International Journal of Multimedia Information Retrieval (2021) 10:199–218
https://doi.org/10.1007/s13735-021-00210-9

TRENDS AND SURVEYS

Different techniques for Alzheimer's disease classification using brain images: a study

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Received: 3 March 2021 / Revised: 4 April 2021 / Accepted: 16 April 2021 / Published online: 19 May 2021

Abstract
Alzheimer's disease (AD) is a kind of dementia that is mostly experienced by people who are in the age of early 60s. In AD, brain cells that are responsible for forming memories and cognitive decisions, get affected which causes overall gray matter shrinkage in the human brain. Since AD patients are growing exponentially in the world, researchers are trying to develop an accurate mechanism for diagnosing the disease using brain images. In this paper, several research articles on AD classification are analyzed along with detailed observations. We have summarized as well as compared the research articles based on their classification performance. Although all the reviewed articles have the potential to classify AD, still there lies major future challenges. Among all the reviewed papers, it is found that the recent deep neural network-based classification techniques can produce the most promising results with an average performance rate of 93%.

Keywords Alzheimer's disease (AD) · Artificial neural network (ANN) · Support vector machine (SVM) · Random forest (RF) · K-nearest neighbor (KNN) · Magnetic resonance imaging (MRI)

1 Introduction

Dementia is a neurological disorder where a person experiences exponential memory loss [1]. AD is a common type of dementia occurring in elderly aged people. Memory loss and cognitive declination are some of the most serious symptoms of AD [2]. AD patients experience shrinkage of the overall gray matter present in the human brain [3]. Although there is not any upper age limit for AD, but most of the AD patients are aged between 60-70 years [4]. In research by the National Institute on Aging, it is concluded that more than 6 million patients from the USA are suffering from AD[5]. Similarly, according to the Alzheimer's and Dementia Resources, in India, near around 4 million people have been affecting by AD [6]. Worldwide, the number of AD patients is increasing exponentially.

Diagnosing AD is a difficult task for the neurologist as the traditional tests such as the memory test may not always indicate the AD, because experiencing memory declination is common in normal aging too [7,8]. The tissue structures in the brain are very complex, and hence, one of the major challenges in developing a brain image-based AD diagnosis approach is that it is difficult to visualize the changes that occurred in the brain due to AD [9].

Hence, a proper classification technique is necessary in AD classification using brain images.

1.1 Motivation: brain imaging for AD classification

AD was first discovered by Dr. Alois Alzheimer in 1906 [20], and since then, worldwide, different health organizations have been proposing the mechanisms for classifying AD [21].

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Table 1 Summary of some of the commonly used AD diagnosis approaches

AD diagnosis approaches	Introduced by	Advantages	Limitations
Based on the score obtained from the Mini-Mental State Examination (MMSE), Clinical Impression of Global Change (CIBIC), Alzheimer Disease Assessment, etc.	American Psychiatric Association	The easiest way for the diagnosis of AD. Less technical steps involved [10]	Time-consuming. May not provide accurate results all the time [10]
AD diagnosis based on the blood-based biomarkers	Alzheimer's Precision Medicine Initiative	one the most feasible approaches in worldwide settings [11]	A variety of molecules such as, proteins, peptides, etc., presents in the blood that can be seen in plasma, cellular compartments, etc. To study such a large number of components is difficult and challenging [12]
Aβ/amyloid-Tau/Neurofibrillary-Neurodegenerative (ATN)-based AD diagnosis (the decision is made based on the amount of Aβ/amyloid and Tau deposits)	National Institute on Aging and Alzheimer's Association Research Framework for AD	This approach imposes less financial burden to the patients. Moreover, this approach does not comprise acquaintance to the radioactivity [13]	The differentiation based on this biomarker is sometimes arbitrary as in many diseases other than AD, almost the same type of differentiation can be seen [14]
Transcranial magnetic stimulation (TMS)-based AD diagnosis approach (the concept of a changing magnetic field is used. A paired-pulse TMS differentiates AD patients)	Alzheimer's Disease and Related Disorders Association	The process is noninvasive. In this approach, the patients can continues with their regular routines [15]	Time-consuming (at an average 30 actions within 6 weeks). Patients may experience nervousness before and throughout the treatment
Electroencephalography (EEG)-based AD diagnosis approach (it archives the electrical action of nerve cells and hence ramblingly signifies fundamental intelligence function in brain)	American EEG Society	One major benefit is the capability to perceive brain activity as it discloses in real-time (in ms) [16]	Its difficult to determine the exact brain position from the electrical activity comes [17]
Electronystagmography (EVestG)-based AD diagnosis approach (based on a test that determines the field potential activity in the exterior ear channel in response to vestibular stimuli)	NeuralDx, Monash University, Clayton	The signals are determined painlessly as well as noninvasively. The approach is cost-effective [18]	The signal depends on the patient's physical condition [19]

Some of the popularly used AD diagnosing approaches are discussed in Table 1.

Since all these mechanisms are time-consuming and may not provide accurate results, researchers have been focusing to identify the biomarkers based on the changes that occur in the human brain [22,23].

Brain imaging techniques can provide detain information about the brain cells which can be used to determine the important biomarkers [24,25]. Among all the diagnosing approaches, brain imaging-based classification is one of the most efficient ways to detect AD [26,27]. In Figs. 1 and 2, a comparison of brain images is shown between a CN and an AD patient at the age of 65 for a particular slice position.

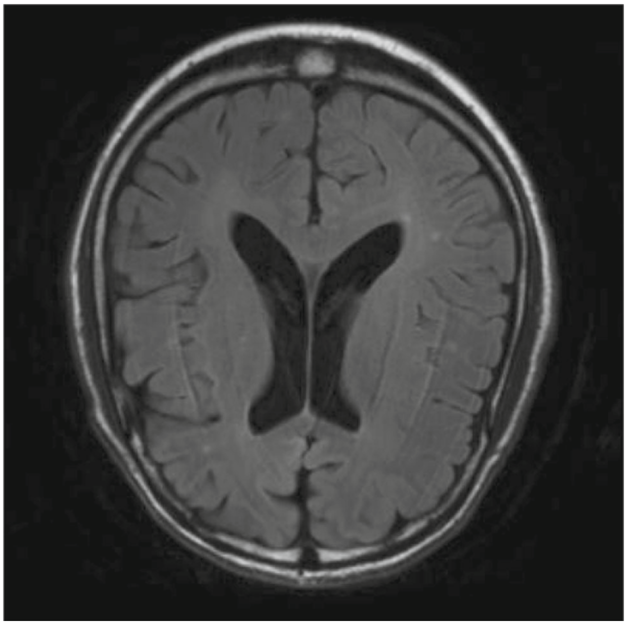

Fig. 1 Brain MR image of a CN, male patient

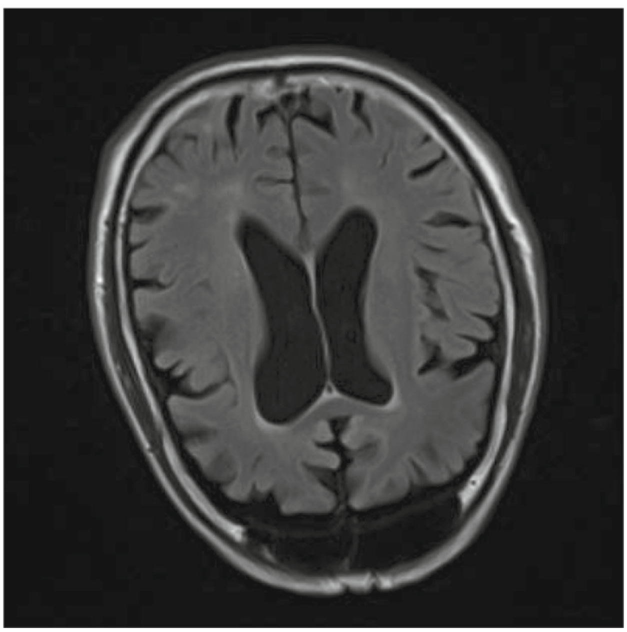

Fig. 2 Brain MR image of a AD, male patient

1.2 Block diagram for AD classification

Although various approaches have been applied for AD classification by different researchers, the most commonly used approaches follows the block diagram shown in Fig. 3.

1.2.1 Data acquisition

The first and the most important step for AD classification is to acquire adequate and accurate data. Acquisition of data for AD classification indicates to obtain brain images, patient's medical history, genetic information, etc. The researchers may get the data from different clinics and hospitals. Some of the most widely used online data sets are Alzheimer's disease neuroimaging initiative (ADNI), Open Access Series of Imaging Studies (OASIS), etc. [28,29].

1.2.2 Pre-processing

Pre-processing is the preliminary step to re-construct an image to make ready for the next major steps [30]. For brain images, the most commonly used pre-processing approaches are skull stripping, de-noising, segmentation, etc. [31]. For AD classification, skull stripping is the most common approach [32,33]. Skull stripping is the process of removing the unwanted pixels from the brain images [34].

1.2.3 Feature extraction and selection

Brain images contains a huge number of information from where only some selective information may help in classification process. The process of extracting the relevant information from the images is called the feature extraction approach [35]. Some of the popularly used feature extraction approaches are partial least squares, principal component analysis, Gaussian mixture model, etc. [36].

Among all the extracted features, contribution of some features may be very less in classification. The process of selecting only the best features among all the extracted features is known as the feature selection [37]. Some of the commonly used feature selection approaches are support vector machine-recursive feature elimination, t test s, statistical dependency, etc. [38].

1.2.4 Classification

Classification is the final output in the form of a decision among a number of possibilities with the help of a classifier [39]. For AD classification from brain images, the most commonly used classifiers are support vector machine, random forest, artificial neural network (ANN), K-nearest neighbor, etc. [40].

1.3 Contribution of our work

Main aim of this survey is to help the researchers to choose one of the best classifiers for AD classification using brain images. The contribution of this article can be summarized as below.

- Some commonly used classifiers namely support vector machine (SVM), random forest (RF), artificial neural

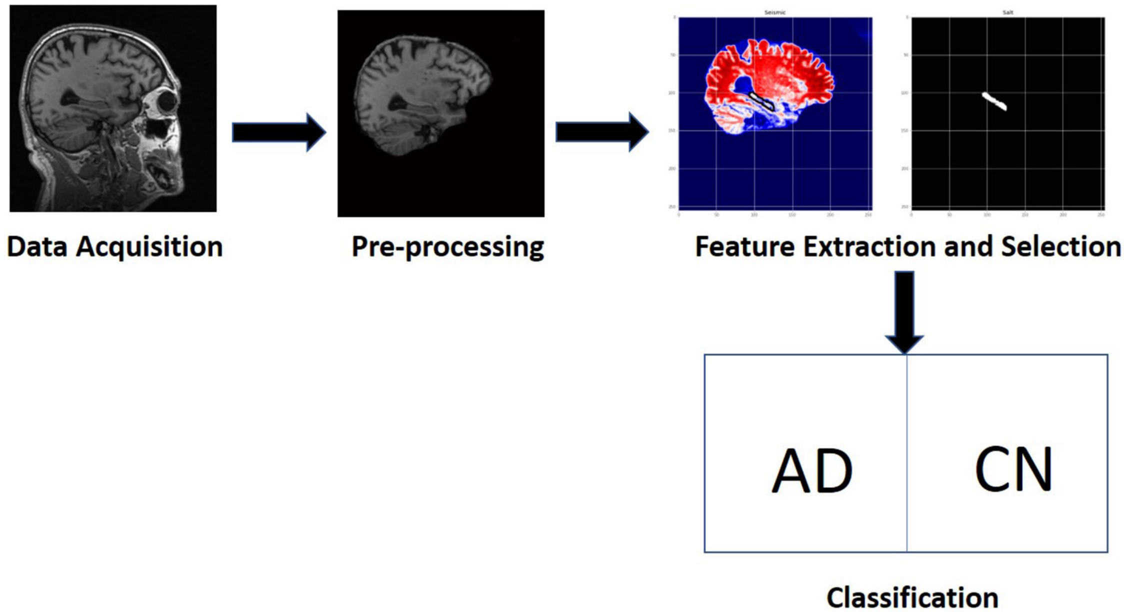

Fig. 3 Block diagram for AD classification

network (ANN), and K-nearest neighbor (KNN) for AD classification are discussed.
- The merits and demerits of each classifiers are discussed and then some recently published research articles based on each of the classifiers are summarized along with their performance comparison.
- A detailed observation from each of the research articles is discussed to present an idea for the future scope of work.

The detailed comparison of this survey work and some other survey paper on AD classification techniques is compared in Table 2.

1.4 Organization of this article

The organization of this article includes the introduction in Sect. 1, followed by the discussion about some of the recently published articles on AD classification in Sect. 2. In Sect. 3, a detailed observation of all the discussed articles is compared along with the performance comparison. In Sect. 4, we have concluded the article along with a short discussion about the future scope of work.

2 Related study on different AD classification methods

Researchers are trying to develop an accurate AD diagnosing approach based on several classification approaches. Some of the related research articles based on some widely used classification techniques are discussed below.

2.1 Support vector machine (SVM)-based AD classification

Support vector machines (SVM) are a supervised learning method widely used in classification purposes [46]. In SVM, each data item is plotted as a single point in n-dimensional space and classification is performed based on the hyperplanes that differentiate the classes. One advantage of SVM is that it can classify well even for the unstructured data [47]. Moreover, SVM works well for multi-dimensional data. One major demerit of SVM is that it cannot work well while working with a large data-set [48] and it is noise sensitive. Some of the SVM-based AD classification methods are discussed below.

Alam et al. [49] proposed a twin SVM-based AD classification approach. The authors have used the dual tree complex wavelet transform (DTWT) and the principal component analysis (PCA) to extract the most discriminative slices and to determine their morphometric changes. For classification, the idea of generalized eigenvalues proximal SVM (GEPSVM) is applied, where two non-parallel optimum hyperplanes for each class are used.

Jongkreangkrai et al. [50] proposed a computer-aided AD classification tool. Authors have determined the volumetric measurements of the hippocampus, amygdala, and the entorhinal cortex using the FreeSurfer toolbox and discriminative features were extracted. Finally, SVM is used to classify AD subjects.

Table 2 Summarization of different survey papers on AD classification approaches

Authors	Title of the survey paper	Publication	Research highlights
Kumar et al. [41]	A Comprehensive Survey: Early Detection of Alzheimer's Disease Using Different Techniques and Approaches	International Journal of Computer Engineering & Technology (IJCET)	1. Compared different research articles on AD classification based on different feature extraction approaches
			2. ADNI is the only data-set for all the compared articles
			3. Only 23 articles are compared
Mareeswari et al. [42]	A Survey: Early Detection of Alzheimer's Disease Using Different Techniques	International Journal on Computational Sciences & Applications (IJCSA)	1. The authors have compared different AD classification techniques
			2. Merits and demerits of different AD classification approaches are compared
			3. No articles on AD classification approaches are discussed and compared
Lohar et al. [43]	A Survey on Classification Methods of Brain MRI for Alzheimer's Disease	International Journal of Engineering Research & Technology (IJERT)	1. The authors have compared different AD classification techniques based on various classifiers
			2. Merits and demerits of different AD classification approaches are not compared
Zheng et al. [44]	Automated identification of dementia using medical imaging: a survey from a pattern classification perspective	Brain Informatics	1. Compared different research articles on AD classification based on different feature extraction approaches
			2. Merits and demerits of different AD classification approaches are not compared
			3. Only 23 articles are compared
Sherin et al. [45]	A Comparative Survey of Feature Extraction and Classification Techniques for Early Diagnosis of ALzhimer's Disease	International Journal of Advanced Research in Computer Science	1. Compared different research articles on AD classification based on different feature extraction approaches and classifiers
			2. Merits and demerits of different AD classification approaches are not compared
			3. Only 25 articles are compared
This literature			1. Compared different AD classifiers and analyzed the merits and demerits
			2. A detail discussion on different research articles on AD classification based on different classifiers is done and compared the performances as well
			3. The datasets for the discussed articles are not only from ADNI but also from other datasets as well

Table 2 continued

Authors	Title of the survey paper	Publication	Research highlights
			4. A sufficient number of research articles are discussed 5. Future scopes of work are discussed thoroughly

In a similar research, a novel AD classification method is proposed by Elshatoury et al. [51]. To find the most discriminate slices from brain images, the Histogram-based approach is used. Based on the majority voting and weighted votingi, most appropriate features were extracted and then SVM is applied for the final classification.

Based on the texture information, Nanni et al. [52] proposed a novel AD classification approach. From each slice of the brain images, the texture information were extracted. From the extracted features, most relevant features were selected using several feature selection algorithms. SVM-based classifier is used to do the final classification.

Zhang et al. [53] proposed an AD classification approach, where the most discriminative features are identified from the training brain images, and then, a landmark identification approach is applied in the testing images. No tissue segmentation approach was required for feature extraction. Finally, SVM-based AD classification approach was applied.

Based on the SVM and recursive feature elimination (RFE) method, Richhariya et al. [54] proposed a novel AD classification framework. A total of 150 MR images for 3 different subject groups (CN: 50, MCI: 50, AD: 50) are acquired. For voxel-wise morphometry analysis, statistical parametric mapping (SPM) toolbox is used. Using the diffeomorphic anatomical registration using the exponentiated Lie algebra (DARTEL) toolbox, all the images are segmented in three parts: gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF). For extracting the relevant voxels, t test-based approach is used, and FreeSurfer toolbox is used for determining the voxel-wise volumetric morphometry. For dimensionality reduction, Fisher score and principle components analysis (PCA) feature selection technique is used. For classification, universum data are used in a feature elimination, support vector machine-based recursive feature elimination (SVM-RFE)-based method.

Performance of the discussed AD classification approaches is compared in Table 3.

From Table 3, it can be observed that among the discussed SVM-based AD classification approaches, the method proposed by Saruar Alam et al. [49] provides the most convincing performance.

2.2 Random forest (RF)-based AD Classification

Random forest is a set of method that functions by constructing a large number of trees (known as the decision trees) in training and produce the output based on the mode of the classes [55]. All the decision trees select their choice of class, and finally the class which gets the majority votes will be the final prediction. One advantage of RF is that it reduces over-fitting and variance; hence, the accuracy is better [56]. One major disadvantage of RF is that the approach is time-consuming while making the decision [57]. Some RF-based AD classification approaches are discussed below.

Gray et al. [58] proposed a RF-based AD classification approach. The authors have used a multi-modality context where the manifolds were built by determining the pairwise likeness resulting by the RF classifiers. The similarities derived from different modalities were wrapped together for generating an embedding which can instantaneously encrypts information of the accessible features. The final classification is done by the help of the coordinates derived from the combined embedding.

Lebedev et al. [59]proposed a novel AD classification approach based on RF classifier. The authors have performed a volumetric measurement of the cortical depth, non-cortical depth, etc., for all the subjects. All the extracted features were evaluated with the inherent characteristic of RF. The proposed method used a total of 10000 trees and applied a recursive feature elimination (RFE) method to select the most relevant features where Gini index was used as the elimination criteria.

Oppedal et al. [60] proposed a novel AD classification approach. In first step, the authors have performed an operation to construct a white matter lesions (WML) maps from the input images. In second step, the authors have used a local binary pattern-based approach to extract texture information from the maps. Finally, all the relevant texture features are extracted and a RF-based classification is performed to classify AD subjects.

Ardekani et al. [61] proposed a novel RF-based classification approach. The hippocampus in brain is targeted as the region of interest and performed a segmentation operation to separate it. The volume of the hippocampus is measured and used as a biomarker. Classification is performed based on a RF approach consisting of 5000 decision trees.

Table 3 Performance comparison of different SVM-based AD classification techniques

Authors and articles	Performance			
	Accuracy (%)	Sensitivity (%)	Specificity (%)	Area under curve (AUC) (%)
Alam et al. [49]	94.67	95.42	93.90	–
Jongkreangkrai et al. [50]	–	–	–	89.06
Elshatoury et al. [51]	69.5	–	–	–
Nanni et al. [52]	86.6	–	–	–
Zhang et al. [53]	88.30	79.61	94.69	87.15
Richhariya et al. [54]	76.8	67.4	77.17	–

In a similar research, Maggipinto et al. [62] proposed an AD classification approach from the diffusion tensor imaging (DTI). The authors have used a diffusion tensor fitting operation for all the subjects, and then, fractional anisotropy (FA) as well as the mean diffusion (MD) maps are mined which are then applied as inputs in a tract-based spatial statistics (TBSS) analysis model. To select the most discriminative features, the authors have used Wilcoxon rank sum test and the ReliefF algorithm is used algorithm.

A Random forest-based AD classification method is proposed in the literature [63]. The authors have used FreeSurfer toolbox for pre-processing and segmenting the input images. For the selection voxel of interests, U-Net-based deep learning method is used. Gini impurity index-based feature selection algorithm is used to extract the most relevant features. Final classification is performed by using the random forest algorithm, where decision trees are built based on different bootstrap samples

The average performance of the discussed articles is compared in Table 4.

From Table 4, it can be observed that among all the discussed AD classification approaches based on RF classifier, the method proposed by Gray et al. [58] can produce the best outcome.

2.3 Artificial neural network (ANN)-based AD classification

ANN is a set of neurons (artificial) that are linked each other and can communicate by transmitting signals to each other functions as similar as the neurons in the biological brain [64]. One major advantage of ANN is that it can learn from the environment and also can improve its outcome in each iteration [65]. One major drawback of ANN is that it never shares the inside details why and how the output appears [66]. Some of the research articles on ANN-based AD classification are discussed below.

Basaia et al. proposed a novel method for classifying AD subjects [67]. The volumetric measurements of the brain images are used as biomarker, and based on that a 3D CNN is developed. To construct the network, the authors have used 12 recurrent blocks of convolutional layers (CL), one rectified linear unit (ReLU), one fully connected layer, and an output layer. The authors replaced the max-pooling layers by the CLs.

An AD classification approach from brain MRI is proposed by Jain et al. [68]. Since to train a CNN model a huge number of training data is required, the authors have used the transfer learning technique for the classification. Based on the entropy values, the authors have compared and considered the slices that contains more information. Finally, the authors have developed a PESECTL-based mathematical model for accurate classification.

Lu et al. [69] proposed a DNN-based approach for AD classification. Initially, the authors have performed the gray matter segmentation operation, and then, patch-wise features were extracted to train a multimodal and multiscale deep neural network (MMDNN). The constructed network have two parts: in the first part 6 independent DNN is considered for each modality and the second part is used to fuse the information mined from the 6 DNNs.

By combining convolutional and recurrent neural networks (RNN), Liu et al. [70] proposed a novel AD classification approach. The authors have converted the 3D images into a set of 2D slices and then combined the CNN and RNNs to learn the intra- and inter-slice information for classification. 2D CNNs are constructed for capturing the features from each slice of the images, whereas the gated recurrent unit (GRU) of RNNs are trained for learning and assimilate inter-slice information.

Liu et al. [71] proposed a novel approach for AD classification-based on neural networks. To train the multi-level and multimodal information from the brain images, the authors have constructed a cascaded CNN. Initially for transforming the input images into dense top-level features, several 3D CNNs were built. After that, a 2D CNN trailed by the softmax layer is built to collaborative the top-level information. Lastly, the learned features were united with the help of a fully connected layer trailed by the softmax layer.

Table 4 Performance comparison of different RF-based AD classification techniques

Authors and articles	Performance			
	Accuracy (%)	Sensitivity (%)	Specificity (%)	Area under curve (AUC) (%)
Gray et al. [58]	89.0	87.9	90.0	–
Lebedev et al. [59]	–	88.6	92.0	–
Oppedal et al. [60]	87	–	–	–
Ardekani et al. [61]	82.3	86.0	78.2	–
Maggipinto et al. [62]	87	–	–	–
Kim et al. [63]	85.03	–	–	93

Table 5 Performance comparison of different ANN-based AD classification techniques

Authors and articles	Performance			
	Accuracy (%)	Sensitivity (%)	Specificity (%)	Area under curve (AUC) (%)
Basaia et al. [67]	98.0	99.0	98.0	–
Jain et al. [68]	95.73	–	–	–
Lu et al. [69]	82.4	94.23	86.3	–
Liu et al. [70]	91.2	91.4	91.0	95.3
Liu et al. [71]	93.26	92.55	93.94	95.68

Table 6 Performance comparison of different KNN-based AD classification techniques

Authors and articles	Performance			
	Accuracy (%)	Sensitivity (%)	Specificity (%)	Area under curve (AUC) (%)
Acharya et al. [76]	94.54	96.30	93.64	–
Kamathe et al. [77]	87	–	–	–
Tufail et al. [78]	68.06	–	–	–
Kruthika et al. [79]	96.31	91.27	89.90	–
Taqi et al. [80]	91.4	–	–	–

The performance comparison of the discussed classification approaches is given in Table 5.

From Table 5, it can be seen that the AD classification approach proposed by Basaia et al. [67] can perform well among all the discussed CNN-based AD classification methods.

2.4 K-nearest neighbor (KNN)-based AD classification

KNN is a classification approach where initially all the obtainable cases are stored, and then, based on the similarity index, new data are classified [72]. For a particular point, the class decides by determining the class that is chosen by most of its neighbors [73]. One advantage of KNN is that it is very simple to understand as well as to implement [74]. It works well in multi-class problem. One major drawback of KNN is that, since every time it keeps checking its neighbors, it is very slow to implement [75]. Some AD classification approaches based on the KNN are discussed below.

Acharya et al. [76] proposed an AD classification method based on KNN classifier. Initially, feature extraction is done by using several techniques such as Contourlet transform (CoT), dual tree complex wavelet transform (DCWT), Shearlet transform (ST), etc. After the feature extraction, Student's t test-based feature selection approach was applied to eliminate the irrelevant data. Finally, KNN is used for the classification of AD subjects.

Kamathe et al. [77] proposed a robust optimized feature set-based automatic classification of AD. The main focus of authors is to extract the most relevant features by using the gray level co-occurrence matrix (GLCM) method. For boosting the performance accuracy, authors have used the Adaboost-based mechanism. Extracted feature sets are optimized, and classification is done accordingly by using the KNN classifier.

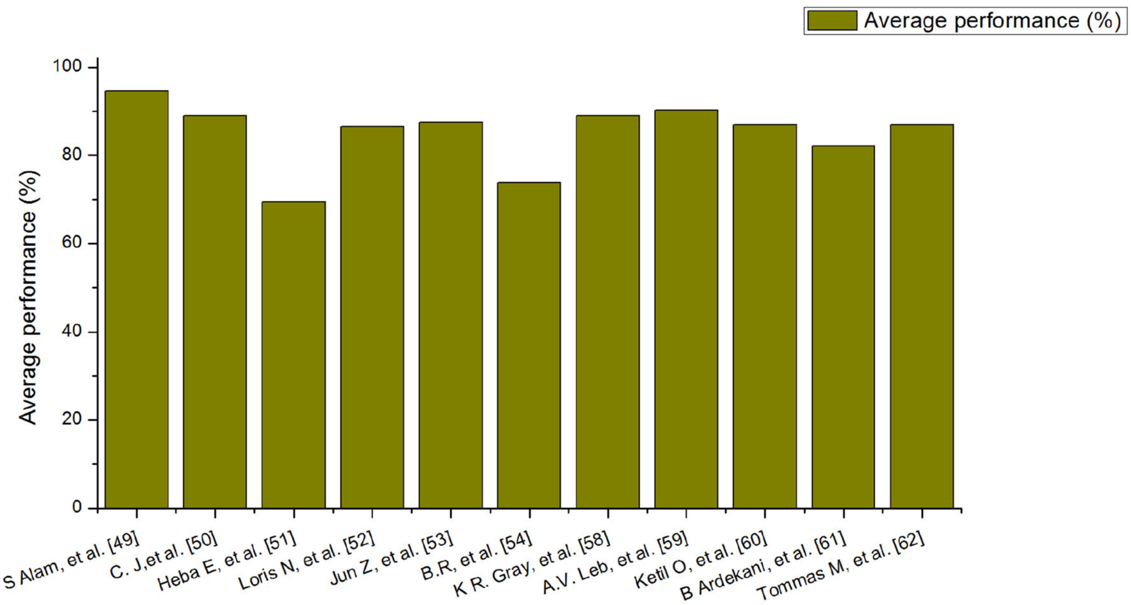

Fig. 4 Average performance comparison graph, part 1

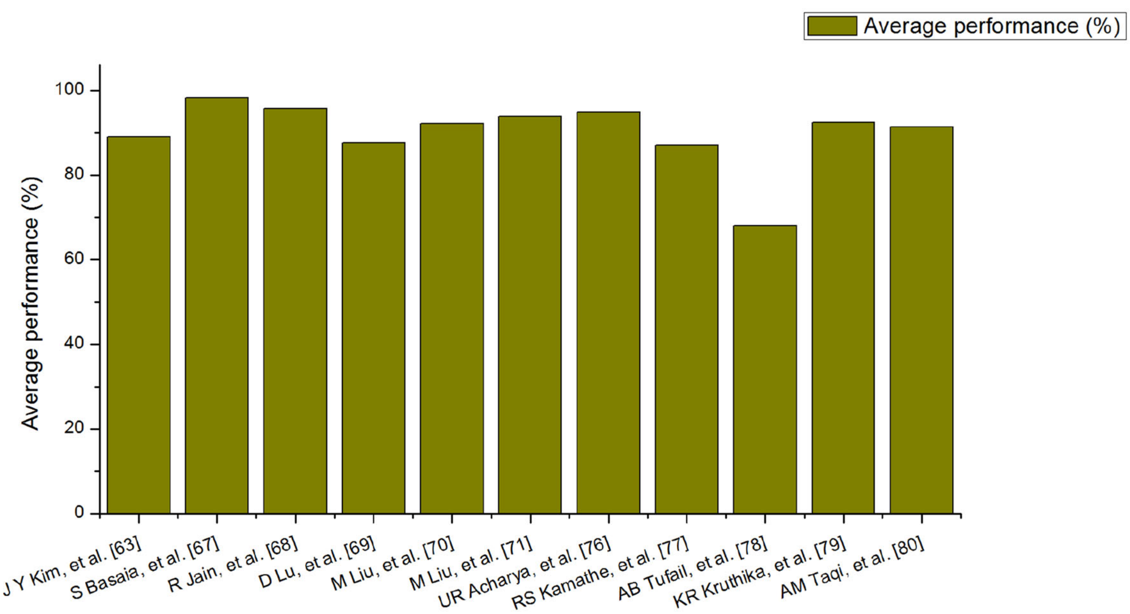

Fig. 5 Average performance comparison graph, part 2

Using the structural MRI, Tufail et al. [78] proposed to develop a mechanism to classify AD by several classifiers. To extract the discriminative features, the authors have adopted the independent component analysis (ICA)-based approach. After getting the extracted features, authors have applied three different classifiers namely SVM, ANN, and KNN and compared the output results. As claimed by the authors, ICA+KNN gives a convincing results.

In a similar research, Kruthika et al. [79] proposed a multistage classifier-based approach for AD prediction and retrieval. To extract the appropriate features, the authors have adopted the particle swarm optimization algorithm (PSO). After extracting the features, the authors have designed the approach according to the two stage classifiers. In first stage, Gaussian naive Bayes classifier is used, and in second stage SVM and KNN classifiers are used. As claimed by the authors, KNN provides a convincing results.

For classifying AD, Taqi et al. [80] proposed a mechanism. The authors have proposed an idea of an invariant interest point descriptor depending on the normalized Hu moment invariants (NHMI). For extracting the features from MRIs, 7 Hu moments are determined and then normalized

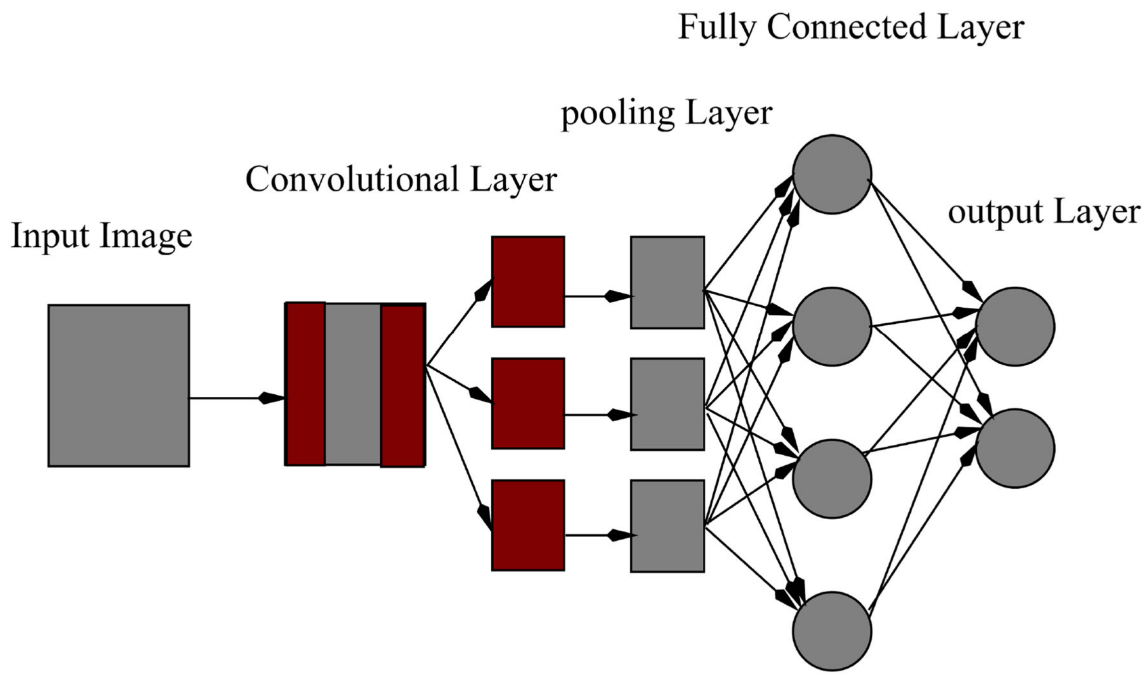

Fig. 6 Steps involved in AD classification approach using ANN approach

the features. Based on the extracted features, classification is performed. Two different classifiers are used by the authors namely SVM and KNN. The authors have claimed that KNN classifier can produce a convincing results.

The average performance comparison of different AD classification approaches based on KNN classifier is shown in Table 6.

From Table 6, it can be noticed that among all the discussed articles on AD classification based on KNN classifier, the method proposed by Acharya et al. [76] can produce a better convincing results.

3 Results and discussion, and comparison on different AD classification methods

In this study, several recently published articles on AD classification using various classification methods are discussed and summarized their performances. The graphical representation of the average performance of all the discussed classification approaches is shown in Figs. 4 and 5.

From Tables 3, 4, 5 and 6 as well as from the graphical representation in Figs. 4 and 5, it can be seen that the highest performance is obtained by Basaia et al. [67], which is around 98%. The authors in this study have acquired data from Alzheimer's Disease Neuroimaging Initiative (ADNI). All input images were normalized and segmented in three parts namely gray matter (GM), white matter (WM), and the cerebrospinal Fluid (CSF) by an expert observer using the statistical parametric mapping (SPM) and diffeomorphic anatomical registration exponentiated Lie algebra (DARTEL) toolboxes. In the CNN architecture used by the authors, in input layer 3D T1-weighted images are used. The input layer is followed by a total of 12 recurrent blocks of convolutional layers, an activation layer (ReLU), and an output layer. The basic architecture of the method proposed by the authors is shown in Fig. 6.

Though the performance claimed by [67] is satisfactory, but instead of performing by some automatic algorithms the authors have performed the segmentation and the normalization operations manually using SPM toolbox which required much expertise knowledge as well as it may not produce accurate results all the time.

For each of the discussed research articles, the detail observations are summarized in Table 7.

From Table 7, it can be noticed that, though each of the classification methods discussed in this article have the capabilities to produce convincing results, still there lies some scopes for further improvements.

Table 7 Summarization of all the discussed AD classification approaches

Authors	Year	Publication	Data-sets	Observations
Alam et al. [49]	2017	Journal of Healthcare Engineering	ADNI	1. Only 172 subjects are considered for the study 2. For feature extraction and reduction, the authors have used the principal component analysis (PCA) approach which cannot explore the spatial information [81]
Angkrai et al. [50]	2016	Journal of Physics	ADNI	1. For cortical thickness measurement, the authors have used the FreeSurfer toolbox that may introduce biases that could require statistical adjustments [82]
Elshatoury et al. [51]	2019	Journal of Alzheimer's Disease	ADNI	1. The authors have not performed any noise filtering technique and used Histogram-based approach for feature extraction, which is noise sensitive [83]
Nanni et al. [52]	2019	Artificial Intelligence in Medicine	ADNI	1. The authors have used the Fisher score (FS) for feature selection which is computationally expensive as it has a low variable acquisition capacity [84]
Zhang et al. [53]	2017	Journal of Biomedical and Health Informatics	ADNI	1. The authors have used the landmark-based feature extraction approach which is dependent on the image acquisition conditions, camera resolutions, movements, etc. [85]
Richhariya et al. [54]	2020	Biomedical Signal Processing and Control	ADNI	1. The authors have used only 150 images for the experiment which is less in number 2. For important pre-processing steps, such as brain image segmentation, voxel selection, etc., authors have used some toolboxes, which requires expertise knowledge
Gray et al. [58]	2013	NeuroImage: Clinical	ADNI	1. The authors have extracted the features manually by using some pre-installed toolboxes which required expertise knowledge and may not provide accurate results all the time
Lebedev et al. [59]	2014	NeuroImage: Clinical	ADNI	1. For volumetric measurement, the authors have used the FreeSurfer toolbox that may introduce biases that could require statistical adjustments [82]
Oppedal et al. [60]	2015	International Journal of Biomedical Imaging	DemWest cohort and ParkWest cohort, Stavanger, Norway	1. The authors have used the local binary pattern (LBP) concept which is sensitive towards noise [86]
Ardekani et al. [61]	2017	Journal of Alzheimer's Disease	ADNI	1. The authors have acquired data for only 164 subjects which is very less in number
Maggipinto et al. [62]	2017	Physics in Medicine and Biology	ADNI	1. The authors have acquired data for only 150 subjects which is very less in number

Table 7 continued

Authors	Year	Publication	Data-sets	Observations
Kim et al. [63]	2021	Psychiatry investigation	Catholic Brain Health Center, Yeouido St Mary's Hospital, the Catholic University of Korea	1. Authors have considered only cortical and subcortical volumes of brain images. Ignoring some other important modalities of brain may affect in the classification accuracy
Basaia et al. [67]	2018	NeuroImage: Clinical	ADNI	For following up the data of convert to MCI (c-MCI), and stable MCI (s-MCI) patients, a period of 36 months is taken. Longer follow-up may help the model to learn about the clinical changes more accurately
Jain et al. [68]	2019	Cognitive Systems Research	ADNI	1. The authors have acquired data for only 150 subjects for training and testing which is very less in number
Lu et al. [69]	2018	Scientific reports	ADNI	1. The authors have performed some of the important pre-processing steps such as skull stripping by using the FMRIB's Linear Image Registration Tool (FLIRT) which required much expertise knowledge
Liu et al. [70]	2018	Original Research	ADNI	1. The authors have acquired only 93 AD and 100 Cognitively Normal (CN) subjects for training and testing which is very less in number
Liu et al. [71]	2018	Neuroinformatics	ADNI	1. The authors have acquired only 93 AD and 100 cognitively normal (CN) subjects for training and testing which is very less in number
Acharya et al. [76]	2019	Journal of Medical Systems	University of Malaya Medical Centre, and the Harvard Brain Atlas	1. For feature selection, the authors have used a t-test approach, which is sensitive toward Type I error, i.e., if the variances or the group sizes are paired negatively then it may lead to incorrect results [87]
Kamathe et al. [77]	2017	Ictact Journal on Image and Video Processing	Open Access Series of Imaging Studies (OASIS)	1. The authors have used the gray-level co-occurrence matrix (GLCM) which is computationally expensive as it contains many zero elements [88] [89]
Tufail et al. [78]	2012	International Journal of Biomedical and Biological Engineering	OASIS	1. The authors have acquired only 25 AD and 83 cognitively normal (CN) subjects for training and testing which is very less in number
Kruthika et al. [79]	2018	Informatics in Medicine Unlocked	ADNI	1. The authors have used the particle swarm optimization (PSO) algorithm for feature selection which has a low convergence frequency in the iterative procedure [90]
Taqi et al. [80]	2017	International Journal of Advanced Computer Science and Applications	ADNI	1. The authors have acquired only 75 AD and 50 cognitively normal (CN) subjects for training and testing which is very less in number

Table 8 Summarization on the future scope of studies for all discussed AD classification approaches

Authors and articles	Algorithm/paradigm	Future scope of studies
Alam et al. [49]	Dual-tree complex wavelet transform (DCWT), principal component analysis (PCA), linear discriminant analysis (LDA), and twin SVM-based classification	The research can be further extended to design a 3D DTCWT, and a multi-resolution study-based approach for extracting the most relevant features. Moreover, a CNN-based classification model can be designed using 3-D MR images
Jongkreangkrai et al. [50]	1. FreeSurfer toolbox for determining cerebral image features (hippocampus, amygdala, and entorhinal cortex)	To increase the training accuracy, more nos of subjects can be integrated. Moreover, various machine learning-based approaches can be compared for improving the classification performance
	2. Hippocampal, and amygdala's volumes are determined	
	3. Extracted features are used in an SVM-based classifier	
Elshatoury et al. [51]	Out of 160 slices in every 3D brain image, the most important slices are selected. Based on the selected slices, some of the machine learning-based classifiers, such as, decision trees, logistic regression, SVM, KNN, majority vote, weighted vote, etc., are used and compared the performances	The authors have performed histogram-based analysis on the slices of brain images in sagittal plane. The analysis can be further extended by considering all three directions, i.e, axial, sagittal, and coronal, as all directions may contain important features
Nanni et al. [52]	1. Introduced two ensembles (one for combining the SVMs (top), which are trained on markers built from MRI voxels, and another for combining the SVMs (bottom), which are trained on 4 different texture descriptors	The texture descriptors (TD) used are, Gabor, WAVE, Gaussian of Local Descriptors (GOLD), and Ternary Coding (TC). The model can be further extended by implementing some more descriptors, including 3D TD. Moreover, more tests can be performed by using CNN-based methods
	2. For feature selection, Fisher score (Fi), kernel partial least squares (KPS), and aggregate selection (AS) methods are used	
	3. Two SVM groups are ensembled based on weighted sum-based rules for producing a final result	
Zhang et al. [53]	1. For each of the input images, 27 registered scans are averaged and then images are linearly aligned according to the Colin27 template	Total 72 spatial and 50 longitudinal features are extracted in the model. In future studies, more important features can be detected and extracted using appropriate mechanisms. The model can be further extended to multi-modal data (MRI, PET, fMRI, etc.)
	2. Voxel-wise comparison is performed amongst different subject groups and extracted morphological features	
	3. A regression-forest-based method is used for landmark detection in testing images	
	4. SVM classifier is used for final classification	
Richhariya et al. [54]	1. All the input images are segmented in three parts (GM, WM, CSF) using the DARTEL toolbox	1. The classification method is computationally expensive, as it uses the concept of universum data. In future studies, more research may be done in selecting most appropriate universum data
	2. From all the input MR images, voxel-wise volumetric and morphometric information are extracted using FreeSurfer and SPM toolboxes	2. Only 150 number of MR images are acquired for this study. A large number of data may be acquired for better training accuracy
	3. For feature extraction, t test, and for feature selection, fisher score, and PCA based approaches are used	
	4. For classification, universum data are used in SVM-RFE-based method	

Table 8 continued

Authors and articles	Algorithm/paradigm	Future scope of studies
Gray et al. [58]	1. For multi-modal features selection (MRI, PET, CSF, genetic features), random forest (RF)-based approach is applied	1. The authors have used manifold learning approach. Some other relevant techniques can also be tried to boost the performance
	2. Similarity matrices are embedded, and multi-dimensional scaling (MDS) is applied for generating a multi-modal classification model. RF is used for final classification	2. For multi-modal classification, MDS may not provide accurate results all the time. Some other multi-modal classification techniques can be tried
Lebedev et al. [59]	1. Using the FreeSurfer toolbox, volumetric segmentation of each MRI is performed, and then, by applying a linear model based approach, 41 intra-ranial Volume (ICV) are selected	1. Since, autopsy data are not present; it is possible that there may be some diagnostic mislabeling in the dataset that can produce wrong diagnosis of data. Some computational approach may be designed to identify he mislabeled data
	2. For feature extraction, principal component analysis (PCA)-based approach, and for feature selection, recursive feature elimination (RFE) method is used	2. For training the model, offline or batch learning method is used, where after training, the model cannot be modified. Instead of that an online mechanism for training purpose may be more beneficial, where the model can be modified as per the requirements
	3. For final classification, random forest-based approach is used	
Oppedal et al. [60]	1. Using SPM8 toolbox, white matter lesions (WML), and the white matter (WM) are segmented from brain images	1. In future, some pre-processing steps, such as denoising, normalization, etc., can be added to improve the accuracy
	2. From each of the RoI's (WML and WM), local binary pattern (LBP), and the contrast-based features are selected, and then, statistical features are determined	2. The authors have ignored texture features, which can be considered in future work for reliable investigation
	3. A joint mechanism for feature selection and classification is performed using a random forest-based approach	
Ardekani et al. [61]	1. Using a priori algorithm, the locality of both the hippocampus (left and right) are determined. To calculate hippocampal volumetric integrity (HVI) (portion of non cerebrospinal fluid (CSF) hippocampus regions), histogram and expectation maximization (EM)-based analysis framework is applied	1. For the study, to determine the brain changes in MCI to AD conversion, authors have followed up the patient's brain images on yearly basis. Instead of following up once in a year, a shorter period, such as, once in a six months may produce more detail information about the brain changes (especially hippocampus region changes)
	2. For classification, random forest-based algorithm is used, along with the out-of-bag (OOB) accuracy estimation approach	2. Instead of considering only one biomarker (HVI), the work may be further extended by including some more AD biomarkers
		3. The concept of multimodalities of brain images can also be included in future study.
Maggipinto et al. [62]	1. Some important pre-processing steps, such as, skull stripping is performed using the functional magnetic resonance imaging of the brain (FMRIB) Software Library (FSL)	1. For the study, only 150 subjects are considered, which may be further increased in future
	2. From each of the input diffusion tensor images, a solo diffusion tensor is fixed at each of the voxels to determine fractional anisotropy (FA) and the mean diffusivity (MD)	2. Most of the steps involved in this classification work are done by some toolboxes/software, for which expertise knowledge may be required. In future, some automatic techniques for those steps can be designed
	3. Using the tract based spatial statistics (TBSS) in FSL toolbox, frame on the white matter fiber tracts are mined	

Table 8 continued

Authors and articles	Algorithm/paradigm	Future scope of studies
	4. For statistic analysis, Wilcoxon rank sum test and the ReliefF algorithm is used. Random forest-based classifier is used for final classification	
Kim et al. [63]	1. Pre-processing is done using FreeSurfer toolbox	1. For the proposed AD classification method, the authors have considered only cortical and subcortical volumes of brain images. In future studies, some more important modalities of brain may also be considered
	2. U-Net-based deep learning architecture is used for volume of interests' segmentation	2. Authors have acquired data from a single data center. In future, more data from several data centers may be acquired for performance comparison
	3. Random forest classifier is used for final classification	
Basaia et al. [67]	deep learning-based architecture is proposed by the authors, where inputs are 3D MR images, and the network consist of (i) twelve repetitive blocks of convolutional layers (CLs), (ii) an activation layer (ReLu), (iii) fully connected layer, (iv) output layer. The architecture of this network is different, because, in place of pooling layers, CLs are used by taking the stride value as 2. Output layer predicts the image class (i.e, AD/MCI/CN, etc.)	1. For following up the data of convert to MCI (c-MCI) and stable MCI (s-MCI) patients, a period of 36 months is taken. Longer follow-up may help the model to learn about the clinical changes more accurately
		2. The model is designed to work only with the image information. In future, it can be improved to work with multi-modal information, such as genetic information, cognitive information, etc.
		3. The model can be further extended to predict early stages of AD/MCI
Jain et al. [68]	Transfer learning-based VGG16 architecture is proposed by the authors. Some important pre-processing steps, such as skull stripping, motion correction, etc., are performed using FreeSurfer toolbox. From each input brain images, the most relevant slices are selected for further processing. The slices are selected based on their entropy information and forwarded to the proposed VGG model. The model of the network is designed to work on a set of operations, like convolution operation, max-pooling operation, dropout regularization, nonlinearity layers, and fully connected layers	1. In future works, some other neural network-based architectures, such as inception network, residual network, etc., can be used to build the classifier
		2. The performance may be improved by introducing the concept of fine-tuning
Lu et al. [69]	1. The authors have used FreeSurfer toolbox for segmenting gray matter (GM), and white matter (WM) from the input brain images. All the GM images are further subdivided in 87 region of interests (RoIs) to extract patch-wise features	1. This is a challenging task to understand the patho-physiologically consequential explanation of features mined by the DNN for classification, which remains as a significant future research area
	2. Based on the features extracted from the MR and PET images, a multimodal and multiscale deep neural network (MMDNN) is designed for the classification	2. Large numbers of data may be acquired to train the model for getting the classification performance more accurately

Table 8 continued

Authors and articles	Algorithm/paradigm	Future scope of studies
	3. The proposed network can be divided in two parts; in first part, 6 DNN are there to extract the features, and in second part, 6 more DNN are there to fuse those features. For training, two approaches are used, namely unsupervised pre-training and supervised fine-tuning	
	4. Finally, each of the parameters of MMDNN are tuned together for final classification	
Liu et al. [70]	1. All input 3D FDG-PET images are decayed into a set of 2D-slices, and divided in few ensembles, where each ensemble consists of a no's of 15 slices	1. The extracted features may not have adequate clinical information to visualize and interpret. Instead of considering the whole brain region, some region of interests can be chosen based on the pathological changes occurred in AD
	2. A 2D-CNN-based framework is designed and trained for extracting the intra-slice features	
	3. For extracting interslice information, two stacked BGRUs are built	
	4. All extracted features are passed through 2 fully connected layers followed by a softmax layer for the final classification	
Liu et al. [71]	1. A set of pre-processing steps are performed, such as skull stripping, cerebellum removal, etc., by using some toolboxes	1. For the proposed multi-modal classification approach, only MRI and PET information is used. In future studies, some more modalities of brain imaging also can be included
	2. Several deep CNN are constructed and trained about the most discriminative properties of MR and PET images based on the local image patches. Each layer of the proposed CNN combines the low-layer feature maps for generating higher-level features	2. The extracted features may not have adequate clinical information to visualize and interpret. Instead of considering the whole brain region, some region of interests can be chosen based on the pathological changes occurred in AD
	3. The model can able to learn standard multi-level as well as the multi-modal properties from various imaging modalities, such as MRI and PET, for the final classification	
Rajendra et al. [76]	1. Features from all the brain images are extracted by applying a Contourlet transform (CoT)-based approach. Then, some other feature extraction approaches, such as Shearlet transform (ST), Curvelet transform (CuT), complex wavelet transform (CWT), dual-tree complex wavelet transform (DTCWT), discrete wavelet transform (DWT), and empirical wavelet transform (EWT) are also applied. After comparison, it is found that ST-based approach can extract more relevant features for classifying AD patients	1. In future studies, a deep learning-based classification approach may be designed using the same dataset, and the performance can be compared with the proposed method
	2. After extracting the features, the most relevant features are selected using a t test-based approach	
	3. For final classification, KNN-based classifier is developed	
Kamathe et al. [77]	1. From the input brain images, relevant features are extracted using gray-level co-occurrence matrix (GLCM)-based approach	The authors have not performed any pre-processing operations. In future studies, some of the pre-processing operations, such as, skull stripping, noise removal, etc., may be performed before extracting the features. Proper pre-processing may increase the classification accuracy

Table 8 continued

Authors and articles	Algorithm/paradigm	Future scope of studies
	2. For classification, the authors have adopted a KNN-based classifier. For boosting the accuracy, concept of the Adaboost classifier is also inherited	
Tufail et al. [78]	1. From all the input brain images, important features are extracted by applying Independent Component Analysis (ICA) based approach	1. Authors in this article have not performed any pre-processing operations. In future studies, some of the pre-processing operations, such as, skull stripping, noise removal, etc., may be performed before extracting the features. Proper pre-processing may increase the classification accuracy
	2. For dimensionality reduction, the authors adopted a principal component analysis (PCA)-based method	2. For the experiment, 25 AD and 83 cognitively normal (CN) subjects are considered. In future, more data may be acquired to enhance the classification accuracy
	3. Three well-known classifiers are applied, namely proximal support vector machine (PSVM), K-nearest neighbor (KNN), and multilayer artificial neural network (ANN). After comparing the performances, it is concluded that KNN-based classifier produced a better result	
Kruthika et al. [79]	1. With the help of FreeSurfer toolbox, three different feature sets are obtained from the input dataset. The feature sets are (i) six volumetric information, (ii) seventy-two thickness information, and (iii) combination of both	1. Identification and selection of proper biomarkers is very important. In future studies, research can be done to identify the proper biomarkers before applying any feature extraction/selection methods
	2. Particle swarm optimization (PSO)-based feature selection method is used	2. In multi-stage classifier, proper selection of the 1st stage classifier is essential. For 1st stage classification, some more commonly used classifiers can be used for performance comparison
	3. For accurate multi-stage classification of dementia stages, combination of Gaussian naive Bayes classifier, K-nearest neighbor (KNN), and support vector machine (SVM) is used	
Taqi et al. [80]	1. From the input brain images, important features are extracted by using the "Hu Moments (HM) Theory"-based approach. Vector of 7 HMs are extracted from each of the input images	1. The authors have not performed some of the important pre-processing steps, such as skull stripping, de-noising, etc. In future, some of the pre-processing steps may be carried out
	2. Extracted HM vectors are then normalized. After normalization, for classifying the images, 2 classifiers are used, namely SVM and KNN	2. In future studies, some more data of different subject groups may be acquired to train the classifiers more accurately

4 Conclusions

Alzheimer's disease is one of the most serious neurological disorders. Since the traditional diagnosis process is expensive and not accurate all the time, researchers are trying to design an accurate and inexpensive procedure for AD classification using brain imaging. In this article, several AD classification approaches have discussed along with their performance comparisons, merits and demerits, and the detail observations. It is noticed from the result comparison that the ANN-based classification approach can produce the most convincing results (approximately 93.19%).

4.1 Future scope of works and challenges

Among all the discussed classification methods, the method proposed by Basaia et al. [67] can produce the maximum performance (approximately 98%). Based on the CNN community, promising directions for improving the work by Basaia et al. [67] are to develop new deep neural architectures which are designed to improve generalization and training (e.g., loss functions, skip connections, pooling, etc.). Moreover, in future work, some more currently published articles on AD classification based on some more classifiers can be compared that may help the researchers to choose a proper classification technique for AD classification.

One of the major challenges that can be faced by the researchers is to acquire a sufficient number of data from different data-sets (both online and offline). Since the structure of brain is very complex, it is a difficult task to differentiate the changes. Hence, proper pre-processing steps including the skull stripping, segmentation of different parts is important as well as challenging.

Future scope of works and challenges for each of the articles discussed are summarized in Table 8.

Author contributions All authors were responsible for concept, study, and writing of the original manuscript. All authors have read and agreed to the published version of the manuscript.

Funding This research received no external funding.

Availability of data and materials Not applicable.

Declarations

Conflict of interest The authors declare no conflict of interest.

Ethics approval Not applicable.

Consent to participate Not applicable.

Code availability Not applicable.

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