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A systematic review on early prediction of Mild cognitive impairment to alzheimers using machine learning algorithms

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ABSTRACT

Background: A person consults a doctor when he or she is suspicious of their cognitive abilities. Finding patients who can be converted into Alzheimer's in the future is a difficult task for doctors. A person's dementia can be converted into several types of dementia conditions. Among all dementia, Alzheimer's is considered to be the most dangerous as its rapid progression can even lead to the death of an individual. Consequently, early detection of Alzheimer's would help in better planning for the treatment of the disease. Thereby, it is possible to reduce the progression of the disease. The application of Machine Learning algorithms is useful in accurately identifying Alzheimer's patients. Advanced Machine Learning algorithms are capable of increasing the performance classification of future AD patients. Hence, this study is made on a number of previous works from 2016 onwards on Alzheimer's detection. The aspects such as the country of the participants, modalities of data used and the features involved, feature extraction methods used, how many follow-up data were used, the period of Mild Cognitive Impairment to Alzheimer's Disease converters predicted, and the various machine learning models used in the previous studies of Alzheimer's detection are reviewed in this study. This review helps a new researcher to know the features and Machine Learning models used in the previous studies for the early detection of Alzheimer's. Thus, this study also helps a researcher to critically evaluate the literature on Alzheimer's disease detection very easily as the paper is organized according to the various steps of the Machine Learning process for Alzheimer's detection in a simplified manner.

1. Introduction

Alzheimer's is one of the deadly dementia as the rate of progression of the disease is rapid. It can even lead to the death of an individual. Alzheimer's can destroy the cognitive abilities of an individual in a dangerous manner [1]. Usually, a person consults when he or she suspects his or her cognitive abilities. The cognitive impairment of a patient can lead to several types of dementia. Among various types of dementia, it is difficult for a doctor to find out the patients who will have Alzheimer's in future [2].

Finding the crucial bio-markers for determining Alzheimer's and other type of dementia are a crucial investigating area among the researchers [3–5]. The study conducted by the researchers in Refs. [3–5] experimented on a rat model for the detection of Alzheimer's patients. The main idea behind the experimentation on rat models is to observe how effective the drug is in reducing the progression of Alzheimer's disease. Hence, much of the latest research mainly revolves around the experimentation of Alzheimer's symptoms and medications on rats [3–8]. All of these studies focus on observing the risk factors of AD among the rats which the doctors believe could be replicated among human beings also. Hence, the physicians are using the neuroimage changes that were observed among the rats for conducting a study on the human body also [3–8].

Finding Alzheimer's patients at the baseline or screening visit itself helps doctors in making better health related decisions. Thus, the doctor can plan better medication strategies that reduce the progression of the disease. Further, early detection of Alzheimer's helps in better health related outcomes of the patient [9]. The treatment strategies are also more effective during the early stages of the progression of the disease. Likewise, the effect of drugs is also more effective during the early stages of the disease [9].

It is also a challenging task to find out patients who will convert to Alzheimer's in future. This is because the exact parameters responsible for conversion of Mild Cognitive Impairment (MCI) to Alzheimer's

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Disease (AD) still has not been found out. Generally, the doctors take this decision by analysing data such as Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET) and Neuro-psychological-assessments data. But, this is challenging to the doctors as the characteristics of MCI to AD converters is very complex and hard to trace. In such a scenario, a predictive Machine Learning (ML) model assists in good decision making process [2,10]. Researchers have focused mostly on longitudinal (visit) data of patients for early prediction. Longitudinal data collected over various follow up periods say first, second, third visits and so on contain the relevant information and parameters that would progress over time [11].

Some patients who have MCI would convert to AD in future namely Progressive Mild Cognitive Impairment (pMCI). However, some patients may remain with MCI without converting to severe AD in the future namely Stable Mild Cognitive Impairment (sMCI). As far as a physician is considered, it is important to find out the future sMCI and pMCI patients [2,10,11]. If the physician can detect future AD patients in advance, then it is possible to recommend the proper diagnosis and medication strategies for an AD patient. This would help in reducing the progression of the dangerous AD to the next level where the patient and their relatives would find it very difficult to deal with. In the same manner, the detection of sMCI also helps a physician to prescribe the required medication for a patient based on his or her cognitive impairment. This would help in saving the unnecessary costs that might spend on the MCI patients [2,10,11].

The biggest challenge in distinguishing between pMCI and sMCI patients are as follows:

- Overlapping of certain characteristics is seen in both pMCI and sMCI patients. For example, the shrinkage of brain regions is commonly seen among both pMCI and sMCI patients [2].
- It is very difficult for a domain expert to find out the crucial bio-markers and features that are responsible for distinguishing pMCI and sMCI. Thus, a physician seeks help from an advanced Machine Learning (ML) technique for deriving out the hidden patterns and relevant features that are responsible for distinguishing the pMCI and sMCI [2,10,11].
- Identifying the crucial bio-markers for distinguishing pMCI and sMCI patients from unstructured data like medical images is a major challenge [2].
- The inability to generalize the characteristics from various multi-modalities of data is also a major challenge [2,10,11].

As it is challenging to identify and distinguish the sMCI and pMCI patients by observation even for an experienced practitioner, a ML algorithm would help in assisting the physician in properly identifying the AD risk patients. The ML algorithms are capable of identifying the distinguishing features that can differentiate a sMCI from a pMCI patient. It is difficult for the physician to generalize or classify a patient as sMCI or pMCI as many of the characteristics and symptoms are common for both sMCI and pMCI patients [2,10–12]. This is where an efficient ML algorithm would be very helpful as it can identify the hidden patterns in the complex AD data of the patients using a mathematical model. Consequently, an efficient ML model can act as a good assist for the physician while making crucial decisions to predict whether a patient will have a sMCI or a pMCI [11–13]. A workflow of ML algorithm for sMCI and pMCI patient includes: 1. Identifying the important features from a huge repository of structured or unstructured dataset, 2. Classifying the patient as sMCI or pMCI using longitudinal visit data.

The above challenges resulted in ML researchers working on various neuro-imaging data, cognitive tests, and other demographic data for model building. It is a major challenge among ML researchers who are working in AD detection to generalize a specific set of bio-markers from unstructured and structured datasets for distinguishing pMCI and sMCI patients. Hence, the ML researchers have already explored various methods for distinguishing pMCI and sMCI patients. This research paper helps a new researcher who is entering MCI to AD detection using multi-modal data in giving a simplified overview of the previous studies. Many researchers have already adopted various types of features and classifiers for detecting MCI to AD converter patients. This paper is a summarized review of the various methods and techniques that are used for identifying MCI to AD converters. Consequently, this study will help an early researcher to find out their research direction in the classification of pMCI and sMCI patients.

Hence, key focus on early prediction of MCI to AD converters using ML models is discussed in this paper. A systematic review of identified 42 research papers are taken into consideration and it is summarized to answer the research questions. The key focus of review is towards the papers implemented longitudinal data in prediction of MCI to AD. The summarized data consists of the study participant's country, features, follow up data characteristics, classifiers and performance metric that are implemented in the Alzheimer's detection. These aspects are explained in detail for every selected study.

This study used a review methodology for finding out how the previous studies addressed the MCI to AD conversion using ML techniques. The literature review is conducted on previous studies from 2017 onwards for MCI to AD conversion. The proposed approach of the review paper involves a detailed study of 42 state of the art articles on MCI to AD conversion.

This paper is organized as follows: section 2 contains the review protocol and methodology, section 3 contains results and discussion, section 4 contains the limitation of the study, section 5 contains the conclusion.

2. Review protocol and methodology

This section contains a detailed explanation of the method of review protocol used in the paper. Initially, a set of research questions are formulated. The answers to the research questions are found after examining the previous literature that deals with the detection of AD using ML techniques. Initially a search strategy is followed based on the research questions. Then, the data from the selected studies are extracted for every research question.

2.1. Research questions

The overall aim of this research paper is to provide an overview of the current state of the art in early detection of MCI to AD converters using machine learning approaches. For providing an overview of the various techniques in AD detection, the following research objectives are framed. The following research objectives are used to address the aspects such as the country of the study participants, the various data modalities used, ways of extracting features from unstructured neuro-image data and classifiers used in predicting sMCI and pMCI patients.

- RQ1:What is the country of the study participants?
- RQ2:What modalities of data are used as features?
- RQ3:Which papers used feature selection techniques for ranking the features?
- RQ4:How many follow up data from longitudinal data are used? What is the duration of follow up data?
- RQ5:What range of MCI Conversion to AD conversions are found out in the papers?
- RQ6:How many papers used machine learning and deep learning models?
- RQ7:Do ensemble models improve the performance in prediction?
- RQ8:When do the models perform better?

RQ1 is the basic question for finding out whether a model is developed for predicting MCI to AD converters from various parts of the world, as AD and MCI can vary in their intensity and causes from region to region depending upon multiple factors [14,15]. The relevance of this

question is to identify whether prediction models are developed in a generalized population, say persons belonging to various regions or countries.

RQ2 concerns the features that are used for prediction. The possible type of features can be from single modality or multiple modalities of data. The most common modalities of data are MRI, PET, functional MRI (fMRI), Electroencephalogram (EEG), Neuro-psychology data, Clinical data and Cerebro-Spinal Fluid data. Here, we search the answer for what type of features are used from various types of modalities. The question is relevant because the parameters that are responsible for MCI to AD conversion are not specifically discovered for distinguishing MCI to AD converters [16].

RQ3 aims to find out if researchers used any feature selection techniques for getting relevant and important features. This is because the exact features responsible for conversion of MCI to AD is not known among the researchers. Therefore, it is important to find out and rank the important features for classifying MCI to AD converters [9,10].

RQ4 aims to find out the number of follow up data used by researchers on the longitudinal classifiers for distinguishing MCI to AD converters. Further, the duration between the follow-up data is also observed for the papers. This is an important research question because it is important to investigate whether the researchers are able to classify the MCI to AD converters within shorter follow up period.

RQ5 investigates the effectiveness of prediction models in finding out the MCI conversion to AD. If we can find out MCI to AD converters early, it will help in a good decision making [9]. Therefore, this question will explore the range of conversion of MCI to AD converters from the literature.

RQ6 explores the various longitudinal models used for the classification of pMCI and sMCI patients. The objective of this question is to explore the different types of longitudinal models used for finding sMCI and pMCI patients and to explore which models achieve better performances. The various performance metrics such as Accuracy, Balanced Classification Accuracy (BCA), Sensitivity and Specificity are assessed to understand the classification performance for distinguishing the pMCI and sMCI patients.

RQ7 aims to explore the ability of ensemble models in improving the prediction results. This question is investigating whether ensemble models are good in improving the results in terms of BCA, Sensitivity, Specificity for distinguishing pMCI and sMCI patients.

RQ8 aims to explore what kind of features and classifier models are improving the classification performance for pMCI and sMCI patients.

2.2. Search strategy

PRISMA guidelines are followed for selecting the review papers [17]. The databases like Google Scholar, IEEE Xplore, Scopus, and Pubmed are searched for selecting the relevant studies. The searching for relevant studies is conducted by using specific keywords and phrases. We have used phrases such as “MCI to AD Converters”, “Early Detection of MCI to AD Conversion using Machine Learning”, “Early Detection of Alzheimers”, “Alzheimers Converters” in the journal search engines. The records identified by searching as on 31/08/2022 with the keywords in each journal are given in table 1.

Table 1
Number of records found for each query in journal search engines as on 03/10/2022.

Search Engine	Keywords	Number of Records Found
Google Scholar	MCI to AD Converters	9970
	Early Detection of MCI to AD Conversion Using Machine Learning	5250
	Early Detection of Alzheimers	4660
	Alzheimers Converters	7545
IEEE Xplore	MCI to AD Converters	2345
	Early Detection of MCI to AD Conversion Using Machine Learning	1610
	Early Detection of Alzheimers	1750
	Alzheimers Converters	1992
Scopus	MCI to AD Converters	1200
	Early Detection of MCI to AD Conversion Using Machine Learning	1809
	Early Detection of Alzheimers	1610
	Alzheimers Converters	1890
Pubmed	MCI to AD Converters	5500
	Early Detection of MCI to AD Conversion Using Machine Learning	5610
	Early Detection of Alzheimers	5890
	Alzheimers Converters	5100

2.3. Study selection

To select the relevant studies, an inclusion and exclusion criteria is developed. They are used in the various stages of the study selection process. The following inclusion and exclusion criteria is followed in this paper.

2.3.1. Inclusion and exclusion criteria

After getting the results from the databases for the keywords as mentioned in Table 1, the duplicate papers are removed from the results. Initially, the papers are selected after screening the abstracts. The papers with no proper explanation about the ML techniques in the abstract are excluded from the study. Then, the inclusion and exclusion criteria is implemented on the resultant selected papers.

The papers are selected on the basis of inclusion and exclusion criteria.

- The papers that used only longitudinal data for the research are selected for the study. The reason is that the longitudinal studies analyze the follow-up data of the patients for making the final decisions about the classification of pMCI and sMCI patients. Hence, the studies with only cross-sectional data for the classification of pMCI and sMCI patients are eliminated from the study.
- The papers that used only longitudinal data for the research are selected for the study because it analyses the follow-up data of the patients for making the final decisions about the classification of pMCI and sMCI patients. Hence, the studies with only cross-sectional data for the classification of pMCI and sMCI patients are eliminated from the study.
- The papers with clear explanation about the performance metrics are used for the study. The studies with clear explanation about any of the performance metrics such as Accuracy, BCA, Sensitivity and Specificity are selected for the systematic review.

2.4. Data extraction

The relevant information for every paper needs to be extracted in this stage. The following information is extracted from each paper that will answer the following research questions: country of study participants, the number of follow-up longitudinal data used, range of MCI conversion predicted, description of the modalities of data, is automatic feature extraction used or not, type of algorithm used (machine learning, deep learning), ensemble learning and the Sensitivity, Specificity, and Accuracy reported in each of the finally selected papers. As far as the results are concerned, the best results in each paper (in terms of Accuracy, Sensitivity, and Specificity) are chosen as the answer to the research questions. The research papers contain many experiments (by varying features, follow-up data, and model combinations), and the best out of the experiments (in terms of Accuracy, Sensitivity, and Specificity) is chosen as the result of our study.

3. Results and discussion

This section contains detailed information about the results and discussions.

3.1. Study selection

In this section the overall study selection procedure is explained in detail. Searching in the journal repositories like IEEExplore, Google Scholar, Pubmed, and Scopus are reported with 15450 results. 735 duplicate papers are removed from the reported results. Then, the abstracts are screened for the resulting 14715 papers. There was an exclusion of 3343 articles after abstract screening. Then, the papers without any Artificial Intelligence applications which explained only the scientific aspects of MCI and AD are excluded at the abstract level screening. Among the 11372 articles assessed for eligibility, there was an exclusion of the papers that do not have MCI to AD converters (n = 3356), longitudinal data (n = 4200), specified either method or features (n = 3513), performance metrics description including Accuracy, Sensitivity, Specificity (n = 391). Consequently, 42 studies were selected for conducting the systematic review. Fig. 1 contains the exclusion criteria used in the paper selection process.

Following are the public datasets used for predicting pMCI and sMCI patients from the literature.

Public datasets for predicting the pMCI and sMCI patients are as follows:

- **Alzheimer's Disease Neuro-Imaging Initiative (ADNI) Dataset:** ADNI dataset is used for uniting various researchers who are working on the progression of MCI to AD. ADNI project consists of multimodal data belongs to MRI, PET, neuro-imaging, genetic and other cognitive test data [18–20]. The dataset consists of participants' data from North American hospitals collected over 5 years. The main aim of the research project is to examine and find out the bio-markers that are responsible for the early detection of Alzheimer's Disease using Machine Learning algorithms [18–20]. ADNI datasets are developed for optimizing, validating, standardizing clinical trial measures and biomarkers developed for clinical research [18,19].
- **Australian Imaging Biomarkers and Lifestyle Study of Ageing (AIBL) dataset:** AIBL dataset consists of 18-month follow-up data of Australian patients ranging from 50 to 90 years. The dataset consists of MRI, PET, cognitive test and lab test data of the patient which is collected over 1 year. The primary objective of the AIBL dataset is to find out which cognitive tests, medical imaging characteristics, and lab tests are crucial in distinguishing MCI and AD patients [20–22]. It consists of a multidisciplinary research team from researchers located in Perth, Sydney, Melbourne, Canberra, and Brisbane [20–22].
- **Open Access Series of Imaging Studies (OASIS) dataset:** OASIS dataset consists of multimodal of more than 1000 patients collected over various points of time. The dataset consists of neuro-imaging, cognitive tests data that are collected over a period of time. The dataset consists of 3D sliced MRI images of more than 10000 images. The objective of the project is to find out the future MCI and AD patients in advance using clinical, neuro-imaging, genetic and other biomarkers [23,24]. The OASIS dataset consists of patient's data collected from 416 subjects aged from 16 to 96 years. The subjects of the study are right handed. Most of the samples of the dataset are more than 50 years old [23,24].
- **Dementia Bank clinical dataset**

Dementia Bank clinical dataset consists of Alzheimer's and Healthy Control patient data from the speech data. It consists of dementia-related data of 500 patients collected over various time points [25,26]. The data set consists of transcripts and video recordings of AD and healthy patients. This data set consists of speech utterances of the AD and HC patients that were observed after performing a recall test on multiple scenes [25,26].

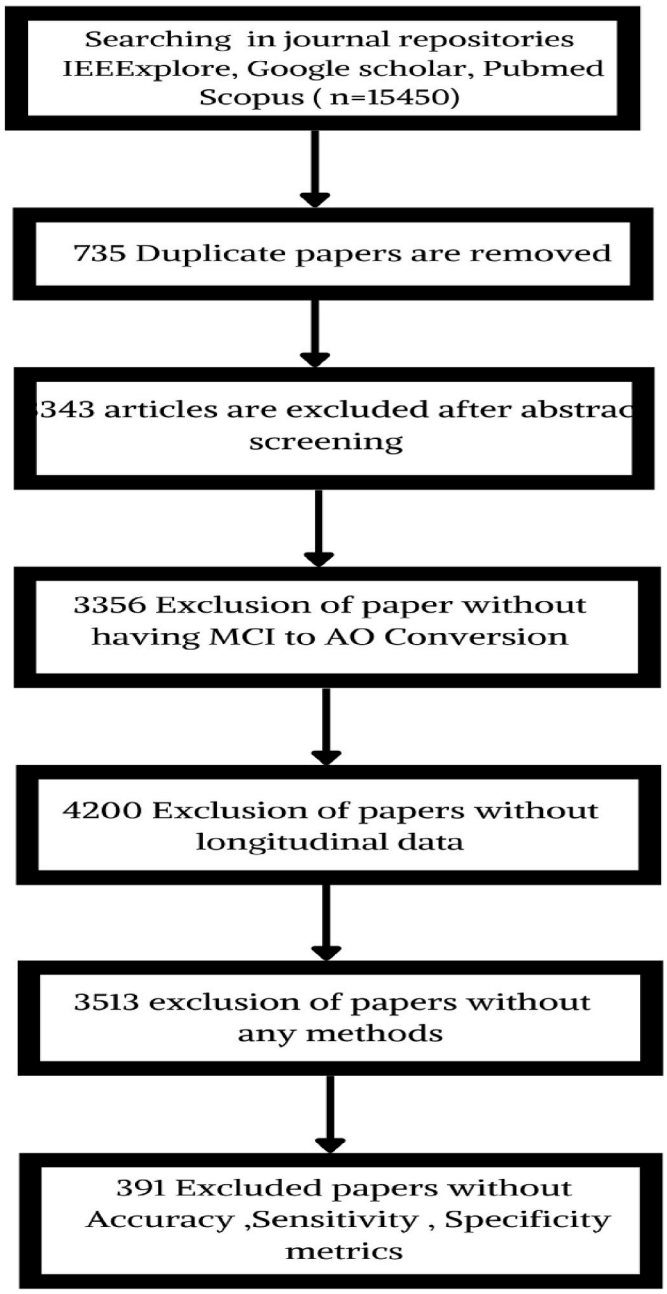

Fig. 1. Exclusion criteria used in the paper selection process.

3.1.1. RQ1:What is the country of study participants?

- Of the included studies, ADNI dataset is used in many studies [18,19]. The participants of the dataset are from various parts of USA and Canada. The papers that experimented on ADNI dataset are: [27–62]. All the studies mentioned above were conducted on study participants from North America. 3 studies were conducted on participants from Europe [50,54,55,63,64].
- One study contains study participants each from Portugal [63] and Germany [64].
- Inter continental study on participants from Milan in Italy is mixed with the ADNI dataset in Ref. [65].

3.1.2. RQ2:What are the modalities of data used as features?

Our main focus on this research question is to find out the papers which used single modality and multiple modalities of features for the prediction purposes.

● Single Modality:

Data from a single modality alone is used for the prediction purpose in many studies.

MRI: Hippocampal volume is selected as feature in Refs. [27,35]. Free Surfer Intensity values of selected regions are used by the researchers [44,49]. Entorhinal Volume is used by the researchers in Ref. [27]. Amygdala distance is used in the experiments [36]. Further, Intracranial volume is also used by the studies [27]. Cortical thickness is also used in the study [34,48]. Distinguishing Voxels of brain MRI are selected by the researchers using Logistic Regression for longitudinal training data in Ref. [38]. Gyrus height is again another feature used by the researchers in Ref. [48]. A network based feature is created for a purely MRI based feature selection technique by Ref. [48]. Whole patches of MRI image is used as a feature in 1 study [29]. The whole 2D slice's intensity features of a brain MRI image is used by the researchers in Ref. [38] for distinguishing sMCI and pMCI. A transfer learning approach is employed in the whole slices of MRI image for distinguishing the pMCI and sMCI patients [54]. The transfer learning approach used by the researchers in Ref. [54] is focused on hyper-parameter tuning of convolutional neural network on the basis of age. An attention based neural network architecture is developed by the researchers in Ref. [66] for predicting MCI to AD conversion patients.

PET: PET data alone is used in Ref. [31]. Metabolic intensity values are extracted from the raw PET images for all patches by the researchers in Ref. [31]. PET imaging techniques are widely used by the researchers for early detection of Alzheimer's disease using convolutional and recurrent neural networks [67]. There were lot of studies conducted for finding out the difference in PET feature like florbet-pair for distinguishing AD and healthy control patients. PET imaging techniques are widely used by the researchers for finding out the Alzheimer's disease patients from the past. PET imaging technique is capable of finding out the metabolic features in the brain. For instance, the cognitive memory is high for people with good metabolism inside the brain [31, 67].

Electroencephalogram (EEG): EEG data is used by the researchers in Ref. [52]. They created a graph structure for the functional connectivity in the EEG signals of sMCI and pMCI patients [52]. Researchers also explored the Time frequency, Bi-Spectral features of EEG data for accurate prediction of MCI to AD converters [55].

● Multiple Modality:

From the selected papers, in 12 papers researchers experimented with multiple modalities of data say MRI, PET, Neuro-psychological and clinical data. A Combination of unstructured data from various modalities say that MRI, PET and clinical data are used by the researchers in Ref. [34]. They used Temporal Gyrus and Hippocampus volumes from MRI, Independent Component Analysis (ICA) from PET and MMSE values as neuro psychological assesement data [34]. A combination of MRI and PET is used by the researchers in Ref. [37].

A combination of functional MRI (fMRI) and MRI is used in the study [46]. A connectivity matrix for 93 ROI is created as a feature and the features of FREESURFER software are extracted from MRI [46].

A combination of structured data from various modalities is used by the researchers in 4 studies [40,42,50,63]. Both MRI and Neuro-psychological data are used by the researchers in Ref. [40]. They used Hippocampus, Ventricles, Fusiform as MRI data, Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog) and MMSE as neuro-psychological data in the study. Another study [63] used both neuro-psychological and clinical data for the prediction purpose. Neuropsychological scores such as MMSE, ADAS-Cog and clinical data such as demographics and cardiovascular scores are used in these studies. Both MRI and CSF data are used in Ref. [41]. Hippocampal Volume is used as MRI feature and A-Beta data is used as CSF features in this study [41]. Researchers used both structured MRI and CSF data for prediction purpose [64]. MRI data consists of Hippocampal volumes and Tau, A-Beta are used as CSF features in the study [64]. Researchers in Ref. [50] used socio-demographics data such as age, sex, years of education, marital status and psychological test data such as MMSE, ADAS-Cog, Rey Auditory Verbal Learning (RAVLT) in the experiments. A health ageing trajectory model was developed on multimodal structured dataset by the researchers in Ref. [58] for predicting MCI to AD converters.

A hybrid of structured and unstructured data from various modalities are used in 5 studies [34,41,43,45,47,53]. Unstructured MRI, PET and neurological, clinical data are used by the researchers in Ref. [34]. The study includes MRI data of voxel based morphometry and volume based morphometry, neuro-psychological data as MMSE and clinical data as demographics medical history data [34]. In another study, a combination of MRI, PET, CSF, Demographics and Neuro-psychological data is used by the researchers in Ref. [43]. Similarly, a mix of MRI, Genetic and Neuro-psychological data is used by the researchers in 2 studies [45,47]. Atrophy score of each MRI, Polyhazard Score is used as a genetic score and MMSE Neuro-psychological data is used as features in the study [45]. In a similar study, researchers used texture value of voxels of MRI, APOE4 Genetic data and MMSE as neuro-psychological data [47]. The texture value of voxels are captured using neural networks. Texture values capture the Gray and White matter intensity inside the brain. These features are combined with the APOE4 genetic data and the most commonly used cognitive score namely MMSE [47]. In another study, Unstructured MRI, PET and CSF are used as features for sMCI and pMCI. MRI data consists of Gray Matter pixel values of 93 ROIs. These 93 ROIs are captured in the three views of neuroimage namely coronal, sagittal, transverse. It is combined with CSF data which consists of TAU and A-Beta protein levels [41]. The Ventricular Cavity and reduction of Gray Matter volumes are extracted from the MRI images by the researchers in Ref. [53]. They also added the cognitive test Mini-Mental State Examination (MMSE) for predicting the sMCI and pMCI patients [53]. The whole patches of brain image and cognitive assessment data is used by the researchers in Ref. [56] for sMCI and pMCI converters.

3.1.3. RQ3:Which papers used automatic feature extraction methods?

Some papers used automatic feature extraction methods for extracting relevant information. The feature selection methods are employed in unstructured data like MRI, PET, EEG.etc. Whereas some papers do not have any feature extraction methods. The papers taken for survey are classified based on feature extraction as given below.

– No Feature Extraction

There are 15 studies without any feature extraction methods. These papers used all the structured features that are already derived from the existing literatures [27,33–36,40–42,47,49,50,63,64].

– Automatic Feature Extraction

16 studies applied automatic feature extraction techniques on unstructured data such as MRI, PET, and EEG [28–33,37–40,43–46,48,51, 65]. Following are the various techniques used for feature extraction from MRI, PET, and EEG data.

3.2. MRI

It is observed that the researchers were mainly focused on using deep neural network architectures for extracting features from MRI data either on entire images or focused areas of the brain.

The studies that considered the whole patches of the brain for automatic feature extraction are as follows:

Whole Patches of the brain: A deep learning method combined with a sparse regression model is used for predicting sMCI and pMCI patients [28]. A deep CNN is used for extracting the neuro-image features which is then combined with a sparse regression model for accurate classification of sMCI and pMCI patients [28]. A multi-domain transfer learning based approach is used by the researchers for classifiying the sMCI and pMCI patients [32]. Transfer learning is applied on various kinds of slice image for classification of sMCI and pMCI patients. A different approach was used by the researchers in Ref. [33] where a graph based network is extracted from the neuroimages and graph based measures are extracted for distinguishing sMCI and pMCI patients. A CNN based architecture is developed for the early conversion of sMCI patients by the researchers in Ref. [38] for predicting 1 year MCI to AD conversion patients. A supervised non-parametric method is implemented by the researchers in Ref. [40] on longitudinal data for sMCI and pMCI prediction. The study conducted by the researchers in Ref. [43] used a deep neural network method combined with an automatic feature selection technique for classifying sMCI and pMCI patients. CNN is used by the researchers in Ref. [44] for classifying sMCI and pMCI patients. An ensemble of CNN is used by the researchers in Ref. [65] for the classification of pMCI and sMCI patients. Researchers also implemented an age adjusted neural network for predicting MCI to AD patients. The neural network has an age adjusting layer which is capable of differentiating the sMCI and pMCI patients [54]. A CNN neural network architecture is implemented for extracting the GM intensity from the MRI images [56]. A variational auto-encoder neural network architecture is used for extracting the image intensity features from MRI images [57]. High dimensional MRI images are processed using CNN for the detection of sMRI and pMRI patients in the study conducted by the researchers in Ref. [56]. The researchers also developed a novel neural network architecture for the detection of sMCI to pMCI patients using neural network architectures [51].

Transfer learning approach with 3D ResNet architecture utilizing a zero shot learning is implemented by the researchers in Ref. [66]. The advantage of this method is that it is implemented on less number of MRI image data but achieved a higher classification performance for sMCI and pMCI detection. Again researchers applied a transfer learning method for extracting the intensity features from MRI images using an attention based network for capturing the functional connectivity of the brain.

The ensemble classifiers are used by the researchers in Ref. [65] for the accurate prediction of sMCI and pMCI patients. They used an ensemble of many CNN classifiers on the entire MRI brain image.

Domain Specific Regions: A deep learning architecture is developed on a specific Region of Interest (ROI) by the researchers in Ref. [29] where a multi-instance based deep learning framework is developed for extracting the features. The relevant features from 91 ROI's are extracted using multiple instance based deep learning architecture. Karuppi et al. [45] used a feature extraction technique focused on finding the structural volume of MRI data from MRI images. In another study, the researchers extracted morphological features from the MRI data on 91 ROI that are relevant in classifying sMCI and pMCI patients [48].

3.3. PET

The study conducted by the researchers in Ref. [30] used a multi-scale approach for the diagnosis of Alzheimer's disease detection. They used a CNN that can extract multiple features from multiple sub-regions of the PET image. They considered all the sub-region features of the PET image at various slices for feature extraction [30].

3.4. Multimodal data

A multimodal image fusion is performed by the researchers in Ref. [33] for the early detection of sMCI and pMCI patients. A hierarchical framework was developed by the researchers in Ref. [39] for selecting the relevant features that are responsible for classifying sMCI and pMCI patients. An automatic feature extraction technique that extracts the functional connectivity using EEG data within brain regions accompanied by cognitive tests is implemented by the researchers in Ref. [52]. A novel multimodal EEG data based study was conducted by the researchers in Ref. [55] for automatic feature extraction. They extracted High Order Statistics from the Bi-Spectrum data for distinguishing sMCI and pMCI patients. The CNN is used by the researchers for extracting neuro-image intensity features from the MRI data [37]. A combination of cognitive tests and lab test data is also used by the researchers for classifying sMCI and pMCI patients [37].

An integration of MRI and Functional MRI is made by the researchers in Ref. [46] for predicting the sMCI and pMCI patients. They used neural network architectures for classifying sMCI and pMCI patients.

3.4.1. RQ4:How many follow-up data from longitudinal data are used? What is the duration of the follow-up data?

Follow-up time period of a patient refers to the frequent time periods in which a patient's conditions are monitored in a hospital or by a doctor.[1] The 3 follow-up duration used by the researchers for prediction of MCI to AD converters are 6 month, 12 month and 1 year respectively. A detailed explanation of the follow up duration and the number of such follow-up (visits) used by the researchers are explained in this section.

– 6 MONTHS FOLLOW-UP:

6 months follow-up are examined in the following studies: [27–48, 50,59].

Following is the information about how long the 6 month follow-up data is used by the researchers. One study contains the complete 1.5 year follow-up data of patients [28]. The complete 2 year follow-up data is used in the study [31]. The complete 2.5 years data is used in the study [42],

Among these complete 3 year follow-up, 6 month duration data are used by the researchers in Refs. [27,29,30,32–34,36,37,39,41,43–46, 48–50,65]. The complete 3.5 years follow-up data is used in Ref. [35]. However, the complete follow-up data till all 3.5 years is not used in this study. The complete 4 years data is used in Refs. [38,47].

– 3 years, 12 month:

The study conducted by the researchers in Ref. [64] contains follow-up data of 12 months duration and it is followed for 3 years (number of follow-up is 3).

– 1 year, 5 month:

The study conducted by the researchers [63] contain follow-up data of 1 year duration and it is followed for the next 5 years (number of follow up data used is 5).

– 3 years

Follow-up data is 2 years for [61].

– Unclear follow up data

[1] https://www.cancer.gov/publications/dictionaries/cancer-terms/def/follow-up.

The follow-up data is unclear for the studies in: [51–58,60,62].

3.4.2. RQ5:What range of MCI conversion to AD is used?

Range of MCI to AD conversion is very vital in proper health care decision making processes. The description of time duration of MCI to AD conversion ranges are explained below.

– Six Month:

The shortest conversion time span in the literature is 6 months [39,49].

– One Year: 4 studies predicted 1 year conversion from MCI to AD [30,37,38,64].
– One and Half Year: 2 studies experimented on 1.5 year conversion prediction of MCI to AD [28,40].
– Three Year: Most of the studies experimented on prediction of 3 year conversion of MCI to AD [29,31–34,36,41–43,45–48,50,65].
– Five Year: Longest time span of prediction of MCI to AD is 5 years which is experimented in the paper [63].
– No Conversion Range (Just MCI to AD Converters Without Time Period Specification). There was no specific time of conversion from MCI to AD in the studies [35,44]. Both studies predicted whether a person will have conversion from MCI to AD without finding the time of conversion.
– The MCI to AD conversion range is unclear in the following studies: [49–62,65].

3.4.3. RQ6:How many papers used machine learning and deep learning separately?

A classification of papers which used machine learning and deep learning techniques is as given below.

– ML algorithms:

Following ML algorithms are used:

SVM is widely used by researchers as a final classifier for predicting the sMCI and pMCI detection. Initially, the deep neural networks such as CNN or different types of CNN are used for extracting the relevant features from the unstructured data. Then, the extracted features are fed into the SVM classifier. SVM is used in the given studies: [34,36–40,42,43,47,48,64].

LASSO is used for both the feature selection and classification purpose in the study conducted by the researchers in Ref. [31]. A feature selection framework is built for selecting the relevant features and a classifier is implemented to classify the sMCI and pMCI patients [31]. In addition, a linear Sparse Regression model is developed by the researchers in Ref. [41].

The Cox based survival event time detection models are used by the researchers in Refs. [33,45]. A Cox regression model is used as a classification model for predicting the sMCI and pMCI patients using the unstructured data collected by CNN models in the study [33]. Similarly, a Cox hazard model is implemented by the researchers in Ref. [45] for classifiying sMCI and pMCI patients. This model helps in identifying whether a patient belongs to sMCI or pMCI category on the basic Cox probability value [45].

Researchers also used longitudinal classifiers for the detection of sMCI and pMCI patients [35,63] for detecting the sMCI and pMCI patients. A Mixed Effects Model is proposed by the researchers in Ref. [63] for the predicting sMCI and pMCI patients. This model considers all the varying visit intervals of the patients. Moreover, a sliding window based approach is also used for the classification of sMCI and pMCI patients [35]. This model is capable of measuring the influence of one visit over the other in predicting a patient as sMCI or pMCI.

An ensemble of Machine Learning classifiers is also used by the researchers [27,50]. An ensemble of SVM and Logistic Regression is used by the researchers in Ref. [27] for sMCI and pMCI detection. Likewise, an ensemble of SVM and LR is used by the researchers in Ref. [50] for distinguishing sMCI and pMCI patients. Table 2 contains the purpose and the available configuration information about the ML algorithms used in the study.

– Deep Learning:

Deep Learning neural network architectures are used by the researchers as classifiers as well as feature extractors by the researchers in Refs. [28,30,44,46,49,52–62,65]. A CNN architecture is used for

Table 2
Configuration of ML algorithms used in previous works. RBF-Radial Basis Function, FCL-Fully Connected Layers, BLR: Binary Logistic Regression.

Reference	ML Configuration	Purpose
[27]	SVM: RBF kernel	Classification of AD based on structural features
[28–30,47] [50,54,66]	CNN: 8 FCL, Sigmoid (Activation)	Capturing Gray and White Matter Intensity
[31]	SAE: Rectified Linear Unit	Capturing Gray and White Matter intensity
[32]	CNN + SVM	CNN: Metabolic Intensity Extraction
	CNN: 3D with Sigmoid	SVM: Classification of sMCI, pMCI
[33,35,36,39,65]	CNN + SVM	CNN: Gray and White Matter Extraction
	CNN: Rectified Linear Unit	SVM: Classification of sMCI, pMCI
[34,44]	Cox Regression Models	Calculating AD survival from multimodal data
[37]	SVM	Classification of sMCI, pMCI patients Using Amygdala distance
[38]	SAE + SVM	SAE: Capturing intensity from multimodal neuroimages
	SVM: RBF Kernel	SVM: Classification of pMCI, sMCI patients
[41]	LR	Selection of significant Voxels classifying sMCI, pMCI
[40,61]	CNN, SVM, SVR	CNN: Automatic Feature Extraction SVR: Estimating mean Gray and White matter SVM: Classification of sMCI, pMCI
[42]	Sparse Learning Regression	Causal Inference Model Identifying relation between features
[38,43,46,59,64]	SVM: Polynomial Kernel	Classifying pMCI, sMCI patients
[45,52]	SVM: RBF Kernel	Classifying pMCI, sMCI using graph measures
[63]	CNN + BLR	CNN: Undefined FCL BLR: classification of pMCI, sMCI patients
[48]	Bayes Classifier	Probabilistic model for speech features
[49]	CNN + Graph networks	CNN: Automatic Extraction of neurimage features
	CNN: Activation function as tanh	Graph Network: Extracting Connectivity measures
[60]	SVM, KNN, MLP SVM: RBF Kernel KNN: 5 MLP: Undefined	Ensemble Voting Classifier
[53]	CNN with attention mechanism	Focusing on ROI more
[55]	CNN	Extracting features from EEG data
[66]	CNN + SVM	CNN: Extracting neuroimage intensity
	SVM: RBF kernel	CNN + SVM: Classifying sMCI, pMCI patients
[58]	Multi-Kernel SVM 2 RBF kernel 1 Polynomial kernel	Classifying pMCI, sMCI patients
[44,49,65]	CNN + RNN	CNN: Automatic Feature Extraction RNN: Capturing Temporal features

extracting the neuroimage intensity features such as Gray Matter and White Matter intensity by the researchers in Refs. [28,30,46,52–55,58–62,65].

Similarly, a combination of CNN and Recurrent Neural Network (RNN) is used by the researchers in Refs. [44,49,65]. These models are capable of extracting the spatial intensity based features using the deep CNN architectures. Then, the deep RNN architectures are used for extracting the temporal information from the extracted features of the unstructured data [44,49,65].

3.4.4. RQ7:Do the ensemble models improve the sMCI and pMCI prediction?

Ensemble learning algorithms are used in Refs. [27,29,33,39,40,44,49,50,50,65]. The ensemble deep learning architectures such as CNN-RNN combination are used by the researchers in Refs. [44,49,65] for capturing the spatio-temporal features from the neuro-images and expected to increase the classification performance. Moreover, the ensemble of classifiers is used for classifying whether a patient is s MCI or pMCI is also expected to increase the classification performance of detecting sMCI and pMCI with a decision making approach that captures the diverse information [29,33,39,40,50].

The range of accuracy reported using ensemble models is 74%–89%. The range of sensitivity reported using ensemble models is 54%–89%. The range of specificity reported using ensemble models is 73%–92%.

On comparing the overall performance of the models, it is observed that the ensemble models have not achieved the best results. In fact, ensemble models give better results but not the best ones. However, this again emphasize towards the importance of finding relevant features.

3.4.5. RQ8:When do the models perform better?

In this section, the range of values reported for various performance metrics such as accuracy, sensitivity and specificity is analysed and analysis of what type of features and models are good in performing better results is given.

– Best Accuracy, Sensitivity and Specificity:

A combination of fMRI and MRI data features has achieved a higher accuracy, sensitivity and specificity of 96%, 94% and 100% respectively on ADNI dataset followed for 3 years within a time duration of 6 months.

– Overall Performance

Overall, the range of accuracy, sensitivity and specificity reported are 65%–96%, 54%–96%, 53%–100% respectively as given in table 3. As far as single modality is concerned, the range of accuracy, sensitivity and specificity are 71%–92%, 42%–96%, 53%–92% respectively as given in table 3. As far as multi-modality of data is concerned, the range of accuracy, sensitivity and specificity are 74%–96%, 54%–94%, 83%–100% respectively as given in table 3. From the above results, in general, it is clear that the models performed comparatively better with multiple modalities of data.

– Parameter Performance within modalities

The range of accuracy, sensitivity and specificity reported for MRI data alone is 65%–83%, 69%–95% and 53%–90% respectively as given in table 3. Free Surfer intensity values experimented by Refs. [44,49] has shown better performance in the result as given in table 3. The accuracy, sensitivity and specificity for the study [31] reported for PET data alone is 83%, 87% and 78% respectively. The extraction of Gray and White Matter from the unstructured raw MRI data using automatic feature extraction and deep learning CNN reported with results <85% (in terms of accuracy, sensitivity and specificity) [28,30]. However, using Support Vector Machine (SVM) on unstructured data reported a better specificity in the range 77%–92% table 3. Structural Volume Ratio and Godesic Length in the study [34] is reported with the highest results <90% (for accuracy, sensitivity and specificity) which is a promising result. One study used neuropsychological data alone on portugal study participants [63] has achieved an accuracy, sensitivity and specificity of 76%, 56% and 76% respectively.

– Parameter performance within populations

However, when mixing ADNI and MILAN study participants using MRI data alone has not shown a better performance with accuracy, sensitivity and specificity of 74%, 75% and 75% respectively which pinpoints towards more research on finding better parameters and learning models while developing algorithms for generalized populations (mixing populations in various geographical locations) as given in Table 3. However, in this experiment researchers used MRI data alone for achieving this. None of the studies in the literature has used multi modalities of data for early prediction of MCI to AD converters for inter continental study participant populations [65]. In addition, the two studies [63,64] conducted on German and Portugal participants has used different modalities for prediction tasks (MRI, CSF for German and Neuro-psychological assesement data for Portuogal). However, the study [64] on German participants with MRI data and CSF performed better than the Neuropsychological data with accuracy, sensitivity and specificity of 82%, 85% and 90% respectively.

– Performance with respect to follow up period:

Following 8 follow-up data for 6 months has achieved a high accuracy of 92% which is a slight increase in 2% accuracy as compared to following 6 month follow up data for 6 months using MRI data (3 years) as given in table 3. In general, the better results are reported using small duration of follow up periods (6 months in the study) as compared to 1 year as given in table 3.

– Performance with respect to the range of MCI converters predicted

The accuracy, sensitivity and specificity for 6 month conversions are 74%, 81% and 71% respectively [49] as given in table 3. In general, better results are reported for 3 year MCI to AD converters with 4 studies reported with accuracy, sensitivity and specificity 85% [36,40,42,47] as given in table 3 respectively.

A full description of the characteristics of data is given in table 3.

3.4.5.1. Research challenges. Following are some the major research challenges that need to be addressed by the researchers:

– Identification of the correct and exact bio-markers from the neuro-imaging data is a challenging task for the researchers. This task becomes even more difficult when it comes to a specific population. For instance, the researchers face a challenging task while identifying the most precise bio-markers that are responsible for classifying the MCI to AD converters and non MCI to AD converters.
– The researchers also face a challenging task for finding out the relevant features that are responsible for classifying the MCI to AD converters and non-MCI to AD converters from a set of multimodal features. Finding the important and relevant features from the multiple-modal features is also a challenging task for the researchers.

The finding of quick MCI to AD converters, say within 6 months to 1 year is also a challenging task. This is a challenging task because there is an urgency required among the research community for immediately finding the quick MCI to AD converters and it is required to develop very good longitudinal models for addressing this.

3.4.5.2. Future directions. Following are the future directions where the

Table 3
SVM-support vector machine, ICV-Intracranial Volume, CNN-convolutional neural networks, ROI-Region of interest, SAE-Spatial auto encoder, GM-Gray matter, ROI-Region of interest, ICA-Independent component analysis, MLP-Multilayer perceptron, BLR-Binary logistic regression.

Reference	Country	Single Modality Description	Multiple Modality Description	Number and Duration of Follow up Data	MCI Range	Machine Learning	Deep Learning	Ensemble Learning	Result
[27]	USA, Canada	✓ MRI Hippocampal Volume, ICV, Entorhinal Volume No Feature Selection	X	6 6 months	Unclear SVM	✓	X	X	Accuracy 71% Sensitivity 96% Specificity 53%
[28]	USA, Canada	✓ MRI 93 ROI Automatic Feature Selection	X	3 6 months	1.5 years	X	✓ CNN	✓	Accuracy 74% Sensitivity 70%% Specificity 78%
[29]	USA, Canada	✓ MRI Whole Patches in Image Automatic Feature Selection	X	6 6 months	3 years	✓ Regression	✓ CNN	✓	Accuracy 76% Sensitivity 42% Specificity 82%
[30]	USA, Canada	✓ MRI Patches of Gray and White Matter Regions Automatic Feature Selection	X	6 6 months	1 year	X	✓ SAE	✓	Accuracy 82% Sensitivity 81% Specificity 82%
[31]	USA, Canada	✓ PET Metabolic Intensity Values Automatic Feature Selection	X	4 6 months	3 year	✓ SVM	X	X	Accuracy 83% Sensitivity 87% Specificity 78%
[32]	USA, Canada	✓ MRI 93 ROI GM	X Automatic Feature Selection	6 6 months	3 years	✓ SVM	X	✓	Accuracy 73% Sensitivity 69% Specificity 77%
[33]	USA, Canada	X	✓ MRI (Temporal Gyrus, Hippocampus), PET (Both ICA)	6 month Clinical Variables No Feature Selection	3 years	✓ Cox Models	X	X	Accuracy 84% Sensitivity 86% Specificity 82%
[34]	USA, Canada	✓ MRI	X Structural Volume Ratio, Godesic Length No Feature Selection	6 6 months	3 year	✓ SVM	X	X	Accuracy 92% Sensitivity 95% Specificity 90%
[35]	USA, Canada	✓ MRI (Cortical thickness	X Hippocampus volume) No Feature Selection	6	Unclear 6 months Not Continous	✓ SVM	X	X	Accuracy 76% Sensitivity 70% Specificity 81%
[36]	USA, Canada	✓	X	6	3 years	✓	X	X	Accuracy 88%

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Table 3 (*continued*)

Reference	Country	Single Modality Description	Multiple Modality Description	Number and Duration of Follow up Data	MCI Range	Machine Learning	Deep Learning	Ensemble Learning	Result
		MRI		6 months					Sensitivity 86%
			Amygdala distance No Feature Selection						Specificity 90%
[37]	USA, Canada	**X**	✓	6	1 year	✓	**X**	✓	Accuracy 90%
			Structural MRI			SVM			Sensitivity 86%
			FDG-PET (Patch Volume, Mean Intensity of GM ROI's) Automatic Feature Selection	6 months					Specificity 83%
[38]	USA, Canada	✓	**X**	8	1 year	✓	**X**	**X**	Accuracy 92%
		MRI		6 months		SVM			Sensitivity 93%
		Gray matter regions Automatic Feature Selection							Specificity 92%
[39]	USA, Canada	✓	**X**	6	Unclear	✓	**X**	✓	Accuracy 79%
	North America	MRI		6 months		Logistic Regression			Sensitivity 87%
		Selection of Voxels Automatic Feature Selection							Specificity 73%
[41]	USA, Canada	**X**	✓	3	1.5 years	✓	**X**	✓	Accuracy 74%
	North America		MRI, PET, CSF	6 months		SVM, SVR			Sensitivity 54%
			MRI - GM 93 ROI PET - Mean Intensity 93 ROI CSF (TAU, A-BETA) Automatic Feature Selection for MRI, PET						Specificity 88%
[40]	USA, Canada	**X**	✓	6	3 years	✓	**X**	✓	Accuracy 89%
	North America		MRI, Neuropsychological	6 months		Sparse Learning Method			Sensitivity 89%
			MRI-Hippocampus, Ventricles MTL, Entorhinal, Fusiform NM- ADASCog, MMSE No Feature Selection						Specificity 92%
[42]	USA, Canada	**X**	✓	5	3 years	✓	**X**	✓	Accuracy 91%
	North America		MRI - Medial Temporal, Etorhinal Cortex Neuropsychological Clinical No Feature Selection	6 months		SVM			Sensitivity 95% Specificity 87%
[64]	Germany	**X**	✓	3	1 year	✓	**X**	**X**	Accuracy 82%
	Europe		MRI-Hippocampal Volume	12 months		SVM			Sensitivity 85%
			CSF - Tau, A-Beta No Feature Selection						Specificity 70%
[43]	USA, Canada	**X**	✓	6	3 years	✓	**X**	**X**	Accuracy 73%
	North America		MRI-Volume based morphometry, Voxel based morphometry PET,CSF Demographics, Medical Medical History, Neuropsychological Automatic Feature Selection	6 months		SVM			Sensitivity 72% Specificity 74%
[46]	USA, Canada	**X**	✓	6	Unclear	✓	**X**	**X**	Accuracy 96%

(*continued on next page*)

Table 3 (*continued*)

Reference	Country	Single Modality Description	Multiple Modality Description	Number and Duration of Follow up Data	MCI Range	Machine Learning	Deep Learning	Ensemble Learning	Result
	North America		rs-fMRI,MRI rs-fMRI- Connectivity matrix for 93 ROI MRI- Free Surfer Features No Feature Selection	6 months		SVM			Sensitivity 94% Specificity 100%
[45]	USA, Canada	**X**	✓	6	3 years	✓	**X**	**X**	Accuracy 78%
	North America		MRI-Atrophy score, Genetic-PHS, MMSE No Feature Selection	6 months		Cox Proportional Models			Sensitivity 79% Specificity 77%
[44]	USA, Canada	✓	**X**	6	3 years	**X**	✓	**X**	Accuracy 79%
	North America	MRI Freesurfer Intensity Values Automatic Feature Selection		6 months			CNN		Sensitivity 84% Specificity 74%
[47]	USA, Canada	**X**	✓	8	3 years	✓	**X**	**X**	Accuracy 93%
	North America		MRI, Genetic, Neuropsychological Assesement MRI-Hippocampal Volume, Texture Value of Voxels, MMSE, APOE-4 MRI-Automatic Feature Selection Others-No Feature Selection	6 months		Binary Logistic Regression			Sensitivity 86% Specificity 83%
[63]	Portuogal	**X**	✓	5	5 years	✓	**X**	**X**	Accuracy 76%
	Europe		Word Recall Test, Cancellation Task Verbal Paired Associate Learning, Cube Draw Digit Span, Raven Progressive Metrics No Feature Selection		1 year	Naive Bayes			Sensitivity 56% Specificity 70%
[48]	USA, Canada	✓	**X**	6	3 years	✓	**X**	**X**	Accuracy 65%
	North America	MRI Cortical Thickness, Surface Area, Volume Sulcal Depth, Gyrus Height Multifeature network, in out network Multifeature network, in out network (*Automatic Feature Selection*		6 months					Sensitivity 70% Specificity 58%
[65]	USA, Canada, Italy	✓	**X**	6	3 years	**X**	✓	**X**	Accuracy 74%
	North America, Europe	MRI-Gray Matter, White Matter Intensity Automatic Feature Extraction		6 months			CNN		Sensitivity 75% Specificity 75%
[49]	USA, Canada	**X**	✓	6	6 months	✓	**X**	**X**	Accuracy 74%
	North America		MRI - Freesurfer CSF- A Beta 42, Peptide, Tau Genetic-APOE4	6 months		SVM			Sensitivity 81% Specificity 71%

(*continued on next page*)

Table 3 (*continued*)

Reference	Country	Single Modality Description	Multiple Modality Description	Number and Duration of Follow up Data	MCI Range	Machine Learning	Deep Learning	Ensemble Learning	Result
			Neuropsychological-MMSE No Feature Selection						
[50]	USA, Canada North America	X	✓ Socio-Demographic Characteristics - Age, Sex, Education Neuropsychological tests - MMSE, ADAS-Cog, RAVLT No Feature Selection	6 6 months	3 years	✓ SVM, KNN, MLP	X	✓	Accuracy 78% Sensitivity 77% Specificity 78%
[62]	USA, Canada	MRI Gray Matter Intensity	Not Clear	✓	✓	✓ SVM	X		Accuracy - 67% Sensitivity - 68% Specificity - 66%
[61]	USA, Canada Australia Australia	X	6 months	Unclear	✓	X	✓ CNN	X	Accuracy - 74% Sensitivity - 73% Specificity - 67%
[60]	USA, Canada North America	✓ MRI patches	Not Clear	✓	X	✓	X SVM	X	Accuracy - 80% Precision - 85% Sensitivity - 82% Specificity - 80%
[59]	USA, Canada, North America	✓ Whole MRI brain image	✓	2 years	Unclear 2 2	✓ CNN attention mechanism	X	X	Accuracy - 99% Sensitivity - 98% Specificity - 100%
[38]	USA, Canada, North America	✓ MRI patches	X	Unclear	Unclear	✓ SVM	✓ SAE	X	Accuracy 92% Sensitivity 93% Specificity 92%
[52]	USA, Canada, North America	✓ MRI Hippocampal MRI Ventricles	X	Unclear	Unclear	✓ SVM	X	X	Accuracy 89% Sensitivity 90% Specificity 88%
[53]	USA, Canada, North America	X MRI 93 ROI	✓	Unclear	Unclear	✓ BLR	✓ CNN	X	Accuracy 77% Sensitivity 79% Specificity 76%
[54]	England, Europe	✓ Whole patches of MRI	X	Unclear	Unclear	X	✓ CNN	X	Accuracy 76% Sensitivity 79% Specificity 76%
[55]	Italy, Europe	✓ Time Frequency EEG data	X	Unclear	Unclear	X	✓ CNN	X	Accuracy 91% Sensitivity 91% Specificity 92%
[56]	USA, Canada, North America	✓ Whole patches MRI Cognitive data	X	Unclear	Unclear	X	✓ CNN Attention mechanism	X	Accuracy 88% Sensitivity 88% Specificity 88%

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Table 3 (*continued*)

Reference	Country	Single Modality Description	Multiple Modality Description	Number and Duration of Follow up Data	MCI Range	Machine Learning	Deep Learning	Ensemble Learning	Result
[66]	USA, Canada, North America	✓ Whole patches MRI Cognitive data	X	Unclear	Unclear	✓ SVM	✓ CNN	X	Accuracy 74% Sensitivity 73% Specificity 72%
[58]	USA, Canada, North America	X Multimodal brain Cognitive data	✓	Unclear	Unclear	✓	X	X	Accuracy 72% Sensitivity 72% Specificity 72%
[65]	USA, Canada, North America	✓ MRI Patches	X	Unclear	Unclear	X	✓ CNN + RNN	✓	Accuracy 81% Sensitivity 82% Specificity 81%
[44]	USA, Canada, North America	✓ MRI brain regions Hippocampus, Ventricles, Amygdala	X	Unclear	Unclear	X	✓ CNN + RNN	✓	Accuracy 73% Sensitivity 71% Specificity 75%
[49]	USA, Canada, North America	✓ MRI brain regions Graph connectivity 93 ROI	X	Unclear	Unclear	X	✓ CNN + RNN	✓	Accuracy 73% Sensitivity 82% Specificity 84% Specificity 82%

researchers can focus their attention.

- It will be interesting to see more experiments on a mix of population from various countries and regions around the world. Consequently, this requires a much larger collaboration among the hospitals and doctors around the globe.[2] There is a large scope for research addressing the creation of a model for a generalized population. As there are few studies that addressed the populations apart from USA and Canada, more number of experiments should focus on AD patients in other parts of the world.
- It will be also interesting to analyze the parameters responsible for AD. How does it vary from region to region and from country to country. A research at this level whereby finding the significant parameters responsible for MCI to AD conversions can give more insights.
- Important challenge in the early prediction of MCI to AD conversion is the identification of the parameters that can report good results in the machine learning process. This would pinpoint towards the necessity for a good feature selection technique. This can be made more specific by creating an algorithm that can find the best set of features and by assigning weight to the features.
- Prediction of MCI to AD conversions within a specific small amount of time is also a challenging task. For example, finding the patients who will convert to AD within the next 3 months or 6 months. Consequently, better studies should be conducted to achieve this.

4. Limitation of the study

The limitations of the existing study is as follows:

- The study is conducted on a selected set of literature from 2017 onwards. Our subsequent work will be to focus on comprehensive literature on Alzheimer's detection from 2012 onwards. This is important for the research community because it will help a new researcher to know the evolution of models and feature extraction from the past.
- The study is focused on finding out the ML papers that identify pMCI, sMCI patients which is the most challenging task. However, we would like to extend our study to identifying AD, MCI, and HC patients.
- A detailed explanation of feature extraction methods is not given in this paper. We are planning an in-depth study on the various feature extraction techniques for classifying pMCI and sMCI.
- We are also planning to focus on a detailed explanation of the various deep learning architectures used for detecting pMCI and sMCI patients. Many studies for pMCI and sMCI patients are performed on medical images using deep neural networks for feature extraction.

5. Conclusion

The parameters responsible for distinguishing MCI to AD converters is not specific and is unknown. This emphasizes the need for good feature selection algorithms that can trace out the best set of parameters out of a big dataset. Moreover, this review also found out a drawback of lack of experiments on various hospital setting data of various countries. A large scale co-operation of AD data will help researchers in experimenting with variables of diverse population and designing a model appropriately, say a single model for generalized population within a country, continent. Etc. In short, the current research requires more generalized models. It is also observed that multiple modalities of data is reporting better results also. This focus on selection of distinguishing features from multi-modalities of data and designing a model

[2] http://www.gaain.org/.

accordingly. Moreover, finding quick MCI to AD converters (say within 6 months) using less number of follow up data is also a challenging task.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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