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Early Identification of Alzheimer's Disease Using Medical Imaging: A Review From a Machine Learning Approach Perspective

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ABSTRACT

Dementia is a medical syndrome resulting in substantial memory loss or deterioration and other cognitive capabilities, beyond the normal aging process. Alzheimer's disease (AD) is the leading cause of dementia in aged adults, affecting up to 70% of the dementia patients, and posing a serious public health hazard in the twenty-first century. With the growing lifespan, the number of AD patients is also increasing, and estimated that by the year 2050, 135 million people will be affected. With age being the predominant dementia factor, the dominance ranges from 1–2 percent in the age group of 65 to 30 percent at 85. AD is a progressive, irreversible and neuro-degenerative disease with a long pre-clinical period, affecting brain cells leading to memory loss, misperception, learning problems, and improper decisions. Given its significance, presently no treatment options are available, although disease advancement can be retarded through medication. Unfortunately, AD is diagnosed at a very later stage, after irreversible damages to the brain cells have occurred, when there is no scope to prevent further cognitive decline. Individual diagnoses of AD are now based mostly on neuropsychological testing and clinical examination, but only post-mortem brain study may confirm the final diagnosis. The use of non-invasive neuroimaging procedures capable of detecting AD at preliminary stages is crucial for providing treatment retarding disease progression, and has stood as a promising area of research. We conducted a comprehensive assessment of papers employing machine learning to predict AD using neuroimaging data. Most of the studies employed brain images from Alzheimer's disease neuroimaging initiative (ADNI) dataset, consisting of magnetic resonance image (MRI) and positron emission tomography (PET) images. The most widely used method, the support vector machine (SVM), has a mean accuracy of 75.4 percent, whereas convolutional neural networks(CNN) have a mean accuracy of 78.5 percent. Better classification accuracy has been achieved by combining MRI and PET, rather using single neuroimaging technique. Overall, more complicated models, like deep learning, paired with multimodal and multidimensional data (neuroimaging, cognitive, clinical, behavioural and genetic) produced superlative results. Our work shows that promising results have been achieved, but still there is a room for performance improvement of the proposed methods, providing assistance to healthcare professionals and clinicians.

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1. INTRODUCTION

The developing countries are witnessing a rise in the population of elderly people because of increase in the people's life expectancy. Although, this can be considered as a positive reality, it may lead to undesirable effects such as rise in the various diseases including AD. Dementia is a medical syndrome resulting in substantial memory loss or deterioration and other cognitive capabilities, beyond the normal aging process [2]. Many variants of dementia exist, of which Alzheimer Disease (AD) and frontotemporal dementia (FTD) being more prevalent types [3]-[5]. Nearly ten million fresh dementia patients are reported every year, with an expectancy of 135 million cases having some form of dementia by 2050 [1]. With age being the predominant dementia factor; the dominance is 1–2% for the age group of 65, however may increase to 30% for the age group of 85. Among the neurodegenerative ailments, nearly 60-90% are categorised to AD dementia subtype [6], which cannot be cured.

Unfortunately, AD is recognised almost at the end stage, after irreversible damages to the brain cells have occurred, where the cognitive decline can no longer be retarded using preventive protocols. It has been proven that behavioural and cognitive symptoms can be reduced using Pharmacological and non-pharmacological treatments, if AD is detected in its early stages [7]. Considering the various available treatment options, current research is focusing on identifying Mild Cognitive Impairment (MCI) individuals haven't yet progressed to dementia, so that the disease progression can be reduced or even prevented. MCI, to a greater extent, can constitute a prodromal stage of dementia, particularly AD [8]. MCI individuals who eventually advance to AD dementia, whose cognitive impairments are not completely manifested, ca be considered as the progression of AD. Hence, distinguishing between MCI individuals advancing to AD dementia and the stable individuals is critical.

Confirmation of AD becomes much easier at later stages where the symptoms of dementia have already manifested using neuroimaging methods and evaluation of cerebrospinal fluid for the existence of neurofibrillary clews, tau proteins and beta-amyloid [9], and temporal cortex atrophy [6]. However, despite the presence of biomarkers in MRI and PET data in the initial phases, detecting MCI to AD advancement in clinical practise poses a great challenge [10],[11]. Furthermore, reliable AD clinical diagnosis remains a tough task, with even the most experienced doctors missing the diagnosis in 10–15 percent of patients [12]. Much of the procedures for diagnosing Alzheimer's disease are time intensive and involve clinician intervention [13], as well as frequent hospital visits, which can be problematic for the elderly. Neuroimaging is becoming more widely utilised because it allows physicians to examine patients' brains even when they are still alive. Early detection of AD can help people get access to medicines that can help postpone some symptoms [14], if the illness hasn't advanced too far [15], and enhance the AD survival rate [16]. To address the issue, research community presently been provided access to large set of longitudinal neuroimaging datasets from healthy, AD, and MCI individuals, including other factors viz. demographic, cognitive assessments, and genetic, stored in open databanks like ADNI (http://adni.loni.usc.edu). Employing the recently established computer assisted methods like machine learning (ML) algorithms, the available datasets may be evaluated and compared and analysed to accomplish classification and automated identification of AD and MCI development [17][18]. Later on, the established tools can assist the clinicians in the forecasting and detection of AD.

The ML framework involves training the classifier using a labelled dataset; neuroimaging findings coupled with medical factors, in order to identify similar elements which can be used to categorise people according to a variable of interest. Recent studies have shown that ML algorithms can accurately classify images from AD, MCI, and healthy subjects [19, 20]. Even though valuable information has been provided by such classification approaches, it remains crucial to predict and ascertain whether MCI subjects will continue to be stable or advance to AD dementia, for these methods to prove a significant clinical impact enabling a medical practitioner to initiate the adapted treatment protocol. The focus of this paper is to examine prevailing ML classification approaches for detecting AD progression, applied to neuroimaging data alongside other factors.

The paper is structured as follows: Section 2 presents the various methods adopted for AD detection, Section 3 compares the performance of the available literature, Section 4 gives the authors perspective, Section 5 summarizes the conclusions from this study.

2. METHODS

Automated AD detection by means of medical imaging and computers can be considered as an image based pattern recognition problem that may be handled in two consecutive stages: feature extraction and pattern classification. Image features capable of representing the patterns of AD are computed during the training stage using quantitative analysis of brain images. Dimensionality reduction of the computed features is performed employing feature selection and/or combination is performed prior to training a supervised classifier [21]. The

trained classifier can be considered as a ‘‘black box”, capable of making predictions using the information gained in the training phase [22]. During the testing phase, the trained classifier is given the same set of extracted, selected and/or combined features for generating the class labels. Figure 1 shows a schematic of a standard automated AD detection system.

In this review, we have selected 41 articles published between 2010 and 2021, employing neuroimaging methods and ML algorithms for predicting MCI to AD progression. A follow-up duration of one year (AddNeuroMed database) and three years (ADNI dataset) is considered for establishing the advancement of MCI to AD, where a subject primarily identified as MCI, is diagnosed with AD (i.e. “progressive MCI” or pMCI) evaluated on clinical assessments (MMSE/CDR scales, and NINCDS/ADRDA assessments) [20][21]. Individuals are classified as having "stable MCI" (sMCI) if identified as MCI at the start of the study and the diagnosis remained the same throughout the study. The following data has been taken from each of the selected studies: (1) Publication year and author(s), (2) sample group, (3) sample count and average age, (4) dataset used, (5) neuroimaging modality and feature extraction, (6) validation approach, (7) classification technique, and (8) performance (% accuracy).

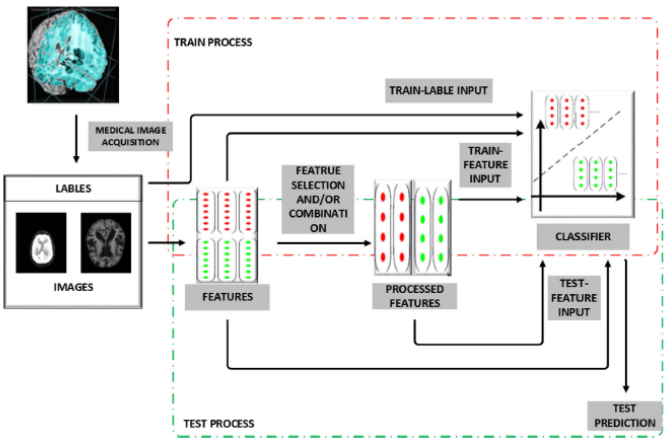

Fig. 1. Schematic of a Standard Automated AD Detection System

3. RESULTS

Table 1 lists the studies that were chosen for qualitative analysis. The most prevalent neuroimaging method was MRI (38 out of 41 research), 2 articles used PET data, a mix of MRI and PET data was used by 10 studies.

Considering variously available public data repositories, ADNI dataset (ADNI-1/2/3, or GO) has been used in 38 articles for obtaining healthy, AD, and MCI subject samples. Two studies have utilised the AddNeuroMed (https://consortiapedia.fastercures.org/consortia/anm/) dataset, and one study have obtained samples on their own. dataset. Both ADNI and Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing (AIBL) were employed by Li *et al.* [23]. Despite the fact that virtually all of the investigations employed the same dataset, the groups differ. The majority of the studies grouped the subjects into four categories: healthy individuals, sMCI patients, pMCI patients, and AD patients.

The size of the selected samples also differed across various studies. The least sample size was 74 subjects in Plant *et al.* [24], and the largest being 3940 individuals in Bae *et al.* [25], with an average sample size of 546 participants. There has been an increasing trend in sample size over time, related to the ADNI database's enhanced data availability. The average age was in the range of 56 to 79 years old.

The most common feature selection methods adopted were whole-brain volumes (26 publications) and glucose metabolism intensity assessments (9 PET studies). There were also 4 research that incorporated genetic variables (APOE4 genotype). Among the other features selected include neuropsychological assessment values (05 studies) and demographic factors viz. age (02 studies). 31 articles employed a single feature, like whole-brain grey matter volumes or 3D MRI data, whereas 10 studies used two or more types. According to the algorithm's findings, the frontal, temporal, and parietal lobes were the major beneficial regions for distinguishing between healthy/sMCI individuals and AD patients. The hippocampus, entorhinal cortex, amygdala, cingulate gyrus, precuneus, and caudal and rostral parts of the medial frontal lobe were the most important regions.

The most prominent machine learning algorithms for classifying patients and detecting likely progression from MCI to AD were the one employing SVM. 19 of 41 investigations have employed SVM, that has been shown to be useful in applications using neuroimaging, particularly in forecasting future clinical outcomes [26]. SVM treats each subject's measurement as a single point in a multidimensional space, with the number of dimensions equal to the total number of features in that dataset. When SVM is combined with additional approaches, it is possible to enhance feature selection and reduce data overfitting, allowing the model to be more generalised (improving the accuracy when applied to dissimilar datasets).

Considering the validation approaches, 35 articles utilised cross-validation, with varying amounts of folds and/ or iterations. The procedure of cross-validation involves splitting the original sample dataset into two partitions, one called the training set for training the algorithm, and the other called testing set for validating the performance of the algorithm.

The performance of ML classifiers is evaluated considering the sensitivity (true positive ratio or % of properly diagnosed pMCI patients) and specificity (true negative ratio or % of healthy or sMCI subjects accurately recognised), or accuracy (% of correctly classified subjects).

Investigations employing MRI achieved an average accuracy of 74.5%, compared to 76.8% for PET scans. With an average accuracy of 77.5 percent, the combination of two strategies produced even better results.

Table 1. Comparison of Literature Studies Listed in Chronological Sequence

Publication year and Author(s)	Sample Group	Sample count (avg. age)	Dataset	Neuroimaging modality & feature extraction	Cross Validation	Classifier	Performance (% accuracy)
(2010) Plant *et al.* [24]	HC AD MCI	18 (64.8) 32 (68.8) 24 (69.7)	Sample collected for the study	MRI: whole-brain volume measures	AD + HS for training MCI as test set	SVM Bayes VFI	pMCI vs. sMCI: SVM: 50 Bayes: 58.3 VFI: 75 AD vs. HC Bayes: 92 SVM: 90 VFI: 78
(2011) Costafreda *et al.* [32]	HC AD MCI	88 (73.6) 71 (74.9) 103 (74.1)	AddNeuroMed	MRI: 3D hippocampal morphometric measurement	Four-fold Cross Validation	SVM coupled with RBF kernel	pMCI vs. sMCI: 80
(2011) Westman *et al.* [33]	HC AD MCI	112 (73) 117 (76) 122 (75)	AddNeuroMed	MRI: whole-brain volume, and age	51 samples	OPLS	AD vs. HC: 82 pMCI vs. sMCI: 73
(2011) Zhang *et al.* [34]	HC AD sMCI pMCI	52 (75.3) 51 (75.2) 56 (75.3) 43 (75.3)	ADNI	MRI + PET: CSF measures, and volume concentration	10-fold	SVM	AD vs. HC: 93.2 MCI vs. HC: 76.4 sMCI: 73.4
(2012) Gray *et al.* [35]	HC AD sMCI pMCI	54 (NA) 50 (-) 64 (-) 53 (-)	ADNI	PET: signal power and comparative variation over 12 months	1000 iterations with 75/25 partition	SVM with RBF kernel	AD vs. HC: 88 pMCI vs. sMCI: 63.1
(2012) Li *et al.* [36]	HC AD sMCI pMCI	40 (73.7) 37 (74.8) 36 (75.3) 39 (75.6)	ADNI	MRI: cortical thickness along with clustering coefficient	Leave-one-out	SVM	AD vs. HC: 96.1 pMCI vs. sMCI: 81.7
(2013) Babu *et al.* [37]	HC sMCI pMCI	232 (76) 236 (74.9) 167 (74.6)	ADNI	MRI: gray matter volume concentration	95(train)/5(test) partition	PBL-McqRBFN	pMCI vs. HC: 88 pMCI vs. sMCI: 79
(2013) Wee *et al.* [38]	HC AD	200 (75.8) 198 (75.7)	ADNI	MRI: cortical thickness and correlation of cortical	10-fold	Mk-SVM	AD vs. HC : 92.35 MCI vs. HC: 83.75

Publication year and Author(s)	Sample Group	Sample count (avg. age)	Dataset	Neuroimaging modality & feature extraction	Cross Validation	Classifier	Performance (% accuracy)
(2014) Apostolova *et al.* [39]	sMCI pMCI HC AD MCI	111 (75.3) 89 (74.8) 111 (-) 95 (-) 182 (-)	ADNI	thickness between pairs of ROIs MRI: hippocampal volumes and demographic, APOE genotype, and CSF measures	Leave-one-out	SVM	pMCI vs. sMCI: 75 AD vs. HC: 80 pMCI vs. sMCI: 68
(2014) Lebedev *et al.* [40]	HC AD MCI	225 (75.9) 185 (75.2) 165 (75.5)	ADNI	MRI: cortical thickness, demographic variables, and APOE4 genotype	Independent test set	RF	AD vs. HC:86.7 pMCI vs. sMCI: 82.3
(2014) Liu M. *et al.* [41]	HC AD	229 (76) 198 (75.7)	ADNI	MRI. whole-brain gray matter volume	10-fold	SVM	AD vs. HC:90.2 MCI vs. HC: 87.2
(2014) Liu F. *et al.* [42]	sMCI pMCI HC AD	236 (74.9) 167 (74.8) 52 (75.3) 51 (75.2)	ADNI	MRI + PET: intensity and volume measures	10-fold	MK-SVM	pMCI vs. sMCI: 70.8 AD vs. HC:94.37 MCI vs. HC: 78.8
(2014) Min *et al.* [43]	MCI HC AD	99 (75.3) 128 (76.1) 97 (75.9)	ADNI	MRI: multi-atlas gray matter volume concentration	10-fold	SVM	pMCI vs. sMCI: 67.9 AD vs. HC:91.64 pMCI vs. sMCI: 72.4
(2014) Suk *et al.* [44]	sMCI pMCI HC AD MCI	117 (75.1) 117 (75.2) 101 (75.8) 93 (75.5) 204 (74.9)	ADNI	MRI + PET: volume and intensity measures	10-fold	DBM	AD vs. HC:95.35 MCI vs. HC:85.67 pMCI vs. sMCI: 75.9
(2015) Moradi *et al.* [45]	HC AD sMCI pMCI	231 (-) 200 (-) 100 (-) 164 (-)	ADNI	MRI: gray matter volume, cognitive scores, and age	10-fold	RF	pMCI vs. sMCI: 81
(2015) Xu *et al.* [46]	HC AD MCI	117 (75.4) 113 (75.6) 110 (75.2)	ADNI	MRI and PET: intensity and volume measures	10-fold	wmSRC	AD vs. HC:94.8 MCI vs. HC:74.5 pMCI vs. sMCI: 77.8
(2016) Zhang *et al.* [47]	AD HC MCI	194 (-) 228 (-) 388 (-)	ADNI	MRI: multivariate hippocampal surface TBM and radial distance	Leave-one-out	AdaBoost	pMCI vs. sMCI: 77
(2017) Long *et al.* [48]	HC AD	135 (76.2) 65 (75.6)	ADNI	MRI: whole-brain white matter and gray matter	10-fold	SVM	AD vs. HC:96.5 pMCI vs. sMCI: with GM: 85.9 with WM: 68.7
(2017) Suk *et al.* [49]	sMCI pMCI HC AD	132 (75.2) 95 (75.1) 226 (-) 186 (-)	ADNI	MRI: gray matter volume	10-fold	CNN	AD vs. HC:90.28 pMCI vs. sMCI: 74.8
(2018) Gao *et al.* [50]	sMCI pMCI HC AD	226 (-) 167 (-) 94 (76.3) 58 (74.2)	ADNI	MRI + PET: hippocampal texture	AD + HS (training)	GPR PLS	pMCI vs. sMCI: GPR:82.2

Publication year and Author(s)	Sample Group	Sample count (avg. age)	Dataset	Neuroimaging modality & feature extraction	Cross Validation	Classifier	Performance (% accuracy)
	MCI	147 (74.8)		features, medical history, and neuropsychological tests	MCI (testing)		PLS:85.5
(2018) Lin *et al.* [51]	HS	229 (-)	ADNI	MRI: hippocampal	Leave-one-out	LASSO + ELM	pMCI vs. sMCI: 79.9
	AD sMCI pMCI	188 (-)		whole- brain cortical			
		139 (-) 169 (-)		volume, cortical thickness, surface area			
(2018) Liu *et al.* [52]	HS	230 (77.1)	ADNI	MRI: whole-brain	10-fold	Multiple Kernel Boost	AD vs. HC:94.65
	AD	200 (76.6)		hierarchical structural			AD Vs. MCI: 89.63
	sMCI	160 (76.2)		network			MCI vs. HC:85.79
	pMCI	120 (75.9)					pMCI vs. sMCI: 72.9
(2018) Lu *et al.* [53]	HS	360 (73.4)	ADNI	MRI + PET: intensity,	10-fold	Deep Neural	pMCI vs. sMCI: 82.9
	AD sMCI pMCI	238 (75) 409 (74) 217 (74)		CSF, and volume measurement		Networks	
(2018) Sun *et al.* [54]	HS	162 (76.3)	ADNI	MRI: GM densities	50/50 partition	LASSO + SVM	AD vs. HC:92.6
	AD	137 (76)					pMCI vs. sMCI: 65.4
	sMCI pMCI	134 (74.5) 76 (74.8)					
(2019) Basaia *et al.* [55]	HS	352 (74.5)	ADNI	MRI: gray matter, white matter	Independent test set	CNN	AD vs. Hc:98
	AD	294 (75.1)		and CSF measures			pMCI vs. sMCI: 74.9
	sMCI pMCI	510 (72.3) 253 (73.8)					
(2019) Cheng *et al.* [56]	HS	112 (-)	ADNI	MRI: gray matter volumes and	10-fold	SVM	AD vs. HC:95.2
	AD	102 (-)		CSF measures			pMCI vs. sMCI: 76.3
	MCI	192 (-)					
(2019) Gupta *et al.* [57]	HS	38 (76.7)	ADNI	MRI + PET: whole-	10-fold	Mk-SVM	AD vs. HC:98.4
	AD	38 (77.1)		brain volume, intensity			pMCI vs. sMCI: 94.9
	sMCI pMCI	36 (74.2) 46 (76.7)		and CSF measures			
(2019) Lee *et al.* [58]	HS	229 (76)	ADNI	MRI: gray matter volumes	10-fold	rDNN + SVM	pMCI vs. sMCI: 88.5
	AD sMCI pMCI	198 (75.4) 214 (75) 160 (74.9)					
(2019) Oh *et al.* [59]	HS	230 (76)	ADNI	MRI data	5-fold	CNN	AD vs. HC: 86.6 pMCI vs. sMCI: 73.9
	AD sMCI pMCI	198 (75.6) 101 (74.1) 166 (74.8)					
(2019) Spasov *et al.* [60]	HS	184 (74.7)	ADNI	MRI: brain volume measures,	90(training)/	CNN	AD vs. HC:100
	AD	192 (75.6)		demographic,	10(testing)		pMCI vs. sMCI: 86
	sMCI pMCI	228 (72.2) 181 (73.7)		neuropsychological, and genetic (APOE4) measures			
(2019) Zhu *et al.* [61]	HS	101 (75.7)	ADNI	MRI + PET: gray matter	10-fold	SVM	AD vs. HC:91.7
	AD	93 (75.4)		volumes and average			pMCI vs. sMCI: 72.6
	MCI	202 (75.1)		intensities			

Publication year and Author(s)	Sample Group	Sample count (avg. age)	Dataset	Neuroimaging modality & feature extraction	Cross Validation	Classifier	Performance (% accuracy)
(2020) Abrol *et al.* [62]	HS	237 (74.3)	ADNI	MRI: 3D whole brain volumes	80(training)/ 20 (testing)	ResNet	AD vs. HC: 89.3
	AD	157 (75.1)	ADNI				pMCI vs. sMCI: 75.2
	sMCI	245 (72.1)	ADNI				
	pMCI	189 (74.2)	ADNI				
(2020) Khatri *et al.* [63]	HS	57 (75.5)	ADNI	MRI: cortical thickness, MMSE	10-fold	SVM with RBFk	AD vs. HC:97.31
	AD	53 (74.4)		surface area, gray matter		Linear SVM	pMCI vs. sMCI:83.38
	MCI	77 (74.1)		volumes, and CSF measures		ELM	
(2020) Lin *et al.* [64]	HS	200 (73.9)	ADNI	MRI + PET: cortical thicknesss	10-fold	LASSO + ELM with Gaussian kernel	AD vs. HC: 84.7
	AD	102 (75.7)		intensity, volume,			
	sMCI	205 (71.8)		existence of APOE4, and			
	pMCI	110 (73.9)		CSF measurements			
(2020) Xiao *et al.* [65]	HS	50 (77.8)	ADNI	MRI: gray matter measurement	10-fold	LR	AD vs. HC:96.10
	AD	51 (75.8)					pMCI vs. sMCI: 72.9
	sMCI	45 (71.8)					
	pMCI	51 (72.5)					
(2021) Bae *et al.* [66]	HS	2084 (76.5)	ADNI	MRI: 3D whole brain volume	70 (training)	CNN	AD vs. MCI: 82.4
	AD	1406 (76.2)		combined with	15 (validation)		
	sMCI	222 (72.2)		neuropsychological scores	15 (testing)		
	pMCI	228 (74.2)					
(2021) Mofrad *et al.* [67]	sMCI	333 (-)	ADNI	MRI: hippocampal entorhinal	15-fold	Ensemble Learning	AD vs. MCI: 77
	pMCI	134 (-)		cortex, ventricles, and neuropsychological measures			
(2021) Phan *et al.* [68]	HS	242 (73.6)	ADNI	PET: 3D images	5-fold	CNN	AD vs. MCI: 83
	AD	237 (75)					
	sMCI	360 (71.7)					
	pMCI	166 (73.9)					
(2021) Syaifullah *et al.* [69]	HS	543 (-)	ADNI	MRI + PET combined with	50/50 partition	SVM	AD vs. HC:88-94.2
	AD	359 (-)		MMSE Scores			pMCI vs. sMCI: 87.8
	MCI	544 (-)					
(2021) Wen *et al.* [70]	HS	46 (72.7)	ADNI	MRI: gray matter volume	10-fold	SVM	AD vs. HC:82 pMCI vs. sMCI: 80
	AD	46 (74.4)					
	MCI	97 (72.9)					
	sMCI	54 (72.6)					
	pMCI	24 (74.2)					
(2021) Zhang *et al.* [71]	HS	275 (76.3)	ADNI	MRI: 3D whole brain	70 (training)	CNN	AD vs. HC:97.35
	AD	280 (76.1)		measurements	15 (validation)		pMCI vs. sMCI: 78.9
	sMCI	251 (77.6)			15 (testing)		
	pMCI	162 (75.1)					

Note. rDNN (Randomized deep neural network), AD-NET (Age-adjust neural network), OPLS (Orthogonal partial least squares), VFI (Voting feature intervals), MMSE (Mini Mental State Examination), ELM (Extreme learning machine), PBL- McqRBFN (Projection-based learning for meta-cognitive q-Gaussian radial basis function network), PLS (Partial least squares), EN (Elastic nets), GPR (Gaussian process regression), MKL (Multiple kernel learning), wmSRC (Weighted multi-modality sparse representation-based classification), HS (Healthy subjects), RF (Random forest), CNN (Convolutional neural network), nl-SVM-RBFk (Non-linear SVM with radial basis function kernel), Res-Net (deep residual neural network), SVM (Support vector machine),ANN (Artificial neural network), AB (Ada-Boost), DBM (Deep Boltzmann Machine), AIBL (Australian Imaging Biomarkers and Lifestyle Flagship Study of Aging), LR (Logistic regression)

SVM and CNN being the widely used classification algorithms achieved mean accuracies of 75.4 and 78.5 percent respectively. Pusil *et al.* [27] achieved the best accuracy of 100 percent with SVM method, but

with a tiny sample size of 54, leaving the classifier ungeneralizable. As for the bigger sample size, the best results (97.2% with 511 samples) was obtained by Guerrero *et al.* [30], followed by Lin *et al.* [31] (97.3% with 164 samples). Plant *et al.* [24] reported the lowest accuracy (50%), by taking a small sample size of 63 individuals.

4. DISCUSSION

In the present study, we looked at 41 papers over the previous ten years employing neuroimaging data and ML algorithms for foreseeing advancement from MCI to AD dementia. Given the complication of neuroimaging analysis, the magnitude of the structural decline and indications present in many AD brain regions makes it difficult to identify MCI patients just by analysing only one individual brain imaging data. Other than accurately differentiating brain images of AD patients and healthy individuals, researchers are also able to forecast the evolution of MCI patients' condition using openly available datasets deposited over the past decades employing recently established ML algorithms. Clinicians can use this information to get a more accurate prognosis and, as a result, create treatment regimens that can delay disease advancement and prevent greater levels of cognitive damage.

Using classification methods built on top of ML algorithms, the 41 papers examined achieved various levels of accuracy. Majority of the articles targeted solely the MCI progression, looking for key characteristics between healthy individuals and patients with AD dementia. Considering the available literature, the hunt for AD biomarkers is far more extensive than the one on forecasting advancement from MCI or even healthy patients. As far as the literature is concerned, studies focusing on the distinction between AD and healthy subjects are more precise, than the ones differentiating sMCI vs pMCI, or combination of both as well as forecasting the progression of AD, thereby indicating the complexity of identifying the biomarkers prior to the manifestation of cognitive decline or dementia.

One of the most difficult aspects of this study was comparing articles with widely disparate methodology, such as distinct samples, pre-processing procedures, varieties of neuroimaging data, and various validation and classification approaches. Studies using more advanced classification techniques coupled with multimodal and multidimensional data have achieved better level of accuracy. Conventional algorithms, such as SVM are making way for advanced ML algorithms built on deep learning techniques like neural networks, capable of detecting minor dementia-related brain morphological changes, thereby improving the classification accuracy. The integration of demographic and cognitive characteristics, as well as genetic data if available, proved to be beneficial for all the methods. However, for the methods to be advantageous for clinicians, there should be a trade-off between the progressed algorithms as well as data, and the methods and data available in the clinical practice. In order for these procedures to be therapeutically effective, the algorithms performance need to be evaluated on varying and diverse group of individuals, rather than the ADNI sample.

Another intriguing effect of incorporating neuroimaging data into machine learning algorithms is the prospect of determining susceptible or prominent brain areas for predicting the transformation from MCI to AD dementia. Considering the accuracy, while the algorithms are beneficial and capable of differentiating the AD brain characteristics, their performance further needs to be evaluated to transfer the whole diagnosis to automated approaches, thereby making clinical judgement vital in the near future.

5. CONCLUSION

Early detection of neurodegenerative diseases using automated methods has shown a great potential in the recent days. Before the manifestation of clinical symptoms, structural deviations tend to appear providing a valuable time period for forecasting morphological and functional changes, beneficial for detecting and delivering effective treatment to retard the progression of neurological disease.

With the establishment of increasingly complex algorithms, research in this field is progressing at a rapid pace, coupled with access to higher levels of processing power, and accuracy of neuroimaging methods. In the near future with a simple scan of a patient's brain, neuroimaging procedures may be directly integrated with expeditious, accurate, and efficient classification algorithms, allowing for the formation of a diagnostic hypothesis. Nevertheless, transforming this information into everyday practice remains a challenge. The solution to the problem lies on enhancing the generalization ability of classifiers when executed on varied and diverse samples, also by balancing the higher accuracy achieved with sophisticated data and promising performance incorporating readily available medical data. Future research should concentrate on producing better results utilising data readily available in clinical practise (viz. sMRI, demographic information, and neuropsychological scores) and employing more generalised models incorporating varied and wide-ranging samples.

In this paper, we started with the diagnosing the various stages of AD, followed by different machine learning methods employed in the classification process such as SVM, CNN, Random Forest, Ensemble learning, Multiple Kernel Boost, and ResNet. Considering the importance of AD classification by machine learning methods, it comes with associated challenges for dealing with the dataset. In this review, we have highlighted the challenges and the solutions to these problems.

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