huge bottleneck for complex tasks like the prediction of MCI-to-AD conversion. As a result, larger datasets are required to improve the generalizability and statistical power of predictive models. Furthermore, The presence of an unknown set of biomarkers has led to variations in research papers, including types of data modalities used, pre-processing methods, feature extraction approaches, and classification algorithms. These variations pose a huge challenge when it comes to comparing and evaluating different models. Data imbalance among classes is also a prevalent issue in datasets. As the number of sMCI individuals is far greater than that of pMCI, there is an unequal representation of classes used for training the model. This would create a bias favouring the majority class (sMCI) in order to minimize the overall loss, resulting in lower sensitivity in most papers and overfitting of the majority class. To address this, techniques like Synthetic Minority Over-Sampling Technique (SMOTE) [15], Data augmentation [16], and Generative Adversarial Networks (GANs) [17] are employed to enlarge the size of the minority class, achieve class balance and mitigate overfitting.

## 6. Recent Studies

In the upcoming section, we examine recent research studies and novel approaches that aim to address some of the limitations discussed in section V.

### 6.1. Parameter-efficient Deep CNNs

Reference [12] introduces a parameter-efficient deep CNN for feature extraction using grouped and separable convolutions. The architecture employs a multi-modal feature extractor, parameterized by  $\theta$ , that extracts representations of the biomarkers from both the pMCI/sMCI and AD/NC ADNI datasets. These latent representations are then passed to two separate dense layers, parametrized by  $\varphi$  and  $\psi$ , to perform the sMCI/pMCI and AD/NC classification tasks individually. The objective function can be expressed as:

$$\operatorname{argmin}(\theta, \varphi, \psi) E_{x,y \sim \tilde{p}(x_1, y_1)}[U_M] + \alpha E_{x,y \sim \tilde{p}(x_2, y_2)}[L_A] \quad (1)$$

Where  $U_M$  and  $L_A$  represent the negative log-likelihoods of the sMCI/pMCI and AD/HC classification tasks respectively.  $\alpha$  was introduced to accommodate for the fact that AD/HC achieves high validation faster than pMCI/sMCI classification. The model performed well against classifying pMCI/sMCI within a 36-month period in terms of accuracy (0.860), sensitivity (0.875), specificity (0.850), and AUC (0.925), the highest achieved performance on the ADNI dataset. The same network achieved 100% accuracy when classifying AD from healthy controls. This study further highlights the potential for combining AD/CN and sMCI/pMCI datasets for feature extraction, while enlarging the dataset to mitigate the effects of overfitting.

### 6.2. Transfer Learning with Contrastive Learning

Transfer learning has emerged as a widely adopted approach in neuroimaging tasks to mitigate overfitting due to a limited sample size. As the model is trained on a larger dataset, feature representations' generalization is enhanced. Transfer learning involves the transfer of parameters

learned from the source domain, which is then fine-tuned on the data from the target domain. Transfer learning has proven to be highly effective in enhancing model performance in medical diagnoses [18].

To improve the correlation between source and target domains of transfer learning, contrastive learning was introduced as a self-supervised learning method. Contrastive learning obtains query view,  $x_q$ , and key view,  $x_k$ , through independent image transformation of a single sample,  $x$ . A feature encoder extracts the feature vectors from the augmented data to attain latent representations  $l_q, l_k$ . Each representation is passed through a project head, which consists of a Multi-Layer Perceptron (MLP), to produce metric embeddings  $q, k$ , which are used as input to the contrastive loss function  $L$ . This would pull representations of similar samples, positive samples, closer together in the embedding space while pushing dissimilar representations, or negative pairs, apart. For the  $i^{th}$  pair, the contrastive loss function is :

$$L_i = -\log\left(\frac{\exp\left(\frac{q_i \cdot k_i}{\tau}\right)}{\exp\left(\frac{q_i \cdot k_i}{\tau}\right) + \sum_{k^-} \frac{\exp\left(q_i \cdot k^-\right)}{\tau}}\right)$$

Where  $\tau$  is the temperature that controls the sensitivity of the product. This could be thought of as a  $|k^-| + 1$  softmax classification where  $|k^-|$  represents the number of negative pairs in the minibatch.

Reference [19] proposed a two-stage model for sMCI/pMCI classification within a period of 36 months. In the first stage, they employed a Med3D pre-trained ResNet-50 as the encoder, initially trained on the 3Dseg-8 dataset. In the second stage, they leveraged contrastive learning, specifically Momentum Contrast (MoCo), on unlabelled sMCI and pMCI samples from the ADNI dataset. This step allowed them to update network parameters, align the source and target domains, and capture essential medical features for sMCI/pMCI classification. In the final step, the network was fine-tuned on labelled sMCI/pMCI samples to further refine the classification performance. The proposed method yielded impressive results in sMCI/pMCI classification in terms of accuracy (0.819), sensitivity (0.786), specificity (0.850), F1 score (0.807), and AUC (0.835). Notably, it outperformed previous deep learning models that solely utilized single-modality MRI data from the ADNI dataset in terms of accuracy, specificity, and AUC.

### 6.3. Graph Neural Networks

Diffusion MRI (dMRI) and anatomical MRI are valuable for describing connectivity patterns among cortical and subcortical regions and have been reported to generate brain network biomarkers for various neuropsychiatric conditions [20]. Growing research has shown that brain ageing occurs at a faster rate for individuals with AD patients compared to CN individuals [21]. Through the utilization of Graph Neural Networks (GNNs) to represent the strength of connections between various brain regions, it becomes possible to differentiate between pMCI and sMCI by modeling how each deviates from the trajectory observed in healthy aging.

Reference [22] combines graph-based and sequential modelling to classify sMCI/pMCI. The proposed architecture consists of three separate models. First, a GNN is pre-trained to extract brain network features from ADNI's AD/CN longitudinal T1 and dMRI images, as it would provide more discriminative features. Second, a Variational Autoencoder (VAE) is trained on longitudinal CN data to model healthy aging trajectories. This would allow the model to extrapolate future features of brain networks based on the starting features.

Third, a Long Short-Term Memory (LSTM) Recurrent Neural Network (RNN) is trained using a cohort containing sMCI and pMCI individuals to predict MCI to AD conversion. The proposed method achieved the highest performance among other benchmark methods in prediction MCI-to-AD conversion within 18 months in terms of accuracy (0.839), sensitivity (0.868), and specificity (0.818).

## 7. Conclusion

AD is a formidable neurodegenerative disease imposing a growing burden on global healthcare. Early diagnosis during stages of MCI offers a crucial window of opportunity for effective treatment. Machine Learning and deep learning methodologies have emerged as powerful tools in predicting MCI to AD conversion. This literature review provided an in-depth exploration of state-of-the-art methodologies and recent trends in the field. Notably, Traditional Machine Learning Models including SVMs and RFs have demonstrated their utility in this field. CNNs have shown remarkable performance in feature extraction and classification, surpassing traditional machine learning methods. GNNs have also emerged as a powerful tool by combining brain network analysis with predictive modelling.

Despite these advancements, limited access to longitudinal datasets, variability in research protocols, overfitting, and class imbalance issues persist and prevent models from being used in a clinical setting. Addressing these challenges through data collaboration, standardization, and advanced techniques like parameter-efficient models, transfer learning and contrastive learning is essential. In future studies, research should focus on two key areas: multi-modal model classification as well as multi-class feature extraction. As multi-modal models have been shown to yield greater diagnostic performance, future research should pay more attention to multi-modal classification, rigorous validation, and clinical trials to push for clinically viable predictive models that can be used to enable early treatment, and ultimately enhance patient outcomes. On the other hand, multi-class feature extraction has showcased substantial promise from recent studies. This technique encompasses various possibilities, including the utilization of CN/AD classes for ROI identification, the integration of CN/AD and sMCI/pMCI datasets for feature extraction, and the potential for improved diagnoses through pretraining on the CN/AD dataset. By incorporating classes beyond our primary focus, we can reduce the risk of overfitting and improve the distinctiveness of the classes by incorporating features from other class categories that offer greater discrimination. This approach enables us to gain a deeper understanding of AD, and through machine learning, we can develop more robust and accurate models for early diagnosis, prognosis, and potentially, the development of effective interventions to combat this complex condition.

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