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The use of artificial neural networks to diagnose Alzheimer's disease from brain images

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Abstract
Since Alzheimer's disease (AD) occurs in multiple stages of cognitive impairment, its early diagnosis can be helpful in the process of treatment. Its early diagnosis is thus drawn the attention of researchers and physicians. This study aims to investigate various types of artificial neural networks (ANNs) used to diagnose and predict AD based on brain images of subjects with mild cognitive impairment (MCI). In this study, articles indexed in the IEEE, Springer, Elsevier, and PubMed Central databases were systematically analyzed over the period from 2010 through the first half of 2020. The initial search was done for the keywords Alzheimer's, Magnetic resonance imaging (MRI), and neural network, continued for the keywords Alzheimer's, brain positron emission tomography(PET), and neural network, and ended with the keywords Alzheimer's, brain computed tomography (CT), and neural network. Eventually, the most relevant articles were selected based on the critical evaluation of the subject under investigation. Searching on the subject through the mentioned databases resulted in 900 articles. Excluding unrelated ones, only 134 articles remained, out of which, 54, 41, 35, and 4 numbers were respectively indexed in

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PubMed Central, Elsevier, Springer, and IEEE databases. The number of studies increased by about 2.5 times from 2016 to 2017 and followed this growing trend at the rate of 2 times by 2018. The number of these studies was increasing up to the first half of 2020. There was a wide use of data from Alzheimer's disease neuroimaging initiative (ADNI) database compared to open access series of imaging studies (OASIS) and other databases by the researchers. MRI images, PET images, and their combination were respectively used in 61%, 21%, and 15% of the researches. This is while only 2% of the studies used CT images, suggestive of their inefficiency compared to other brain imaging techniques in diagnosing AD. Most studies either grouped subjects into Alzheimer's patients and healthy people or classified them under three groups of subjects with Alzheimer's, cognitive impairment, and in good health. However, different stages of cognitive impairment have merely considered in 16% of the studies. The main purpose of all studies was AD classification and diagnosis. Further research should be conducted to classify and diagnose this disease in subjects with MCI. It is recommended to use ADNI as a comprehensive database of images from people with various degrees of cognitive impairment, AD, and health control (HC) in future research.

Keywords Alzheimer's disease · Artificial neural network · Deep learning · MRI · PET · CT · Diagnosis

1 Introduction

Dementia is a clinical syndrome with symptoms of decline in memory, cognitive, and discourse skills, which leads to difficulties in managing behaviors or living independently. AD was first discovered by the German psychiatrist, Alois Alzheimer, and named after him. It is the most common form of dementia and contributes to 75% of the cases. Research has made significant advances in the epidemiology of dementia and AD during the last few decades as aging is getting a worldwide phenomenon. According to the United Nations Program on Aging and the US Centers for Disease Control and Prevention, older population (over the age of 65) in the world has been estimated to be 420 million in the year 2000 and reach nearly 1 billion by the year 2030. The highest increase belongs to developing countries whose contribution to the older population will have increased from 59% to 71% of the world. Public health and elderly care systems in all countries across the world are expected to face challenges of AD occurrence due to its strong association with growing age [127]. The early and exact diagnosis of AD gives patients a better chance of prevention and cure by rising their awareness about and taking control of risk factors before irreversible brain damages. Machine learning is a branch of artificial intelligence that makes use of various probabilistic and optimization methods allowing computers to use large and complex datasets. Driving pattern recognition and prediction with the focus on machine learning and artificial neural networks, researchers can diagnose AD at the early stages. By extracting related features from recorded brain images, those who are exposed to Alzheimer's can be classified into AD, MCI, and HC using artificial neural networks.

Dementia is a wide class of brain illnesses implying not only to a sporadic impairment but also to a number of syndromes distinguished by various emotional, cognitive, and behavioral disorders that make a long-time and usually slow decrease in the strength of thinking and remembering which is great sufficient to impact on the normal functioning of a person [127].

Alzheimer's disease (AD) known as a neurodegenerative disease or a permanent neurodegenerative disorder that typically begins gradually, worsens over time, and causes a loss of connections between neurons. The AD prevalent is the same on the average of 1.4% of men and women aged 65–70, and on the average of 24% of men and women over age 85. In recent years, pathology, biochemistry, imaging, and genetic review have provided ways for patients to recognize and help treat. The most common initial sign is hardness in recalling new events (losing short-time memory). As the disorder progresses, the signs can involve problems in speech, losing the direction (involving getting lost easily), losing motivation, mood swings, lack of self-care managing, and behavioral matters. As a condition of person decreases, he/she usually recede from society and family. Slowly, the functions of the body are losing, finally leads to death. Although the progress speed can change, the life expectancy average after recognition is three up to nine years [98].

Mild cognitive impairment (MCI) is well known as isolated memory disorder and early dementia. It is a neurological impairment that arises in elders, which includes cognitive disorders with a minimal disorder in daily living necessary activities. MCI includes the beginning and progress of cognitive disorders beyond those expected relying on the education and age of the person, though which are not sufficiently important to meddle in their ordinary activities. It may happen as a transmutation phase between the natural aging and dementia. The progression of MCI to Alzheimer's is usually progressive. An MCI is an interstitial process between the natural cognitive analysis of aging and acute cognitive impairment resulting from the intellectual decline. This disorder involves more severe problems than the usual expectation of aging in memory, speech, thinking, and judgment. Mild cognitive impairment increases the risk of dementia due to Alzheimer's and other neurological disorders, but the disorder of some patients does not intensify and some will eventually recover. Symptoms of MCI may persist for many years, end in Alzheimer's or another type of mental decline, or may improve over time. Evidence suggests that MCI is often (not always) due to mild changes in Alzheimer's or other types of dementia. Some of these changes have been identified in the autopsy of corpses with MCI [115]–[128]. Electroencephalogram (EEG) signals catch the brain's electrical activity and are one of the most important references and sources of information for studying brain activities and neurological disorders. For this reason, automated systems for detecting EEG changes have been investigated for consecutive years. Psychiatrists cannot make decisions easily because of the existence of considerable overlaps of signs among various mental impairments. Electroencephalogram (EEG) produces, in principle, a strong and almost inexpensive way to investigate dementia and Alzheimer disease (AD) in their early stages, however, is not used to prescribe to special clinical uses. The appropriate analysis of this electrical signal of biologic acts an important role in the scope of the interface of brain-computer which its aim is forming the communication channels between computers and the human brain. Former research by using EEGs have focused on the reducing the oscillatory rhythms of the brain, accompanied with reducing the complexity of the relative time-series and the raised compressibility of them. The aforementioned analyses have been usually done on One-Channel EEGs. However, little research has been carried on the probability produced by intelligence computation methods and new machine learning strategies implemented to multichannel EEG signals. The investigation of the level of screening on recorded EEGs of patients at peril could be used to underline the emergence of underscored progression of AD or leastwise protect more clinical attention. According to the above important expressions about AD and MCI, we find that the accurate classification of AD and its early stage, MCI, plays a vital role in intercepting the progression of memory disorders and contributing to ameliorate the quality of life of AD patients. Signal pre-processing methods must be used to extraction suitable and complete features from these signals. Empirically Continuous Wavelet Transform (CWT) with the Mexican Hat function selected as mother wavelet have been proposed in the literature. Machine learning (ML) techniques have been widely employed to classify EEGs of AD and MCI subjects. ML methods are not suitable to process high-dimensional volumes of data. Deep learning (DL) is an advanced ML technique able to extract the most relevant features directly from raw input data, and widely used in last studies. In this context, a dataset of 180 EEGs (63 AD, 56 MCI, 61 HC) were collected at IRCSS Centro Neurolesi Bonino-Pulejo of Messina (Italy) and here used. In this study, we propose two deep learning networks include corrected Convolutional Neural Network and Convolutional Auto-encoder of differentiating the EEGs of AD, MCI and HC subjects. The proposed system includes an EEG signal dived into 2 s epochs based on a frequency of 256 Hz, time-frequency representation of the signals by using the Mexican hat wavelet transform function and multilayer Convolutional Neural Network and multilayer Convolutional Auto-encoder for training and classification. Convolutional Neural network consists of 4 convolution but 2 pooling layers and 3 fully connected layer were used to classify data into 3 classes with a softmax-activation function. Convolutional Auto-encoder architecture consists of two parts; the first part includes a Convolutional auto-encoder network for training data, and the second part includes a convolutional network for classification making use of the last encoder layer output of the first part. The proposed Convolutional Neural Network and Convolutional Auto-encoder are compared with standard classifiers (Support Vector Machine (SVM), Nearest Neighbor (NN), Random Forest (RF), Random Gradient Decrease (SGD), Logical Regression (LR) and Multilayer Perceptron (MLP)). Results showed that the proposed convolutional network and the convolutional auto-encoder network outperformed all other approaches achieving average accuracy rate up to 92% and 89% respectively, in 3-ways (AD vs MCI vs HC) classification. There has been a marked increase in the number of studies on the diagnosis of AD from recorded images of brain function and tissue using machine learning and deep learning networks since 2017. Different network architectures of convolution layers and different machine learning classifiers such as support vector machine (SVM) and random forest (RF) have high performance and accuracy for image classification. Among various brain imaging techniques, MRI images give useful information for AD classification, diagnosis, detection, and prediction. Moreover, neural network models can be used in computer-aided diagnosis and clinical decision-making systems. The specific brain features of Alzheimer's patients can also be extracted by these networks. It is recommended to use ADNI as a comprehensive database of images from people with various degrees of cognitive impairment, AD, and health control (HC) in future research. Searching on the subject through the mentioned databases resulted in 900 articles. Excluding unrelated ones, only 134 articles remained, out of which, 54, 41, 35, and 4 numbers were respectively indexed in PubMed Central, Elsevier, Springer, and IEEE databases. The number of studies increased by about 2.5 times from 2016 to 2017 and followed this growing trend at the rate of 2 times by 2018. The number of these studies was increasing up to the first half of 2020. There was a wide use of data from Alzheimer's disease neuroimaging initiative (ADNI) database compared to open access series of imaging studies (OASIS) and other databases by the researchers. MRI images, PET images, and their combination were respectively used in 61%, 21%, and 15% of the researches. This is while only 2% of the studies used CT images, suggestive of their inefficiency compared to other brain imaging techniques in diagnosing AD. Due to the fact that AD occurs in multiple stages of cognitive impairment, its early diagnosis can be helpful in the process of treatment. Most reviewed studies either grouped subjects into Alzheimer's patients and healthy people or classified them under three groups of subjects with Alzheimer's, cognitive impairment, and in good health. However, different stages of cognitive impairment have merely considered in 16% of the studies. The main purpose of all studies was AD classification and diagnosis. Further research should be conducted to classify and diagnose this disease in subjects with MCI. The organization of the paper is as follows: Section 2 includes the proposed method. The results are given in Section 3. The discussion and conclusion is given in Section 4.

2 Method

This research is a systematic review study searching for published sources in Latin in the Google Scholar database since 2010 to the first half of 2020. In the first stage, Alzheimer's, MRI, and neural network were searched as the keywords to which 250 articles were related. The search for the keywords Alzheimer's, PET, and neural network resulted in 550 articles while only 100 articles were found to be associated with Alzheimer's, CT, and neural network keywords. The articles indexed in most databases were listed in Google Scholar search results. In the second stage, those papers indexed in IEEE, Springer, Elsevier, and PubMed Central were reviewed and others were ignored in this study. In the third stage, review papers and articles using other methods than artificial neural networks were discarded. In the fourth stage, articles using other diagnostic tools than MRI, PET, and CT images were excluded from the study. The included articles were also studied in terms of the type of brain images. After reviewing their abstracts, a total of 134 studies remained with the used images including 82 PET, 28 MRI, 20 PET/MRI, 2 CT, and 2 PET/ CT. Out of 134 studies, the number of papers indexed in IEEE, Springer, Elsevier, and PubMed Central databases was 54, 41, 35, and 4 respectively. In the last stage, the full paper texts were studied to extract the used artificial neural networks and their accuracies. The papers were then categorized and summarized based on the type of neural network in Table 3. The selection procedure is represented in Fig. 1 and the retrieved articles from each database are shown in Fig. 2.

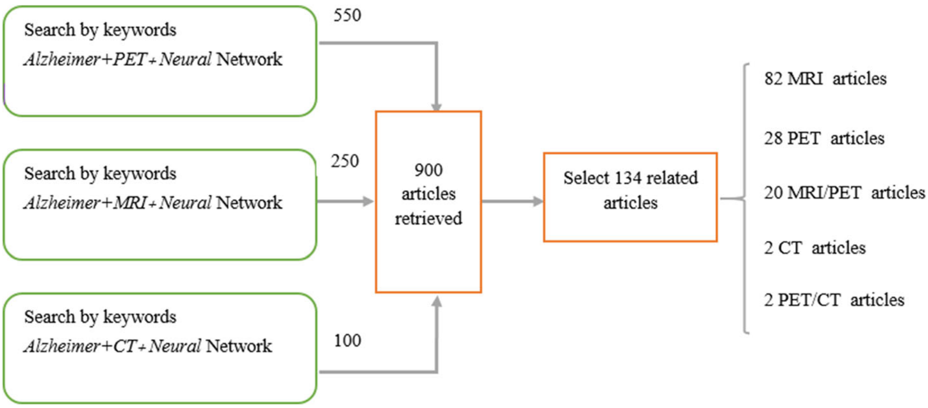


Fig. 1 The process of selecting the reviewed articles

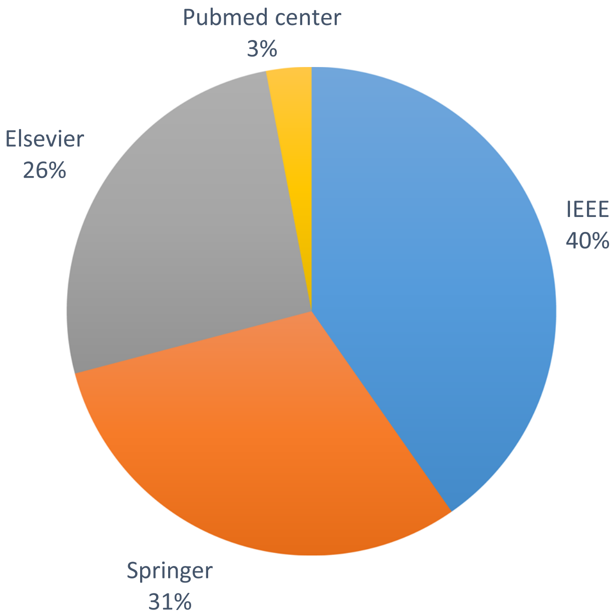


Fig. 2 Number of articles retrieved from various databases

3 Results

This study aims to evaluate the accuracy of neural networks and machine learning methods in predicting and classifying Alzheimer's patients by the use of brain image processing. Having reviewed a number of related articles, we shed light on the contribution of various neural

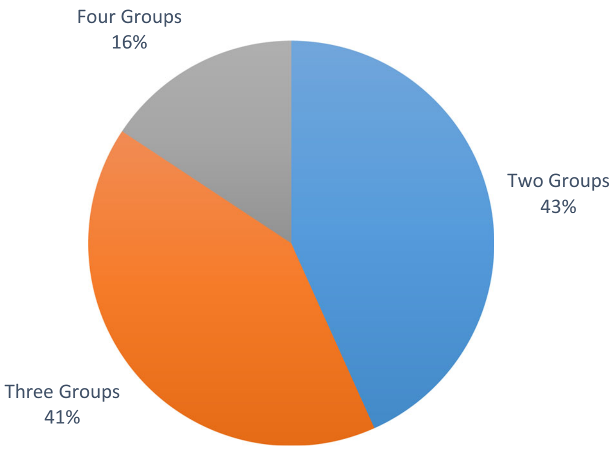


Fig. 3 Categorizing of articles based on the number of groups

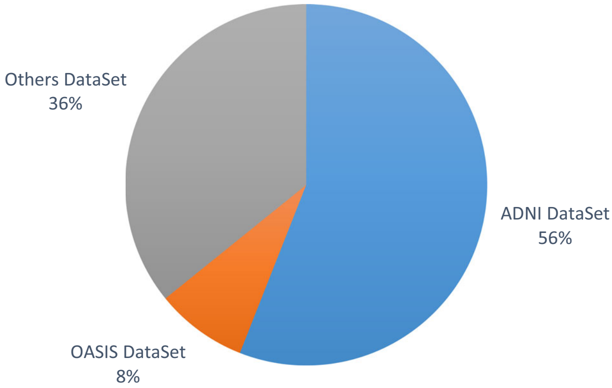


Fig. 4 Categorizing of articles based on the dataset

networks and machine learning methods to network training and data classification. In most studies, subjects have been grouped into Alzheimer's patients and healthy people. Some studies have classified them into AD, MCI, and HC people, while some others have classified them into four groups of AD, Severe Cognitive Impairment, MCI, and HC. The classification accuracies vary according to the number of classes (two, three, or four). Among 134 retrieved articles, there are 58 two-class classifications, 55 three-class classifications, 21 four-class classifications, represented in Fig. 3.

These studies have mostly used images from valid databases of Alzheimer's Disease Neuroimaging Initiative (ADNI) and Open Access Series of Imaging Studies (OASIS). There are 75, 11, and 48 articles that respectively download images from ADNI, OASIS, and other databases, illustrated in Fig. 4.

The summary of all articles according to the image type, neural network type, number of data that used and results are shown in Table 1, providing their references.

3.1 Magnetic resonance

Magnetic resonance imaging (MRI) is an imaging technique used to generate images of body organs. MRI scanner includes a large tunnel inside which the patient is placed during the process of imaging and controlled by a computer. MRI scans are used to take pictures of internal parts of body, such as brain, spinal cord, bones, heart, blood vessels, and other organs.

3.2 Positron emission tomography

Positron emission tomography (PET) is another type of imaging test which depicts the way body tissue and organs function. PET scanner uses a radioactive substance to look for body organs. The radioactive substance is injected into the body (usually the circulatory system). The patients' body emitted waves from which a 3D image on the computer monitor is provided by the imaging device. These images help specialists diagnose cancer, heart diseases, brain disorders, and so forth [115].

Table 1 Summary of all articles

Reference	Image Type	Description	Dataset		Results	
[95]	MRI	• 2-Class Classification • 2 Dimensional CNN • For Alzheimer's Classification	AD LMCI EMCI HC	50 43 77 61	ACC	54%–88%
[47]	MRI	• 2-Class Classification • 2 Dimensional CNN • For Alzheimer's Classification	AD CMCI SMCI HC	418 280 533 407	AD vs HC CMCI vs SMCI	99% 75%
[12]	MRI	• 2-Class Classification • 2 Dimensional CNN • For Alzheimer's Classification	AD HC	100 135	ACC	92.85%
[75]	MRI	• 3-Class Classification • Using SVM for Classification • For Alzheimer's Classification	AD MCI HC	116 119 110	ACC	86%
[102]	MRI	• 2-Class Classification • Using CNN for Classification • For Alzheimer's Classification	AD HC	193 151	ACC	92%
[78]	MRI	• 2-Class Classification • Pre-trained Alexnet CNN as generic feature extractor For MRI and classify with KNN and Navies Bayes Classifier • For Alzheimer's Classification	AD MCI HC	137 75 162	ACC	67%
[2]	MRI	• 2-Class Classification • Using CNN for Classification • For Alzheimer's Classification	AD HC	98 98	ACC	97.65%
[42]	MRI	• 2-Class Classification • Using Pre-trained VGG16 and Inception for Classification • For Alzheimer's Classification	AD HC	100 100	ACC	74%–96%
[25]	MRI	• 2-Class Classification • Using SVM for Classification • For Alzheimer's Classification	AD HC	130 130	ACC	83%–86%
[172]	MRI	• 2-Class Classification • Using CNN for Classification • For Alzheimer's Classification	AD MCI HC	635 548 637	ACC	98.72%–99.75%
[4]	MRI	• 2-Class Classification • Using CNN for Classification • For Alzheimer's Classification	13,733 images from 266 subjects		ACC	91.75%
[57]	MRI	• 2-Class Classification • Using CNN for Classification • For Alzheimer's Classification	AD HC	60 60	ACC	91%
[33]	MRI	• 2-Class Classification • Using Graph convolutional neural networks (GCNNs) for train and SVM for Classification • For Alzheimer's Classification	AD LMCI EMCI HC	12 12 12 12	GCNN SVM	89% 65%
[135]	MRI	• 3-Class Classification • Using VGG-16 for Classification • For Alzheimer's Classification	AD MCI HC	50 50 50	ACC	95.73%
[43]	MRI	• 4-Class Classification • Using CNN for Classification • Multi-class Classification Method for Alzheimer's Disease Detection	AD HC	100 316	ACC	73%
[20]	MRI	• 2-Class Classification	AD	30	ACC	89%

Table 1 (continued)

Reference	Image Type	Description	Dataset		Results	
		• Using SVM for Classification	HC	30		
		• For Alzheimer's Classification				
[8]	MRI	• 2-Class Classification	AD	199	ACC	88.31%
		• Using CNN3D and convolutional auto-encoders (3D CAEs)	HC	229		
		• For Alzheimer's Classification				
[92]	MRI	• 2-Class Classification	AD	279	ACC	88%
		• Using CNN for Classification	HC	427		
		• For Alzheimer's Classification				
[89]	MRI	• 2-Class Classification	AD	90	AD vs HC	84%
		• Using auto-encoder for network training and multi-layer perceptron	EMCI	160	EMCI vs HC	56%
		Classification	LMCI	160	LMCI vs HC	63%
		• For Alzheimer's Classification				
			HC	150	AD vs EMCI	81%
					AD vs LMCI	67%
					EMCI vs LMCI	63%
[160]	MRI	• 3-Class Classification	AD	94	ACC	88.73%
		• Deep network based feature fusion	MCI	121		
		strategy through stacked de-noising sparse auto-encoder	HC	123		
		• For Alzheimer's Classification				
[73]	MRI	• 2-Class Classification	AD	35	ACC	92.06%
		• Using CNN for Classification	AMCI	30		
		• For Alzheimer's Classification	HC	40		
[101]	MRI	• 2-Class Classification	AD	554	ACC	97%
		• Using SVM for Classification	HC	326		
		• For Alzheimer's Classification	Tumor	284		
[17]	MRI	• 2-Class Classification	AD	4	AD vs NC	97.63%
		• Combining the Kernel fuzzy	MCI	4	MCI vs NC	95.4%,
		K-means clustering and Back--propagation	HC	4	AD vs MCI	96.4%
		• For Alzheimer's Classification				
[103]	MRI	• 2-Class Classification	AD	100	ACC	
		• Using Random Forest for	MCI	100	AD vs NC	100%
		Classification	CMCI	100	MCI vs NC	91.90%
		• For Alzheimer's Classification	HC	100	AD vs MCI	97%
[169]	MRI	• 2-Class Classification	AD	90	ACC	64%
		• Using CNN for Classification	HC	90		
		• For Alzheimer's Classification				
[134]	MRI	• 3-Class Classification	AD	27	ACC	100%
		• Using SVM for Classification	MCI	20		
		• For Alzheimer's Classification	HC	25		
[122]	MRI	• 2-Class Classification	AD	47	ACC	64%
		• Using 3D-ResNet with global average pooling layer	HC	56		
		• For Alzheimer's Classification				
[148]	MRI	• 2-Class Classification	AD	459	ACC	935–96%
		• Using SVM for Classification	MCI	448		
		• For Alzheimer's Classification	HC	443		
[11]	MRI	• 2-Class and 4 class Classification	AD	181	2 Classes	93%
		• Using CNN3D for Classification	SMCI	165		

Table 1 (continued)

Reference	Image Type	Description	Dataset		Results	
		• For Alzheimer's Classification	PMCI HC	225 226	4 Classes	51%
[13]	MRI	• 4-Class Classification • Using deep neural network (DNN) and Fuzzy logic for Classification • For Alzheimer's Classification	AD CMCI MCI HC	60 60 60 60	DNN Fuzzy	56% 52%
[113]	MRI	• 4-Class Classification • Using AlexNet, ResNet-18 and GoogleNet • For Alzheimer's Classification	3000 images		ACC of AlexNet ACC of ResNe-t-18 ACC of Google-Net	93% 91% 88%
[96]	PET	• 2-Class Classification • Using CNN3D for Classification • For Alzheimer's Classification	AD HC	93 100	ACC	92.2%
[26]	PET	• 2-Class Classification • Using SVM and KNN for Classification • For Alzheimer's Classification	AD HC	126 219	ACC of SVM ACC of KNN	90% 88%
[53]	PET	• 2-Class Classification • Using CNN for Classification • For Alzheimer's Classification			ACC	89%
[126]	PET	• 2-Class Classification • Using SVM and KNN for Classification • For Alzheimer's Classification	AD MCI HC	20 27 32	AD vs HC AD vs MCI MCI vs HC	80.88% 73.55% 78.33%
[120]	PET	• 2-Class Classification • Using CNN3D for Classification • For Alzheimer's Classification	AD MCI HC	141 529 179	ACC	96%
[158]	PET	• 2-Class Classification • Using VGG19 network for Classification • For Alzheimer's Classification	176 subject with AD and MCI		ACC	92.39%
[163]	PET/MRI	• 2-Class Classification • Using BP for Classification • For Alzheimer's Classification	AD HC	20 20	–	
[159]	PET/MRI	• 2-Class and 3-Class Classification • Using CNN3D for Classification • For Alzheimer's Classification	AD MCI HC	114 132 133	AD vs. HC MCI vs. NC AD vs. MCI vs. HC	93.55% 78.92% 68.86%
[156]	PET/MRI	• 2-Class Classification • Using CNN3D for Classification • For Alzheimer's Classification	AD HC	93 100	ACC	89.64%
[147]	CT	• 2-Class Classification • Using both 2D and 3D CNN networks for Classification • For Alzheimer's Classification	285 subject of AD, MCI and HC		ACC	87.6%
[63]	CT	• 2-Class Classification • Using CNN for Classification • For Alzheimer's Classification	AD LESION HC	51 118 113	ACC	86.8%
[48]	PET/CT	• 2-Class Classification	AD HC	139 347	ACC	94.33%

Table 1 (continued)

Reference	Image Type	Description	Dataset		Results	
		• Using Auto-encoder for training and SVM for Classification • For Alzheimer's Classification				
[66]	PET/CT	• 2-Class Classification • Using sparse Auto-encoder for Classification • For Alzheimer's Classification	–		ACC	98.67%
[82]	MRI	• 2-Class Classification • Using CNN3D for Classification • For Alzheimer's Diagnosis	AD MCI HC	70 70 70	AD vs. HC AD vs. MCI MCI vs. HC	97.6% 95% 90.8%
[146]	MRI	• 2-Class Classification • Using hierarchical fully CNN for Classification • For Alzheimer Detection	AD SMCI PMCI HC	159 239 38 200	ACC	64%–90%
[77]	MRI	• 2-Class Classification • Using hierarchical fully CNN for Classification • For Alzheimer Diagnosis	AD MCI HC		AD vs. HC AD vs. MCI	94.97% 91.98%
[74]	MRI	• 2-Class Classification • Using Siamese Convolutional Neural Network (SCNN) is implemented with three branches of ResNet-34 for Classification • For Alzheimer Diagnosis	235 Subjects		ACC	98.72%
[109]	MRI	• 2-Class, 3-Class and 4-Class Classification • Using CNN3DResNet-34 • For Alzheimer Diagnosis	AD MCI LMCI HC	346 450 358 574	2 Classes 3 Classes 4 Classes	94% 87% 66%
[1]	MRI	• 2-Class Classification • Using construct cascaded convolutional neural networks (CNNs) for Classification • For Alzheimer Diagnosis	AD PMCI SMCI HC	93 76 128 100	AD vs. HC PMCI vs. HC	93.26% 82.95%
[125]	MRI	• 2-Class Classification • Using CNN3D for Classification • For Alzheimer Diagnosis	AD HC	50 62	ACC	98.37%
[100]	MRI	• 2-Class Classification • Using SVM, KNN and PNN for Classification • For Alzheimer Diagnosis	The classifiers were trained with around 600 images		SVM KNN PNN	70% 75% 85%
[94]	MRI	• 2-Class Classification • Using a CBIR system using 3D Capsule Network, 3D-Convolutional Neural Network and pre-trained 3D-autoencoder technology for early detection of Alzheimer's • For Alzheimer Detection	AD MCI HC	345 991 605	AE	88%–94%
[76]	MRI	• 3-Class Classification • Using CNN3D • For Alzheimer Diagnosis	AD MCI HC	221 297 315	ACC	94%
[5]	MRI	• Multiclass classification • Using GoogLeNet and ResNet model for the diagnosis of AD	AD MCI LMCI	33 49 22	ACC	99.7%

Table 1 (continued)

Reference	Image Type	Description	Dataset		Results	
		• For Alzheimer Diagnosis	HC	45		
[37]	MRI	• 2-Class Classification • Using 3D full convolutional DenseNet for Classification • For Alzheimer Diagnosis	AD HC	300 300	ACC	94.8%
[140]	MRI	• 2-Class Classification • Using ResNet-18 for Classification • For Alzheimer Classification	AD MCI SMCI EMCI LMCI HC	25 13 25 25 25 25	AD vs. HC AD vs. MCI AD vs. SMCI AD vs. EMCI AD vs. LMCI	100% 96.85% 97.38% 97.43%
[141]	MRI	• 2-Class Classification • Using CNN3D for Classification • For Alzheimer Diagnosis	331 Subjects		ACC	85.27%
[142]	MRI	• 2-Class Classification • Using ResNet network, and anenhanced ResNet (EResNet) for Diagnosis • For Alzheimer Diagnosis	AD MCI HC	179 254 182	AD vs. MCI MCI vs. HC	96.47% 90.70%
[85]	MRI	• 2-Class Classification • Using CNN for network train and using RF, SVM and KNN for Classification • For Alzheimer Diagnosis	AD HC	46 23	SVM RF KNN	96.07% 88.32% 87.45%
[164]	MRI	• 2-Class Classification • Using CNN for Classification • For Alzheimer Diagnosis	416 Subjects		ACC	78%
[144]	MRI	• 2-Class Classification • Using Auto-encoder Classification • For Alzheimer Diagnosis	MCI HC	91 79	ACC	86%
[161]	MRI	• 2-Class Classification • Using SVM and RF Classification • For Alzheimer Diagnosis	AD MCI HC	144 302 189	AUC AD vs. HC AUC MCI vs. HC	81%–97% 68%–92%
[22]	MRI	• 2-Class Classification • Using CNN3D for Classification • For Alzheimer Diagnosis	–		ACC	94.1%
[110]	MRI	• 2-Class Classification • Using CNN for Classification • For Alzheimer Diagnosis	AD MCI PMCI SMCI HC	86 393 167 226 226	ACC	73%–90%
[15]	PET	• 2-Class and 3 Class Classification • Using Auto-encoder network for Classification • For Alzheimer Diagnosis	AD SMCI PMCI HC	226 409 112 304	AD vs. HC SMCI vs. PMCI 3 Classes	93.58% 81.55% 82.51%
[14]	PET	• 2-Class Classification • Using AlexNet • For Alzheimer Diagnosis	AD MMCI SMCI HC	241 306 127 288	AD vs. HC	91%

Table 1 (continued)

Reference	Image Type	Description	Dataset		Results	
[36]	PET	• 2-Class Classification • Using CNN for Classification • For Alzheimer Diagnosis	AD	177	ACC of AD	92%
			EMCI	709	ACC of EMCI	93%
			LMCI	577	ACC of LMCI	94%
			HC	742	ACC of HC	93%
[24]	PET	• 2-Class Classification • Using SVM for Classification • For Alzheimer Diagnosis	AD HC	81 61	ACC	94.36%
[79]	PET	• 2-Class Classification • Using SVM for Classification • For Alzheimer Diagnosis	AD MCI HC	45 61 60	AD vs. HC MCI vs. HC	88.1%–92.4% 66.1%–76%
[155]	PET	• 2-Class Classification • Using SVM for Classification • For Alzheimer Diagnosis	AD HC	10 12	ACC	100%
[175]	PET	• 2-Class Classification • Using SVM for Classification • For Alzheimer Diagnosis	AD HC	140 140	ACC	92.50%
[166]	PET	• 2-Class Classification • Using CNN by AlexNet algorithm • For Alzheimer Diagnosis	AD MCI HC	78 26 97	ACC	98.14%
[86]	PET	• 3-Class Classification • Using CNN • For Alzheimer Diagnosis	AD MCI HC	237 87 428	ACC	85%
[68]	MRI and PET	• 2-Class Classification • Using 3D Cycle-consistent Generative Adversarial Networks (3D--cGAN) • For Alzheimer Diagnosis	AD PMCI SMCI HC	199 167 226 229	AD vs. HC PMCI vs. SMCI	92.50% 79.06%
[104]	MRI and PET	• 2-Class Classification • Using a multimodal stacked DPN (MM-SDPN) algorithm by MVC Classifier • For Alzheimer Diagnosis	AD MCI-C MCI-NC HC	51 43 56 52	AD vs. HC MCI vs. HC	97.13% 86.99%
[29]	MRI and PET	• 2-Class Classification • Using Sparse Auto-encoder (SAE) and CNN • For Alzheimer Diagnosis	AD HC	145 172	ACC	90%
[9]	MRI and PET	• 2-Class Classification • Using CNN3D for Classification • For Alzheimer Diagnosis	AD PMCI SMCI HC		AD vs. HC PMCI vs. HC SMCI vs. HC	94.29% 84.66% 64.47%
[45]	MRI and PET	• 2-Class Classification • Using VGG-16 for network train and SVM, Linear Discriminate, K means clustering, and Decision tree for Classification • For Alzheimer Diagnosis	AD	900	Average ACC of the MRI dataset	99.95%
			HC	1775	Average ACC of the PET dataset	73.46%
[71]	MRI and PET	• 3-Class and 4-Class Classification • Using DNN for Classification	AD LMCI	159 193	ACC of 3 Classes	33%–75%

Table 1 (continued)

Reference	Image Type	Description	Dataset		Results	
		• For Alzheimer Diagnosis	EMCI HC	296 248	ACC of 4 Classes	25%–48%
[112]	MRI and PET	• 2-Class Classification • Using CNN • For Alzheimer Diagnosis	AD MCI HC	91 200 101	ACC	85%–98%
[145]	MRI and PET	• 2-Class Classification • Using K-sparse auto-encoder • For Alzheimer Diagnosis	AD HC	150	ACC	74.05%
[27]	MRI and PET	• 2-Class Classification • Using a 3D-CNN and fully stacked bidirectional long short-term memory (FSBi-LSTM) • For Alzheimer Diagnosis	AD PMCI SMCI HC	93 76 128 100	AD vs. HC PMCI vs. HC SMCI vs. HC	94.82% 86.36% 65.35%
[10]	MRI and PET	• 2-Class Classification • Using SVM for Classification • For Alzheimer Diagnosis	AD MCI HC	200 400 200	ACC	71%–81%
[108]	MRI and PET	• 3-Class Classification • Using SVM for Classification • For Alzheimer Diagnosis	AD MCI HC	51 99 52	ACC	73%
[136]	MRI and PET	• 2-Class and 4-Class Classification • Using ResNet for Classification • For Alzheimer Diagnosis	AD EMCI LMCI HC	119 113 105 163	AD vs. HC EMCI vs. LMCI 4 Classes	95.21% 89.79% 86.15%
[176]	MRI and PET	• Using GAN for Classification • For Alzheimer Diagnosis	192 Subjects		–	
[80]	MRI and PET	• Using FGAN for Classification • For Alzheimer Diagnosis	1466 Subjects		–	
[31]	MRI and PET	• 2-Class Classification • Using Stacked Auto-Encoder (SAE) and Deep Boltzmann Machine (DBM) • For Alzheimer Diagnosis	AD MCI PMCI SMCI HC	93 204 76 128 101	SAE for 2 Classes DBM for 2 Classes	76%–97% 73%–90%
[44]	MRI	• 2-Class Classification • Using SVM and RF for Classification • For Alzheimer Detection	AD HC	55 110	ACC	93.9%
[56]	MRI	• 2-Class Classification • Using CNN2D with LSTM for Classification • For Alzheimer Diagnosis	132 Subjects		ACC	84.38%
[90]	MRI	• 2-Class Classification • Using SVM for Classification • For Alzheimer Diagnosis	416 Subjects		ACC	72%–87%
[165]	MRI	• 2-Class Classification • Using CNN for Classification • For Alzheimer Detection	AD MCI HC	336 542 785	AD vs. MCI AD vs. HC MCI vs. HC	97.2% 96.9% 94.5%
[19]	MRI	• 2-Class Classification • Using Particle Swarm Optimization (PSO) and a Genetic algorithm (GA) used for feature selection • For Alzheimer Detection	AD HC	100 98	ACC	87.23%
[107]	MRI	• Using from ANN • For Alzheimer Detection	18 Subjects		–	

Table 1 (continued)

Reference	Image Type	Description	Dataset		Results	
[30]	MRI	• 2-Class Classification • Using CNN3D and LSTM3D • For Alzheimer Detection	AD MCI HC	198 408 229	AD vs. MCI MCI vs. HC	94.19% 79.01%
[35]	MRI	• 2-Class Classification • Using CNN and SVM • For Alzheimer Detection	AD MCI HC	101 234 169	ACC of SVM ACC of CNN	84.4% 96%
[87]	MRI	• 5-Class Classification • Using CNN3D for Classification • For Alzheimer Detection	AD MCI SMCI EMCI HC	718 1274 186 1222 1520	ACC for 5 Classes	84%
[64]	MRI	• 2-Class Classification • Using CNN for Classification • For Alzheimer Detection	AD HC	56 79	ACC	93.3%
[99]	MRI	• 2-Class Classification • Using SVM-Poly 1 and random forest(RF) for Classification • For Alzheimer Detection	AD HC	55 110	ACC	93.9%
[91]	MRI	• 3-Class Classification • Using SVM for Classification • For Alzheimer Detection	AD MCI HC	24 57 97	ACC	81.5%
[88]	PET	• 3-Class Classification • Using SVM for Classification • For Alzheimer Detection	AD MCI HC	53 114 52	ACC	89.52%
[139]	MRI and PET	• 2-Class and 3-Class Classification • Using convolutional auto-encoder and CNN • For Alzheimer Detection	AD MCI HC	193 215 207	ACC for 2 Classes ACC for 3 Classes	93%–98% 91.13%
[167]	MRI	• 2-Class Classification • Using APANN • For Alzheimer Prediction	AD LMCI HC	145 326 198	–	
[162]	MRI	• 2-Class Classification • Using SNCNN • For Alzheimer Prediction	AD MCI HC	288 272 272	AD vs. HC AD vs. MCI MCI vs. HC	91.07% 87.72% 85.45%
[111]	MRI	• 2-Class Classification • Using SVM • For Alzheimer Prediction	AD MCI HC	2 24 18	AD vs. HC AD vs. MCI	92% 75%
[137]	MRI	• 3-Class Classification • Using CNN3D • For Alzheimer Prediction	AD MCI HC	192 409 184	ACC	86%
[150]	MRI	• -- Class Classification • Using CNN3D • For Alzheimer Prediction	847 Subjects		ACC	0.79
[168]	MRI	• 2-Class and 3-Class Classification • Using LSTM • For Alzheimer Prediction	AD MCI HC	965 1741 1272	AUC of AD vs. HC AUC of AD vs. MCI AUC of AD vs. MCI vs.	93.5% 79.8% 77.7%

Table 1 (continued)

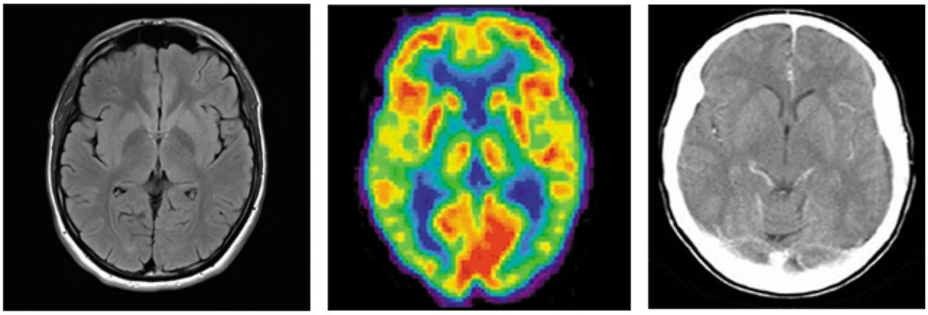
Reference	Image Type	Description	Dataset		Results	
					HC	
[133]	MRI	• 2-Class Classification • Using modified ResNet • For Alzheimer Prediction	251 Subjects		ACC	83%
[118]	MRI	• 2-Class Classification • Using CNN3d and CNN-AE • For Alzheimer Prediction	4046 MRIs from 1092 Subjects		ACC of CNN ACC of CNN--AE	81% 77%
[143]	MRI	• Using CNN-AE • For Alzheimer Prediction	AD SMCI CMCI HC	528 769 645 853	–	
[157]	PET	• 2-Class Classification • Using CNN3D • For Alzheimer Prediction	79 pet image		ACC	82%
[6]	PET	• 2-Class Classification • Using CNN3D • For Alzheimer Prediction	AD MCI HC	139 171 182	ACC	84.2%
[49]	PET	• 2-Class and 3-Class Classification • Using CNN • For Alzheimer Prediction	EMCI LMCI HC	131 96 100	ACC of 2 Classes ACC of 3 Classes	95% 75%
[84]	PET	• 2-Class Classification • Using Convolutional Architecture for Fast Feature Embedding (CAFFE) • For Alzheimer Prediction	AD MCI HC	192 398 229	ACC	72.19%
[51]	MRI and PET	• 3-Class Classification • Using Recurrent Neural Network (RNN) and LSTM-based RNN • For Alzheimer Prediction	AD MCI HC	336 364 521	ACC	84%
[171]	MRI	• 2-Class Classification • Using Unsupervised CNN • For CAD system	1075 Subjects		AD vs. MCI MCI vs. HC	97.01% 92.6%
[21]	PET	• 2-Class Classification • Using SVM • For CAD system	MCI HC	65 19	ACC	100%
[50]	PET	• 2-Class Classification • Using AlexNet-SVM • For CAD system	68 Subjects		ACC	96.39%
[105]	PET	• 2-Class Classification • Using SVM • For CAD system	292 Subjects		ACC	92.9%
[65]	PET	• 2-Class and 3-Class Classification • Using stacked auto-encoder • For CAD system	AD MCI HC	51 99 52	AD vs. HC AD vs. MCI MCI vs. HC AD vs. MCI vs. HC	98.8% 83.7% 90.7% 83.3%
[106]	MRI	• 2-Class Classification	AD HC	17 17	ACC	98.5%

Table 1 (continued)

Reference	Image Type	Description	Dataset		Results	
		• Using non-linear discriminant analysis (NDA) with artificial neural network (ANN)				
		• For Alzheimer Detection				
[173]	MRI	• 2-Class Classification	AD	49	ACC	78%–86%
		• Using Genetic algorithm	HC	49		
		• For Feature Selection				
[117]	PET	• 3-Class Classification	AD	330	89%	
		• Using CNN3D	MCI	662		
		• For Alzheimer Detection	HC	396		
[152]	MRI	• 2-Class Classification	MCI	48	ACC	87.50%
		• Using auto-encoder	HC	52		
		• For Alzheimer Detection				
[119]	MRI	• 2-Class Classification	–		ACC	92.3%.
		• Using CNN for network training and SVM for Classification				
		• For CDSS				
[28]	MRI	• 2-Class Classification	AD	28	ACC	96.85
		• Using LeNet-5	HC	15		
		• For Alzheimer Recognize				
[149]	PET	• 2-Class Classification	AD	29	ACC	97.9%
		• Using CNN with multinomial regression classifier	EMCI	24		
			LMCI	24		
		• For Alzheimer Recognize	HC	28		
[153]	MRI	• 2-Class Classification	AD	347	ACC	93.9
		• Using CNN3D	HC	417		
		• For Alzheimer Identification				
[55]	PET	• 2-Class Classification	154 Subjects		–	
		• Using Genetic algorithm				
		• For Alzheimer Identification				
[54]	PET	• 2-Class Classification	AD	243	ACC	94%
		• Using CNN	HC	393		
		• For Alzheimer discriminating				
[93]	MRI	• 2-Class Classification	AD	18	ACC	73%
		• Using CNN	HC	22		
		For Alzheimer Differentiating				
[16]	MRI	• 2-Class Classification	AD	73	ACC of ResNet	98.01%
		• Using ResNet and GoogleNet for Classification	MCI	84		
			LMCI	61	ACC of Google-Net	98.88%
		• For Alzheimer Classification	HC	137		

3.3 Computed tomography

Computed tomography (CT) is a type of X-ray imaging test which allows a layer-by-layer picture of the body in slices. In this procedure, as the X-ray tube and the detector are rotating around the patient, a cross-sectional or sliced image is displayed on a computer. These images can be applied to diagnose appendicitis, kidney stones, or cerebral artery diseases [128].



(a) (b) (c)

Fig. 5 Examples of brain images: **a**) MRI **b**) PET scan **c**) CT scan

3.4 Multimodal imaging (PET/MRI hybrid imaging and PET/CT hybrid imaging)

PET/MRI is multimodality imaging that combines anatomic and metabolic data at the same time. PET imaging is useful in combination with anatomical imaging such as CT and thus multifunctional PET/CT scanners that combine both PET and CT scans are available [23]. Some studies have applied neural networks to diagnose and classify diseases using PET/MRI or PET/CT hybrid imaging after preprocessing and improving the quality of combined images. Figures 5 and 6 illustrate commonly brain images.

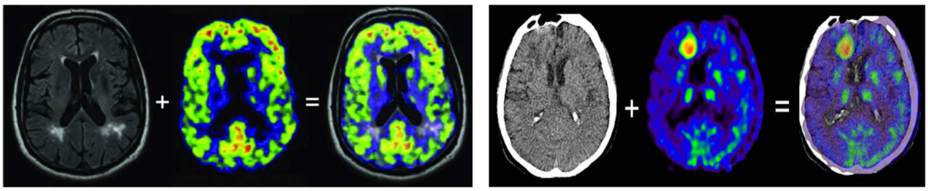
In some other studies, images are separately tested by a neural network. This study investigates the use of these images to diagnose AD and found that various types of imaging procedures (82 MRI, 28 PET, 20 PET/MRI, 2 CT, and 2 PET/CT) have been used in the reviewed articles (Fig. 7). The classification of articles according to the used imaging techniques are shown in Table 2, providing their references.

Figure 8 represents the number of articles by the year of publication (ranged from 2010 to the first half of 2020).

The reviewed studies have been conducted for purposes of classification, diagnosis, prediction, and so forth, listed in Table 3.

3.5 Artificial neural network

Artificial neural networks (ANNs) are biologically inspired computer programs designed to simulate the way in which the human brain processes information. ANNs gain their knowledge by detecting the relations and patterns in data and are trained (or learn) through experience, rather than programming. ANNs are made of hundreds of units, artificial neurons or processing elements, which are connected to coefficients (weights)



(d) (e)

Fig. 6 Examples of brain images: **d**) PET/MRI hybrid imaging and **e**) PET/CT hybrid imaging

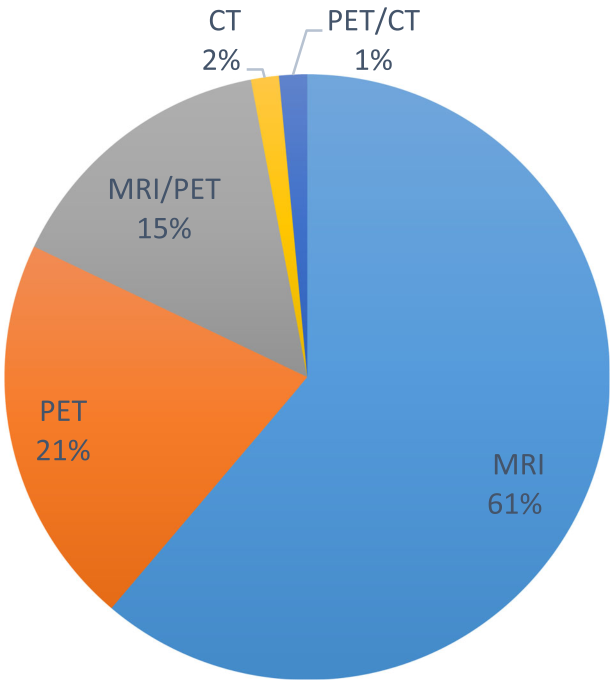


Fig. 7 Categorizing of articles based on the imaging type

to form the neural structure in organized several layers. The power of neural computations results from the connections between neurons in a network. Each processing element has a transfer function, weighted inputs, and one output. The neural network behavior is specified by the transfer function of its neurons, the learning rule, and its architecture.

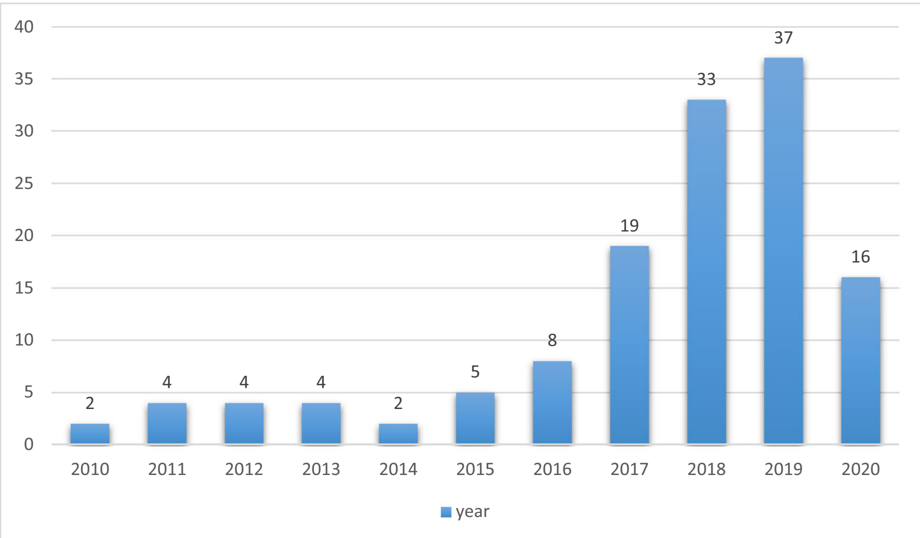


Fig. 8 Comparison of the articles count based on publication year

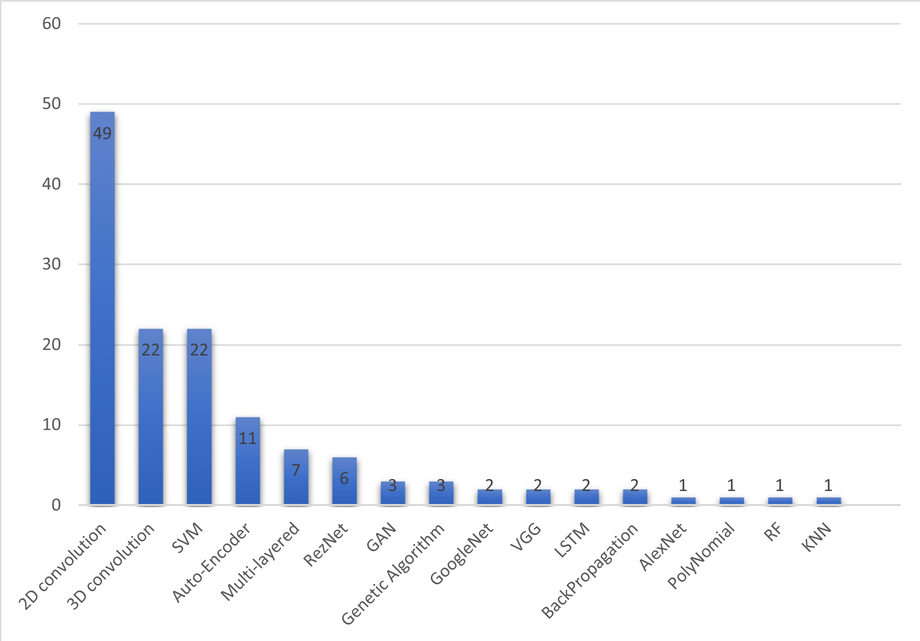


Fig. 9 Categorizing of articles based on the Neural Network type

After network training and testing, new input information can be made for output prediction. ANN provides the desired modeling approach, specifically for data sets of nonlinear relationships. ANN programs can be summed up in pattern classification, recognition, modeling, and prediction [3, 7, 38–41, 46, 52, 58–60, 69, 70, 81, 83, 97, 114, 123, 124, 129, 130, 132, 138]. There are various types of neural network architectures used in various studies. In the current research, articles published in journals, conferences, and books of scientific databases were subjected to scrutiny. It was revealed that either a type of artificial neural networks or other combined techniques have been used in 134 published papers. The research findings suggest that making use of neural networks have superiority over other image processing techniques. The neural networks or machine learning approaches used in the reviewed papers are given in Table 4, providing their references. The types of neural networks used in these articles are also summarized in Fig. 9.

Table 2 Categorizing of articles based on the imaging type

Imaging type	Number of studies	References
MRI	82	[1, 2, 4, 5, 8, 9, 11–15, 17, 20, 22, 24–26, 29, 33, 36, 37, 42, 43, 45, 47, 48, 53, 57, 63, 66, 68, 71, 73–79, 82, 85, 86, 89, 92, 94–96, 100–104, 109, 110, 112, 113, 120, 122, 125, 126, 134, 135, 140–142, 144–148, 155, 156, 158–161, 163, 164, 166, 169, 172, 175]
PET	28	[10, 19, 27, 30, 31, 35, 44, 56, 64, 80, 87, 88, 90, 91, 99, 107, 108, 111, 133, 136, 137, 139, 150, 162, 165, 167, 168, 176]
MRI/PET	20	[6, 21, 28, 49–51, 65, 84, 105, 106, 117–119, 143, 149, 152, 153, 157, 171, 173]
CT	2	[54, 55]
PET/CT	2	[16, 93]

Table 3 Categorizing of articles based on study type

Study Type	Count	References
Classification	45	[4, 12, 13, 17, 25, 43, 47, 73, 77, 82, 92, 94, 95, 100, 109, 120, 140, 142, 147, 156, 160], [6, 9, 10, 14, 16, 19, 24, 27, 28, 36, 54, 55, 65, 68, 87, 88, 93, 104, 110, 136, 145, 155, 161, 166]
Diagnosis	45	[75], [102], [78], [8], [89], [103], [11], [113], [96], [159], [48], [66], [125], [37], [164], [144], [79], [86], [29], [45], [71], [108], [176], [80], [56], [35], [99], [137], [168], [133], [118], [143], [157], [49], [84], [51], [171], [21], [50], [105], [106], [173], [117], [119], [149]
Detection	14	[2], [42], [57], [169], [134], [126], [163], [63], [146], [5], [85], [175], [107], [153]
Prediction	14	[20], [101], [122], [148], [53], [74], [1], [15], [112], [165], [30], [64], [167], [152]
CAD (Computer Aided Diagnosis)	5	[22], [44], [139], [111], [150]
Select Best Features	3	[172], [33], [90]
CDSS (Clinical Decision Support System)	2	[76], [141]
Recognition	2	[135], [91]
Identification	2	[26] [162],
Discrimination	1	[75]
Differentiation	1	[158]

Table 4 Categorizing of articles based on neural network type

Neural Network Type		count	References
Convolutional Neural Network (CNN)	2 Dimensional	49	[95], [12], [102], [78], [42], [25], [135], [43], [8], [92], [160], [101], [103], [169], [13], [96], [120], [158], [156], [147], [63], [82], [77], [94], [5], [141], [144], [161], [22], [24], [79], [71], [145], [136], [80], [31], [165], [30], [64], [91], [88], [139], [167], [168], [157], [171], [50], [55], [54]
	3 Dimensional	22	[75], [89], [148], [11], [26], [53], [163], [159], [66], [146], [100], [37], [15], [104], [45], [27], [90], [87], [49], [84], [65], [28]
	Resnet	5	[1], [125], [164], [166], [173]
	Googlenet	2	[47], [48]
	VGG	2	[73], [153]
	Alex Net	1	[176]
Auto-Encoder Neural Network		11	[76], [140], [142], [86], [112], [108], [150], [21], [149], [93], [16]
Multi layer Neural Network		7	[172], [20], [126], [9], [107], [133], [51]
3D Generative adversarial network (GAN)		3	[118], [117], [119]
Genetic Algorithm Neural Network(GA/ANN)		3	[33], [134], [162]
LSTM		2	[74], [152]
Backpropagation		2	[14], [6]
Polynomial Neural Network		1	[143]
Machine Learning Classifier	Support Vector Machine (SVM)	22	[4], [57], [17], [122], [113], [109], [85], [110], [155], [175], [68], [29], [10], [44], [56], [19], [35], [99], [111], [137], [105], [106]
	Random Forest(RF)	1	[36]
	K-Nearest-Neighbors (KNN)	1	[2]

3.6 Convolutional neural network

Convolutional neural networks (CNNs) are one important class of deep learning methods in which multiple layers are strongly trained. These networks have very efficient and popular applications in neural computer vision. In general, a CNN network consists of three main layers: a convolution layer, a pooling layer, and a fully connected layer, as illustrated in Fig. 10. Different layers function in different ways which lead to the ultimate learning. This network can be applied alone or alongside other networks for data classification [170].

3.7 Residual neural network

Residual neural network (Res Net) is a type of convolutional neural network proposed by Microsoft Corporation that won first place in the ILSVRC 2015 competition. With a depth of 152 layers, this architecture was named as the deepest at that time. The network consists of multiple residual modules stacked upon each other to form the main building block of ResNet architecture (Fig. 11). The residual module has two options; it can either perform a series of operations on the input or skip all of them. These stacked residual modules fit a complete network [67].

3.8 AlexNet neural network

AlexNet is the first deep architecture introduced by one of the pioneers of deep learning and his colleagues. AlexNet is a simple but powerful architecture dates from the 1980s, paving the way for great research on deep learning. The AlexNet architecture is composed of complicated layers stacked on and fully connected to the top of each other (Fig. 12). The use of graphic processing unit (GPU) and its performance speed make this architecture distinguished from other models of learning. In the 1980s, central processing unit (CPU) was being used to learn neural networks until the application of GPU in the AlexNet model that led to a tenfold increase in the learning speed. Despite its old use, this architecture is still viewed as the inception of deep neural networks [131].

3.9 VGG net neural network

The VGG network was first proposed by the researchers at Visual Graphics Group at Oxford. This network is typically known for its pyramidal shape in which wide layers are closer to the image and deep layers are more distant. It consists of a series of computational layers along

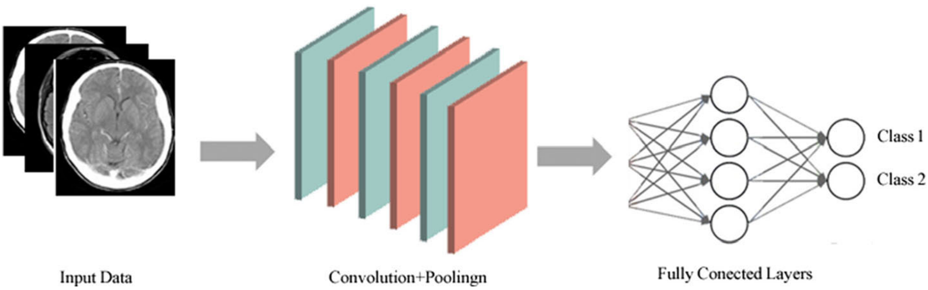


Fig. 10 Convolutional Neural Network

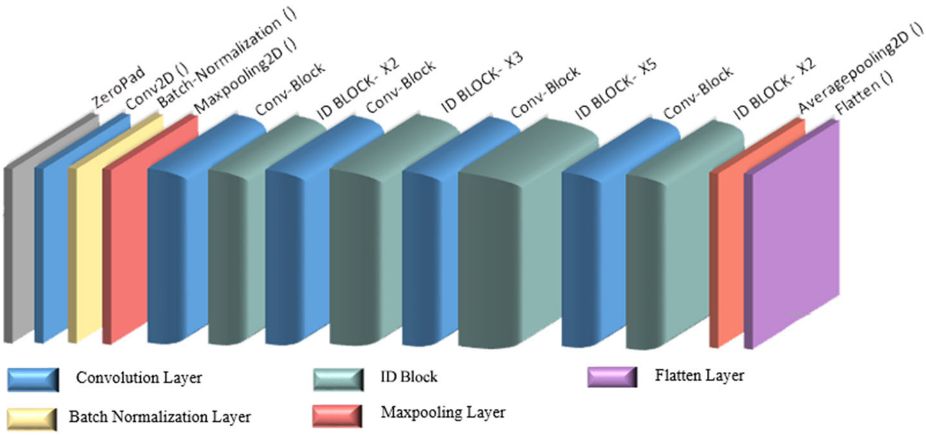


Fig. 11 Residual neural network Architecture

with pooling layers, as shown in Fig. 13. This research group has proposed different networks with varying depths of architecture [174].

3.10 GoogleNet neural network

GoogleNet network architecture is designed by researchers at google as the most powerful model of ImageNet 2014. Achieving a clear distinction from previous architectures, this architecture has 22 layers (Fig. 14). There are several feature extractors in each layer that convert input data to a kind of data for computation. This architecture contributes to the better performance of a self-learning network that has multiple options to solve various tasks. This module can either use direct inputs or summarize them in computations directly. [151]

3.11 Autoencoders

Autoencoders (AEs) are a class of artificial neural networks used for unsupervised learning of efficient data coding. An autoencoder aims to learn a representation of a set of data, typically for dimensionality reduction and noise ignorance. Alongside the dimensionality reduction, the other reconstructing side is learned while the autoencoder is striving to reduce the encoded side

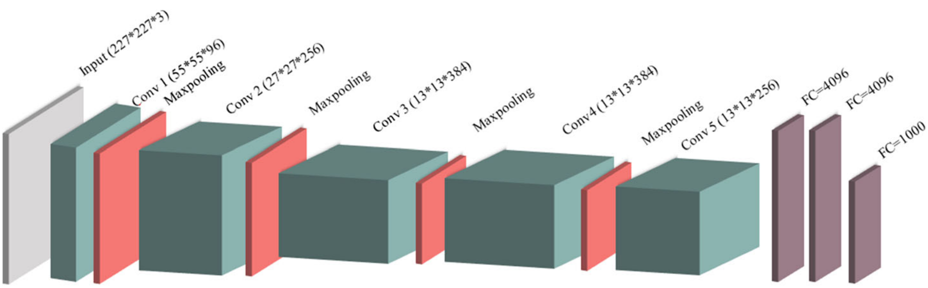


Fig. 12 AlexNet neural network

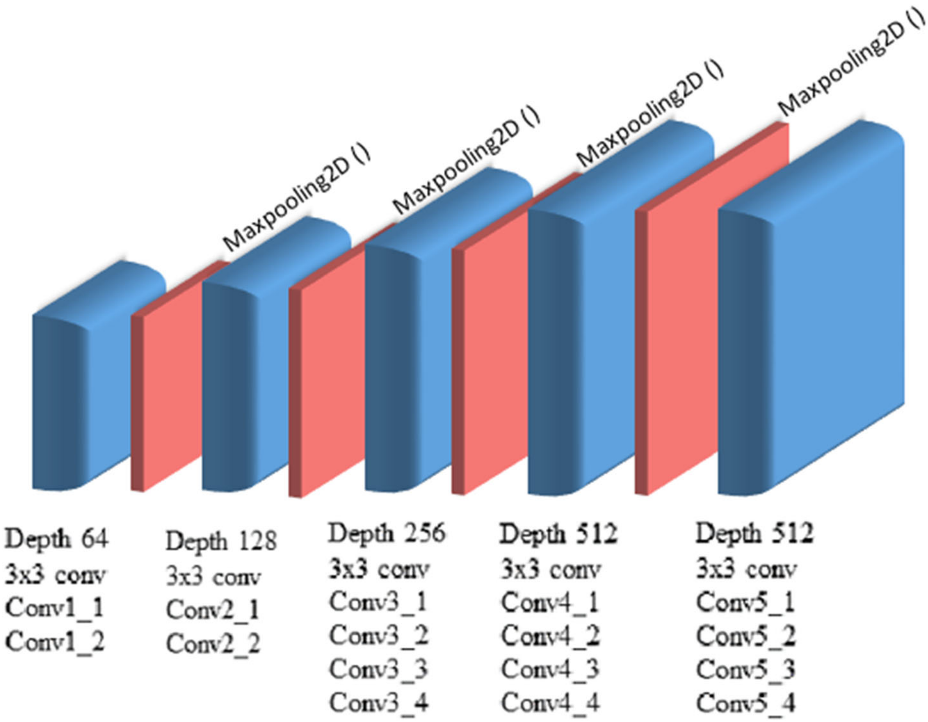


Fig. 13 VGG Net neural network Architecture

for representing data as close as possible to its original input [62]. According to the above mentioned, this network has been widely used in many studies presented in Fig. 15.

3.12 Multilayer perceptron artificial neural networks

Multilayer perceptron (MLP) is a class of feedforward artificial neural network. MLPs are commonly referred to as vanilla neural networks especially when having a single hidden layer. MLP is composed of at least three layers of nodes: an input layer, a hidden layer, and an output layer (Fig. 16). Each node, except for the input nodes, is a neuron using a nonlinear activation function. MLP adopts a learning method called backpropagation in a supervised manner for training [154]. This type of neural network is one of the first-used artificial neural networks. It

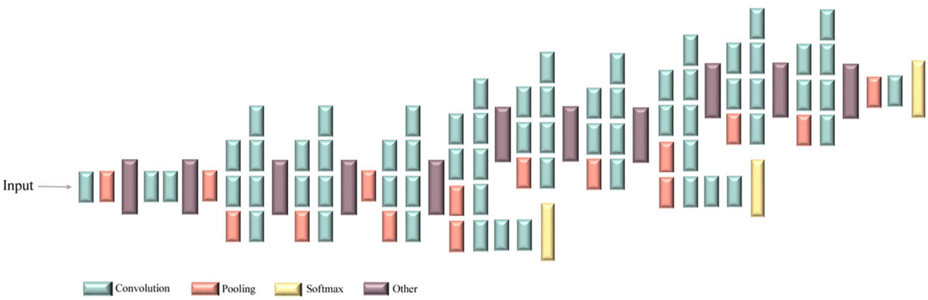


Fig. 14 Google Net neural network Architecture

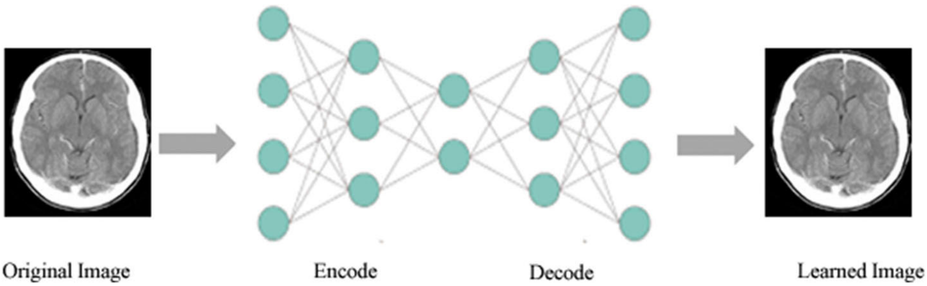


Fig. 15 Autoencoders neural network Architecture

allows problem solving algorithm of high speed and reliability for the classification of Alzheimer's patients and healthy people.

3.13 Generative adversarial networks

Generative adversarial networks (GANs) are a class of machine learning systems proposed by Ian Goodfellow in 2014 and his colleagues. There are two neural networks competing with each other in this architecture (Fig. 17). This system learns to generate new data similar to the utilized training dataset [61].

3.14 Artificial neural network with genetic algorithm (GA/ANN)

Genetic algorithm (GA) is a searching and optimization method that mimics biological evolutions and natural processes. This network is in widespread use in various fields including local search and often used for recursive networks such as Elman neural network. Problem-solving is encoded in a structure called a chromosome. Initially, a certain number of chromosomes constituting the initial population are generated through random selection (as shown in Fig. 18), where the fitness function evaluates the quality of the chromosome (solution). The algorithm assigns a quality indicator to each solution to sort and select the best and then chromosomes find appropriate network weights [18], [69].

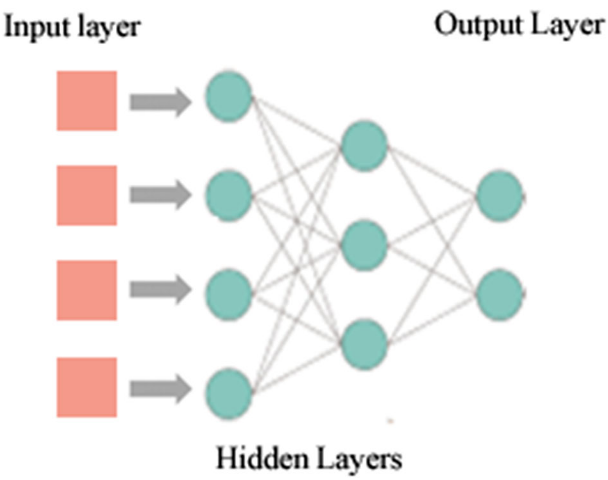


Fig. 16 Multilayers perceptron artificial neural networks Architecture

3.15 Long short-term memory (LSTM) neural network

This network is a model or structure deals with sequential data, emerged in 1995 as a development of recursive neural networks (RNNs). The respective long and short-term memories refer to the learned weights and internal states of cells. To solve the problem of vanishing gradient in RNNs, this architecture was developed in which RNN middle layer is replaced by a block called LSTM (Fig. 19). The superiority of LSTM over RNN lies in its ability to learn long-term dependency. To predict the next time-step, the values of network weights must be updated which entails preserving information from the initial time-steps. Hence, RNNs can learn a limited number of short-term dependencies. In other words, while RNNs are not able to learn long-term time series, these long-term dependencies can be learned by LSTMs [72].

3.16 Error backpropagation

In deep learning, a backpropagation network is a widely used algorithm for training artificial neural networks having more than one hidden layer for more accurate computation of weight gradient (Fig. 20). In this method, the learning algorithm is optimized, neuron weights are stabilized, and cost function gradient descent is calculated. It is also used to train feedforward neural networks in a supervised manner [62].

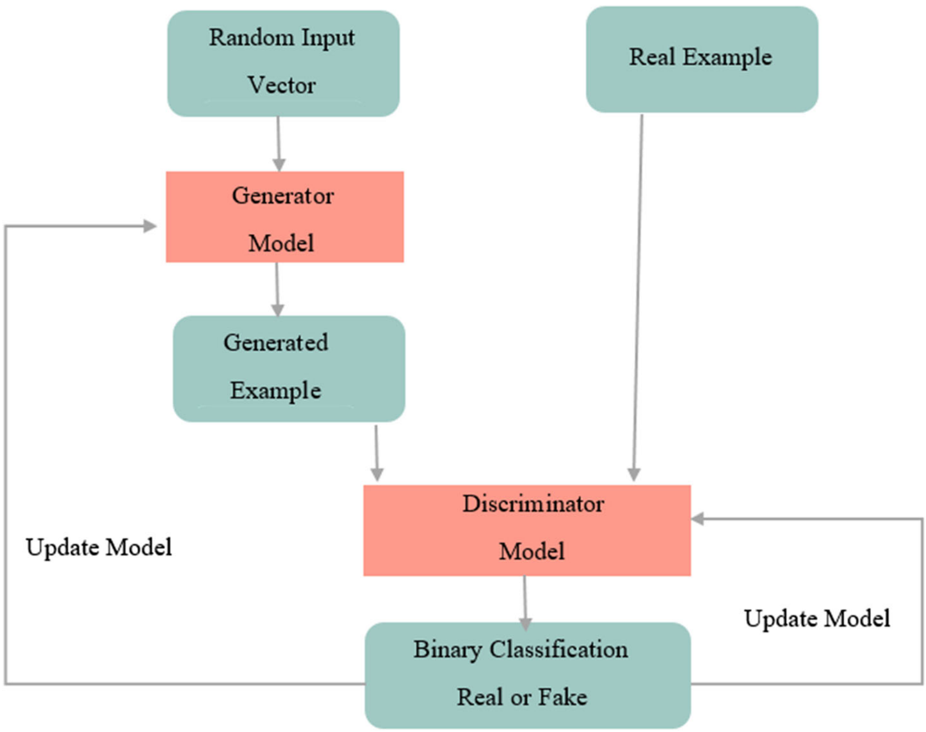


Fig. 17 Generative adversarial network Architecture

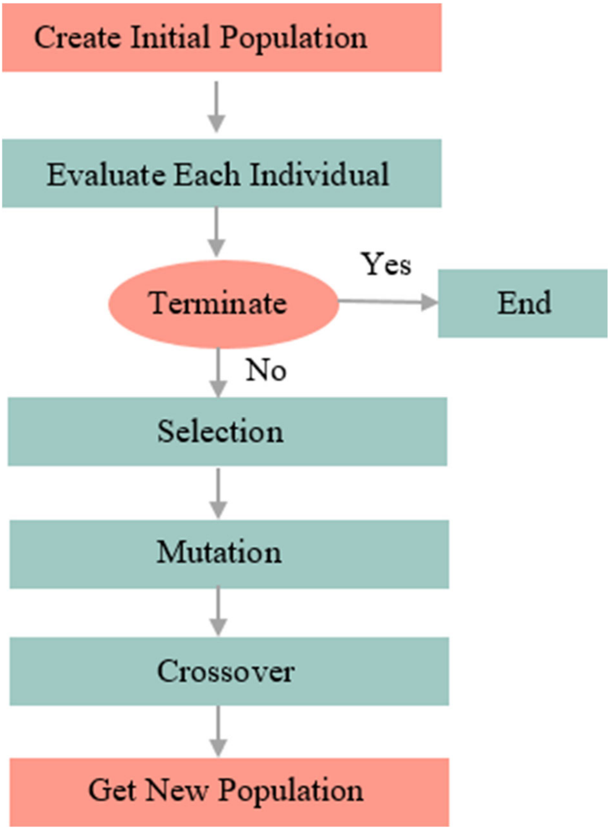


Fig. 18 Genetic algorithm Architecture

3.17 Support vector machine

Support vector machine (SVM) is a method for classification into two classes. This method functions in a way that nonlinear input vectors correspond to a multidimensional feature space. In this space,

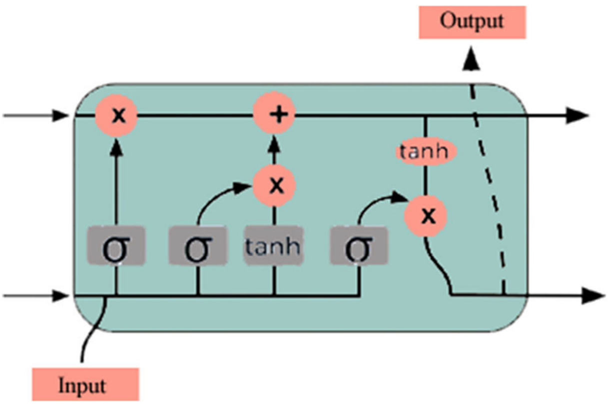


Fig. 19 Long short-term memory (LSTM) neural network Architecture

there is a linear decision level whose features ensure learning machine generalizability. Although the previously implemented SVMs were able to separate training data for limited cases, SVMs are currently applied to inseparable training data with high generalization that can be manifested through polynomial conversion [34].

3.18 Random Forest

Random forest (RF) is a hybrid learning method for classification and regression, which works on the training time and class outputs (classification) or prediction of each decision tree from a structure composed of plenty of decision trees. They preserve decision trees from overfitting problems. RFs exhibit a higher performance than decision trees, albeit depending on the type of data. For instance, there is no exact pattern for a too deep decision tree of low bias and high variance. In spite of slight increase in bias and small decrease in interpretability, this method significantly improves the model performance [121].

3.19 K-nearest neighbor

The k-nearest neighbor (KNN) algorithm is a simple, supervised machine learning algorithm that can be used to solve either classification or regression problems. Despite its ease of implementation and interpretation, KNN algorithm is slow when dealing with large data. This algorithm votes for the maximum number of labels (in case of classification) or the average of labels (in case of regression) by finding the distance between a query and all data samples and choosing the nearest neighbors to the query (K value) [116].

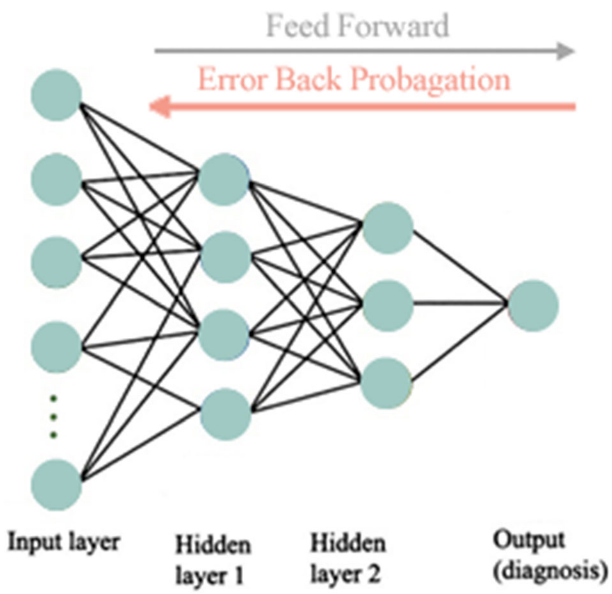


Fig. 20 Error Backpropagation neural network Architecture

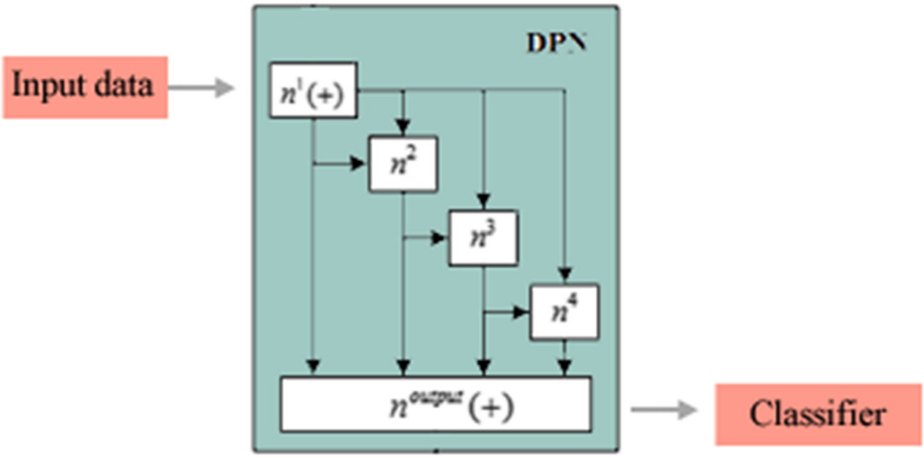


Fig. 21 Deep Polynomial Network Architecture

3.20 Deep polynomial network

Deep polynomial network (DPN) is a new supervised deep learning algorithm in which each node computes a linear or quadratic function of its inputs. The learned predictions are thus polynomial functions in the input space (Fig. 21). This operation is easy to perform with no reliance on complex computations. Compared to other deep learning algorithms, DPN shows a good performance in processing large-scale image data. Also, this algorithm well performs on a limited dataset as its structure was originally developed for small data size. DPN is devoted to polynomial nature of the neural network predictions, providing a reasonable basis for values achieved by polynomials in the training dataset [32].

In the following, these neural network results are discussed and given in Table 5. The criterion for comparing the results is the accuracy obtained from the classification of images into multiple groups.

Table 5 Classification of articles based on the accuracy of classification types of artificial neural networks

Neural Network Types	Classification accuracy range		
	Two groups	Three groups	Four groups
2 Dimensional CNN	64%–99.87%	72.19%–89.78%	73%
3 Dimensional CNN	64%–98.37%	86%–94%	51%–84%
SVM	68%–100%	73%–97%	–
Auto-Encoder	63%–98.80%	82.51%–88.73%	–
Multi-layer Neural Network	75%–98.5%	85%–89.52%	52%–56%
Res Net	64%–100%	83%	86.15%
3D Generative adversarial network (GAN)	64%–94%	–	–
Genetic Algorithm Neural Network(GA/ANN)	78%–86%	87.23%	–
Google Net	98.88%–99.7%	–	–
VGG Net	74%–98%	91.13%	–
Long short-term memory (LSTM)	77%–93%	84%	–
Error Backpropagation	95.4%–97.63%	–	–
Alex Net	91%	–	–
Deep Polynomial Network (DPN)	97.13%	–	–
Random Forest (RF)	91.90%–100%	–	–
K nearest neighbor (KNN)	94%	–	–

Accuracy refers to the proximity of measurement to the standard or true value. With respect to Formula 1, accuracy can be obtained.

$$Accuracy = \frac{Correct}{Correct + Incorrect}$$

According to the above formula, accuracy refers to the number of samples that were truly predicted by the algorithm. From the turbulence matrix, accuracy can also be defined as:

$$Accuracy = \frac{TP + TN}{TP + TN + FP + FN}$$

The maximum classification accuracy (100%) for classifying subjects into HC and AD or HC and MCI achieved by SVM, RF, and ResNet (Table 3). In [44], the recorded PET images from 19 HC and 65 MCI cases were used. These images were first preprocessed and divided into 116 regions of the brain. Using SVM, features of each region were then extracted by Gaussian functions and classified into two classes of HD and MCI. In [99], PET images recorded from 10 AD and 12 HC cases were classified by SVM algorithm. In this study, a series of SVM sequences is formed on 9 datasets. Five sequences were obtained from clinical trials and four sequences were the outcome of features extracted from images. All the sequences were merged and used to classify data into two groups.

In [36], MRI scans from 100 healthy people as well as 100 patients with slow cognitive impairment, MCI, and AD were classified into two classes with 60% training and 40% test data. Initially, scans were divided according to the anatomical regions of interest (ROI). Then, features were extracted, selected, and classified by RF algorithm. The accuracy obtained from classification into two groups of HC and AD was 100%. This accuracy ranged from 97% to 91% for classification among other groups.

In [125], MRI images of 138 subjects including 25 HC, 25 people with stable mild cognitive impairment (SMCI), 25 people at early stages of mild cognitive impairment (EMCI), 25 people with late mild cognitive impairment (LMCI), 13 MCI and 25 AD patients. In this study, 18-layer ResNet network was applied to train and classify images where an accuracy of 100% achieved from HC and SMCI classification. The accuracy of classification into HC and other groups was quite high varying in the range of 98% to 96%.

In the following, studies with an accuracy of more than 98% and less than 100% are to be argued. Convolutional networks have suitable architecture for feature extraction of images. In [13], a 5-layer 2D Convolutional network with MRI scans of 635 AD, 548 MCI, and 637 HC cases was trained and classified. The accuracy of classifying subjects into MCI and AD patients was obtained at 99.87%.

In [48], MRI scans were collected from 33 AD, 22 LMCI, 49 MCI, and 45 HC people and trained by GoogleNet and ResNet. The study findings suggested a higher accuracy (99.7%) for GoogleNet than ResNet. These two types of networks were also employed in research [47]. In this study, MRI scans of 61 LMCI, 84 MCI, 73 AD, and 137 HC people were trained by both networks and divided into two classes. With a slight difference, network accuracies were obtained at 98.88% and 98.01% for GoogleNet and ResNet, respectively.

In [150], a deep autoencoder was used to extract features of PET images. The extracted features and latent information of images were integrated to reach an accurate model for AD and MCI classification with an accuracy of 98.8%. In [172], MRI images were semi-automatically recorded from 17 AD 17 HC people, then trained and classified with an accuracy of 98.5% by a deep multilayer network. In another study, a 5-layer 3D convolutional network was employed to extract influential features of MRI scans recorded from 50 AD and 62 HC cases with an accuracy of 98.37% [11].

In the present research, two-class classifications yielding less than 98% accuracy were not reviewed in detail. The remaining is devoted to three or four-class classifications. In [110], MRI images were recorded from 554 AD, 326 HC, and 284 people with brain tumor. Afterward, they were preprocessed by SVM algorithm and finally classified into three classes with an accuracy of 97%. Deep learning architectures are effective in feature extraction of MRI images for AD diagnosis. In [159], a 3D convolutional network extracted, trained and classified features of MRI scans from 221 AD, 297 MCI, and 315 HC people with an accuracy of 94%. In [153], the database included MRI and PET images of 207 HC, 215 MCI, and 193 AD cases that were first combined, next classified, and then normalized with dimensions of 79 × 95 × 79. The resulting images were trained by a 13-layer VGG network and classified by 2 fully connected layers. For this study, the three-class classification accuracy was estimated to be 91.13%.

In [173], research was conducted on MRI and PET images of 163 HC, 113 EMCI, 105 LMCI, and 119 AD participants. In the first step, PET and MRI images were separately trained by a convolution layer. In the next step, extracted features from the first layer were combined and trained by 18-layer ResNet network. In the last step, four-class classification was done in the final layer where the model was estimated to be 86% accurate. In [146], MRI images of 186 people with memory disorders, 1222 EMCI, 1274 MCI, 636 LMCI, 718 AD, and 1520 HC were trained and classified into five-classes with a classification accuracy of 0.84. In all the reviewed articles in this research, classification accuracy was not the single criterion for network evaluation. Some other criteria were also considered such as backpropagation network used for ultimate determination of MRI images corresponding to HC and AD people in [6]. Further in [112], MRI images were processed to distinguish healthy people from patients by a convolutional auto-encoder.

4 Discussion

The study findings suggest that research in the field of AD prediction and diagnosis by the use of artificial neural networks is of great importance. Since AD is a progressive disease occurring at different stages of MCI, its early diagnosis assists doctors in controlling brain damage and saving patients' lives. According to Fig. 5, the number of studies increased at the rate of 2.5 times from 2016 to 2017 and at the rate of 2 times from 2017 to 2018. The number of studies has been growing by the first half of 2020. Neural networks are useful tools for predicting and diagnosing cognitive impairments based on recorded images of brain function or tissue. Many factors must be considered for the selection of neural networks including the complexity of data, required hardware/software, number of subjects, network compatibility with the problem, and the performance time. On the other hand, these networks have flexible architectures that can be modified to yield better results. The 2D and 3D multi-layer convolutional networks and other convolution-based architectures such as ResNet and GoogleNet are compatible with feature extraction. The images were classified in terms of their effective features extracted from anatomical regions. For semi-automatic and other extraction methods than deep learning, machine learning algorithms of SVM and RF provide a high classification performance.

In general, participants have been classified into 2, 3, 4, or 5 classes in the reviewed studies. Most studies have divided people into two-class classification of HC and AD or three-class classification of HC, MCI, and AD. People have been classified into four or five groups of different MCI stages in a small number of studies. The reviewed studies have been carried out for the main purposes of classification, diagnosis, detection, prediction, and so forth. Some of them have been conducted for research application in the practical models of computer-aided diagnosis (CAD) and clinical decision support systems (CDSS). Several studies have aimed at extracting the most influential features of recorded brain images from patients. This study review reveals MRI images and their combination with PET images were more helpful than CT in diagnosing the disease. In sum, images from ADNI database were the most downloaded by the researchers. In the future, two deep learning networks including modified convolutional and convolutional auto-encoder neural networks will be proposed for differentiating between subjects of AD, MCI and HC.

It is suggested to develop other accurate and efficient neural networks for image processing such as Inception V3. It is also recommended to use a combination of two neural networks for future work. Moreover, other image analysis techniques or data augmentation merit further investigation. Since time is an important parameter for analyzing images and making decisions on CAD or CDSS systems, fast networks are more suggested such as Mobile net and so on. There is a need for more comprehensive and integrated datasets to extract the influential features of brain images. These features are expected to act as a ground for future research on the detection and segmentation of brain diseases.

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