



Article

A Practical Multiclass Classification Network for the Diagnosis of Alzheimer's Disease

Rizwan Khan ¹, Zahid Hussain Qaisar ², Atif Mehmood ³, Ghulam Ali ⁴ , Tamim Alkhalifah ⁵ , Fahad Alturise ^{5,*} and Lingna Wang ^{1,*}

¹ School of Computer Science and Mathematics, Zhejiang Normal University, Jinhua 321004, China; rizvan@zjnu.edu.cn

² School of Computer Science, Huazhong University of Science and Technology, Wuhan 430074, China; zahidqaisar@hust.edu.cn

³ School of Computer Science, National University of Modern Language, NUML, Islamabad 44000, Pakistan; atif.mehmood@numl.edu.pk

⁴ Department of Software Engineering, University of Okara, Okara 56310, Pakistan; ghulamali@uo.edu.pk

⁵ Department of Computer, College of Science and Arts in Ar Rass, Qassim University, Ar Rass 58892, Saudi Arabia; tkhliefh@qu.edu.sa

* Correspondence: falturise@qu.edu.sa (F.A.); lingna@zjnu.edu.cn (L.W.)

Abstract: Patients who have Alzheimer's disease (AD) pass through several irreversible stages, which ultimately result in the patient's death. It is crucial to understand and detect AD at an early stage to slow down its progression due to the non-curable nature of the disease. Diagnostic techniques are primarily based on magnetic resonance imaging (MRI) and expensive high-dimensional 3D imaging data. Classic methods can hardly discriminate among the almost similar pixels of the brain patterns of various age groups. The recent deep learning-based methods can contribute to the detection of the various stages of AD but require large-scale datasets and face several challenges while using the 3D volumes directly. The extant deep learning-based work is mainly focused on binary classification, but it is challenging to detect multiple stages with these methods. In this work, we propose a deep learning-based multiclass classification method to distinguish amongst various stages for the early diagnosis of Alzheimer's. The proposed method significantly handles data shortage challenges by augmentation and manages to classify the 2D images obtained after the efficient pre-processing of the publicly available Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset. Our method achieves an accuracy of 98.9% with an F1 score of 96.3. Extensive experiments are performed, and overall results demonstrate that the proposed method outperforms the state-of-the-art methods in terms of overall performance.

Keywords: Alzheimer's disease; multiclass classification; deep learning



Citation: Khan, R.; Qaisar, Z.H.; Mehmood, A.; Ali, G.; Alkhalifah, T.; Alturise, F.; Wang, L. A Practical Multiclass Classification Network for the Diagnosis of Alzheimer's Disease. *Appl. Sci.* **2022**, *12*, 6507. <https://doi.org/10.3390/app12136507>

Academic Editor: Vladislav Toronov

Received: 25 April 2022

Accepted: 1 June 2022

Published: 27 June 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

The causes of Alzheimer's disease and related dementias result in several neurological disorders. These disorders affect a significant population of the world. AD and associated dementias also affect the functionalities of the brain and cause problems of memory loss depending upon the degenerative changes in the brain. The underlying causes for these changes are unknown and limit the cognitive capabilities of the brain. The cognitive decline evolves rapidly with the passage of time and results in the progression of AD [1,2]. The marked increase in AD heavily affects the health care system due to the irreversible and incurable nature of this fatal disease. AD can cause more than only a loss of memory or cognitive ability, and in the latter stages of the disease, the patient may have difficulties in walking and eating, which ultimately cause death. Patients suffering from various dementias are subjected to brain image testing to understand the loss of brain cells associated with the AD [3].

The progression of AD is categorized into various stages ranging from normal control (NC) to early mild cognitive impairment (EMCI) and late mild cognitive impairment (LMCI). It is a complicated task to determine the normal brain cells with the MRI scans and distinguish among various stages of Alzheimer's [4,5].

Current high-dimensional diagnostic techniques generate 3D MRI images with thousands of voxels in a single image. The direct use of these images in the convolutional neural network raises the challenges of computational complexity and data management [6]. One of the major challenges in the target domain is the unavailability of the large-scale balanced dataset, whereas the deep learning-based framework is data-hungry and is heavily dependent on the large-scale input training data [7]. It can be observed in Figure 1, where the working principle for capturing MRI images is shown, that skull stripping and slice extraction are the main issues while feeding the data samples to the neural network. In the absence of large-scale datasets, learning distinctive features in brain images with similar pixel intensities is challenging for multi-scale classification. The discriminative learning of the existing binary classification methods are hardly applicable for the multi-level classification; therefore, new methods are imperative to handle these challenges [8].

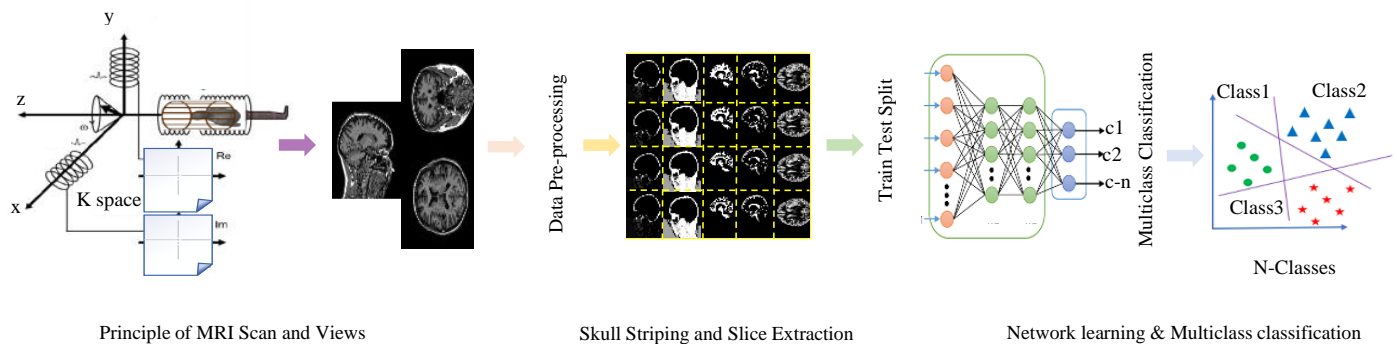


Figure 1. The workflow of the proposed architecture. MRI scans are pre-processed with data cleaning operations for the train-test split to feed in the network for multiclass classification.

The capacities of the traditional methods are limited and might be prone to several artifacts due to the similar brain pattern and pixel intensity of the images. The recent advancements in machine learning and deep learning provide a unique way to distinguish such brain scans. The convolutional neural networks (CNNs) can automatically detect and distinguish among the various pattern and play a vital role in computer vision and medical image analysis [9,10]. Thus, deep learning approaches contribute to predicting the above-mentioned stages of AD. The authors of [11] suggested a pairwise similarity analysis for each modality based on the multimodal framework by using non-linear graph fusion for distinct modalities for classification. Some methods used support vector machine-based (SVM) classifiers with a mixed kernel approach [12] for the multimodal classification of AD and mild cognitive impairment. Some methods also used the combination of MRI biomarkers for volumetric measurement, hippocampal shape, and texture following the multiclass classification [13]. The recent methods proposed in the literature are becoming very popular for identifying and detecting Alzheimer's disease. By using these frameworks, researchers have recently conducted a plethora of experiments on the early identification of Alzheimer's disease using machine learning and deep learning technologies. Consequently, computer-assisted methods have been proposed for detecting Alzheimer's disease, particularly in individuals with severe dementia [14]. The computer-assisted smart system can significantly improve the detection without the involvement of the neuro-physicians [15].

The fundamental problem of image classification is based on the network's training on the labelled data. Next, the network is asked to predict the novel test sample of various categories for the accuracy of predictions. The classification problem is further categorized as binary and multiclass classification [16]. This work proposes a practical multiclass classification network for the primitive diagnosis of Alzheimer's disease (PMCAD-Net).

The workflow of the proposed framework is shown in Figure 2. It demonstrates the whole pipeline ranging from the collection principle of capturing the MRI images with intermediate processing stages to multiclass classification. The proposed method is capable of handling the challenges of data shortages, as we apply a data augmentation strategy to resolve the challenges. The 3D MRI images obtained from the ADNI data repository are pre-processed and converted into 2D images. Data cleaning operations are performed, including skull stripping normalization, registration, and segmentation. The proposed multiclass classification network avoids the negative transfer learning challenges faced by the previous methods and gets trained from scratch. It is important to note that the dataset in the image classification tasks are typically very large, whereas it is a complicated task to obtain a sufficiently large-scale dataset in the target domain. The data augmentations improve the data diversity. The operation of random cropping, rescaling, flipping and brightness changes are employed to obtain sufficiently large-scale generalized data as shown in the first part of Figure 2. These operations improve the learning capabilities of the network shown in the same figure for key aspects of the input data classes. Extensive experiments are conducted for the performance evaluation of the proposed network. The overall comparison demonstrates that our method outperformed the state-of-the-art approaches.

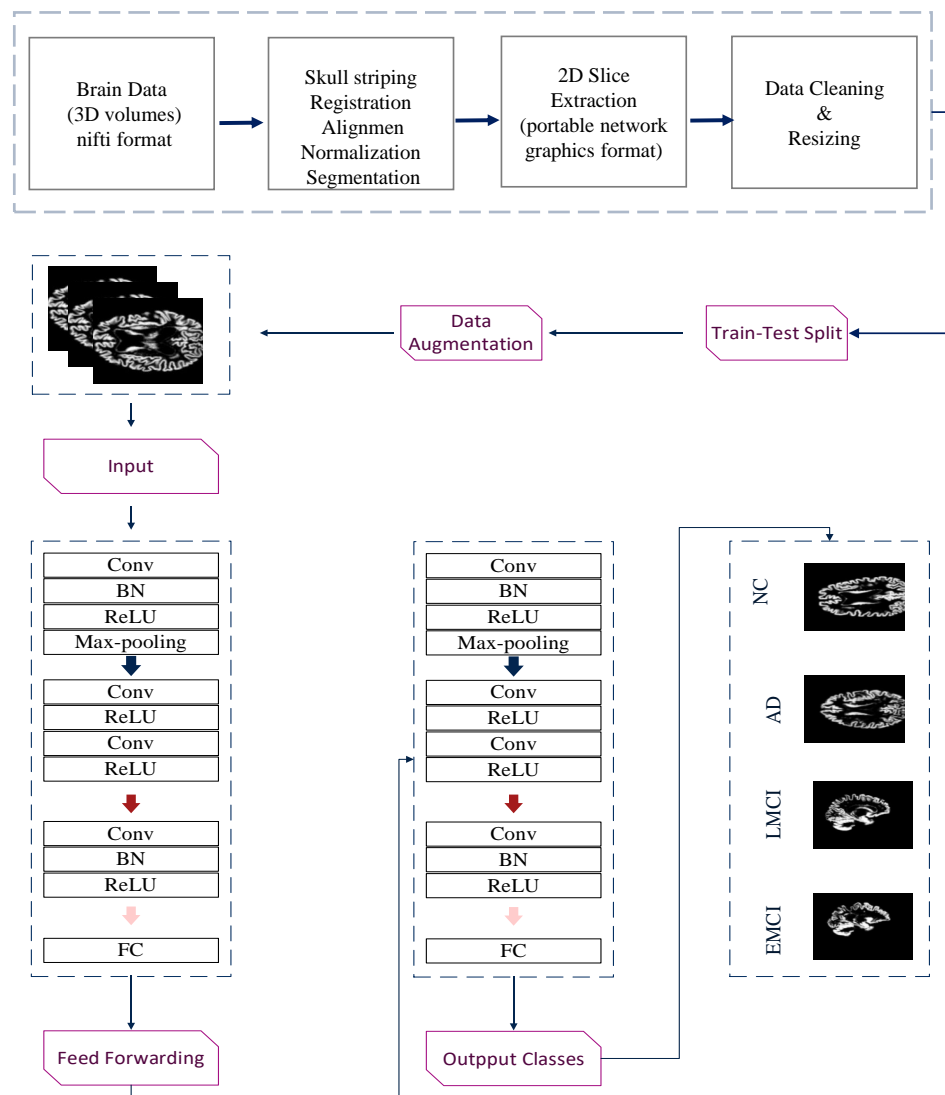


Figure 2. Framework of the proposed framework, with several pre-processing steps, and detailed architecture of the practical multiclass classification network for the diagnosis of Alzheimer’s disease (PMCAD-Net).

This work focus on multiclass classification, where we also resolve the challenges of the data shortage. There are several problems, including perspective fluctuation, size, scale, class, and data variation [17]. The extant methods in the literature rely on the pre-trained models and suffer several problems, including computational complexity and layer freezing.

2. Related Work

Alzheimer's disease is one of the most common kinds of neurological dementia, resulting in various memory-related neurological disorders. According to the 2015 World Alzheimer's Report, around 50 million people worldwide have dementia, with Alzheimer's disease accounting for 70–80% of cases [18]. Alzheimer's disease will impact 131.5 million people globally by the year 2050 according to projections [19]. The number of AD patients is increasing day by day, and it is one of the primary causes of death among older adults. The extant methods for the detection of the AD are heavily dependent upon neurological scans and high-dimensional data, including several imaging modalities such as MRI, functional MRI (fMRI), positron emission tomography (PET), amyloid-PET, and diffusion tensor imaging. However, due to nuance in patterns, it is still very challenging to distinguish between the patterns with radiological reading. Thus, it challenging to diagnose AD at an early stage. Recently, several methods have been proposed for image enhancement [20–22] based on machine learning, deep learning and few shot learning [23]. These feature extraction- and classification-based approaches [24,25] are commonly used to design predictive models for intelligent and expert system-based applications [9,26].

Based on MRI, a multi-modal framework is proposed to extract neurological features with a consistent metric constraint for the classification of various dementias [27]. A deep Siamese convolution neural network (SCNN) for the multiclass classification of AD is proposed in [28] to classify various stages of the disease. A natural image-based network to represent neuroimaging data (NIBR-Net) is a significant approach in the target domain, based on sparse autoencoder [29], where the network learns from a set of bases from natural images with the help of convolution to extract features from the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset. Another deep sparse multi-task learning method, along with a feature-adaptive weighting scheme for feature selection in AD (DSMAD-Net), is proposed in [30]. It selects the useful features in a single hierarchy and iteratively filters out undesired features hierarchically. It also uses regression coefficients as context information and reflects the complex distributional characteristics in each class. In a similar fashion, a deep learning-based 4-way multiclass classifier (DLMCC-Net) is proposed in [31]. This framework follows some extant frameworks such as Google-net architecture [32] for the multiclass classification of various stages of the disease. A network-based transfer learning approach for the early diagnosis of AD (TLEDA-Net) is proposed in [33], and another Alzheimer's disease classification using transfer learning (ADTL-Net) is proposed in [34]. At the same time, the class imbalance issue is handled in [35] with a DEMNET by using the pre-processed Kaggle dataset. Another convolutional neural network-based Alzheimer's disease classification from MRI brain data (CNN-AD) is proposed in [7].

The earlier techniques for multiclass classification were developed in the target domain with a substantial gradient flow strategy to improve the performance [36]. Using three-dimensional image features, a Sobolev gradient-based optimization approach was proposed for the accurate diagnosis of AD following a 3D convolutional network (SGO-3D) [37]. The authors of [38] proposed a neuroimaging study based on a 3D convolutional neural network for predicting Alzheimer's disease (3D-CNN-PAD). Another multiclass classification method in [39] employed CNN architecture following a transfer learning-based framework for the AD. The authors of [40] developed a 3D deeply supervised adaptable convolutional neural network (CNN-3D) to predict AD. This framework can work without the skull striping, such that the CNN-3D can learn the generic features capturing AD biomarkers. The transfer learning approach requires the complex optimization and fine-tuning process, which raises the complexity of multiclass classification. It can be seen in Figure 3,

where the overview of the 3D images illustrates the capturing strategy with the 3D views. On the other hand, the 3D subjects without skull stripping have several challenges besides computational complexity.

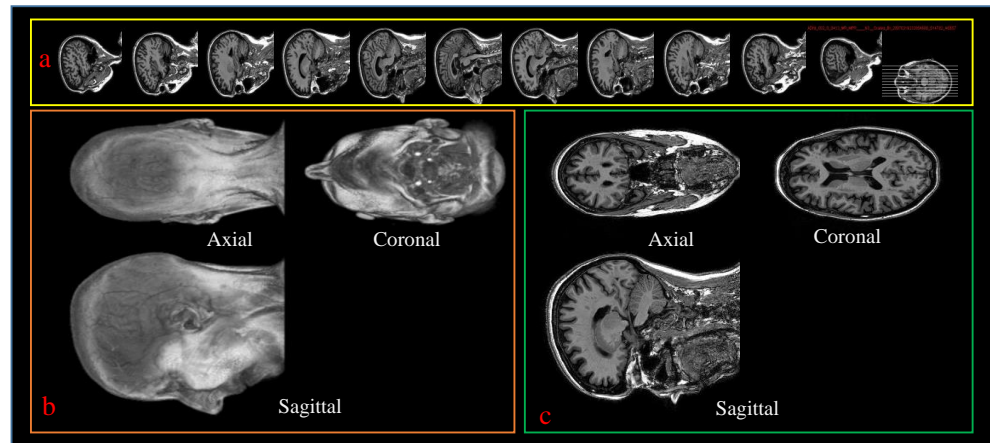


Figure 3. Overview of the capturing process. (a) The scans, (b) pre-processed 3D images of axial, sagittal, and coronal views, and (c) processed axial, sagittal, and coronal views.

Classification among multiple classes with overlapping features and similar pixel intensity is challenging. The proposed network can handle the challenges of multiclass classification and overcome the aforementioned data shortage problems. We perform several experiments and tune hyperparameters to obtain optimal accuracy. The experimental results demonstrate the superiority of the proposed method.

3. The Proposed Methodology

In this work, we proposed an effective and practical multiclass classification network for the primitive diagnosis of Alzheimer’s disease. Input data samples (i.e., 3D MRI scans) are pre-processed via statistical parametric mapping software (SPM12), where the respective operations (i.e., skull stripping, registration, normalization, and segmentation) are applied to the input images to extract the useful 2D image slices after the segmentation of the MRI scans as shown in Figure 1. The challenges of the data shortage are handled with the help of the data augmentation technique. The input data samples are fed into a lightweight yet effective PMCAD-Net. The architecture of the network is shown in Figure 2, which is designed while considering the target problem of classifying multiple classes in the absence of large-scale data samples. The proposed network is suitable for the user-specific multiple classes available for classification based on the optimal layering and loss adjustments of our PMCAD-Net.

3.1. The Proposed Practical Multiclass Classification Network for Alzheimer’s Disease

In this section, we explain the framework of the practical multiclass classification network to classify various stages of Alzheimer’s disease based on the MRI data. A comprehensive pre-processing pipeline was designed to extract the 2D images from the 3D MRI volumes for the proposed network to detect AD at the earliest possible stage (pre-dementia). Because of the complexity of the pattern, it is difficult to discriminate between the patterns with quantitative analysis and even radiological scans at the early stages of AD. To detect changes in the biomarkers, the pre-processed data (i.e., 2D slices extracted from the MRI volumes) were fed to the network. The network learned to classify changes in the information to distinguish EMCI, LMCI, NC, and AD. The proposed learning-based framework limits the complexities of diagnosing and monitoring disease at an early stage.

Convolutional layers extract the features and initialize the process in deep learning-based frameworks. The images in the data were multiplied with the convolutional kernel following the window. The formula for the height and width of the convolution output after the convolution filter is expressed below.

$$C_o = \frac{I_h - R_h + 2P}{S} + 1 \quad (1)$$

$$C_o = \frac{I_w - R_w + 2P}{S} + 1 \quad (2)$$

where I_h , and I_w , show the image height and width, with R_h and R_w representing the kernel height and width along with filter size with the padding P and stride S . The proposed convolutional neural network takes the pre-processed data with a size of 224, beside a kernel size of 3, stride of 1, and padding of 1. After that, we applied batch normalization to normalize the data. To bring non-linearity, a rectified linear unit (ReLU) was applied, and next to it, a max-pooling was applied with a kernel size of 2 to adjust the output shape. It reduced the height and width of the convolutional output following a factor of 2. The shape of the convolutional layer output was next adjusted with a stack of convolutional layers and a ReLU layer (3×3 , Conv+ReLU). Finally, a fully connected layer was applied with the input features following the convolutional layer output. It resulted in the general output features following the output class. This output, when fed to the fully connected layer, reshaped the desired matrix, providing the final output. The output classes in PMCAD-Net were 4 when we utilized the Adam optimizer and backpropagation in the proposed framework. The learning rate was 0.0001 for 100 epochs in the presence of categorical cross-entropy loss. It is critical to improve the model's performance in terms of accuracy. The performance and accuracy of the model are improved by the loss function, which also depicts the model's deviation from the correct predictions. In general practice, logistic regression following linear classification algorithms and convolutional neural networks are utilized for classification problems. These tasks involve the prediction of one or more input variables with class labels for the classification models. Where binary class classification has only two labels, multiclass classification has more than two labels. Thus, the loss function also varies from binary class to multiclass problems.

The proposed PMCAD-Net can predict more than two class labels for a given pre-processed ADNI data sample. Thus, we utilized the categorical cross-entropy loss function for the available classes, including NC, EMCI, LMCI, and AD. The cross-entropy for this data can be categorically described by assigning the probability values as variables. In our model, we modified model weights during training by utilizing the categorical cross-entropy loss \mathcal{L}_{CrE} , with p_i probabilities for i^{th} labels with truth values t_i in the range of $[0, 1]$, for the N number of classes.

$$\mathcal{L}_{CrE} = \sum_{N=1}^n \sum_{i=1}^{n(size)} t_i \log(p_i) \quad (3)$$

The goal was to reduce the loss as much as possible; the less the loss, the better the model. In each case, the cross-entropy for the i number of classes was estimated for the dementia's d_i , where $i = 1 \dots 4$ in this case. The probability of the output y for each class can be estimated for the dementia, where the cross-entropy for each category NC, EMCI, LMCI and AD is $CE_{NC}, CE_{EMCI}, CE_{LMCI}$, and CE_{AD} , respectively.

3.2. Data Pre-Processing for the Proposed Network

MRI technology has revolutionized the detection and diagnosis of neurological diseases, and researchers are continuously improving and refining MRI technology. The advantages are multi-fold, including the improved view of the tissues and non-ionizing radiation. However, deficiencies in the uniform intensity scale of the image make it difficult to visualize and evaluate the information. Moreover, the artifacts arising due to

mechanical deficiencies, motion, scanner-based changes, and capturing inefficiencies must be considered before processing these images. MRI scans face several artefacts during the capturing process due to their capturing inefficiencies (i.e., wrong lens, slit position, etc.) or device limitations. These limitations contribute to the loss of the necessary information in the scans. It ultimately limits the performance of the image processing and detection frameworks [41].

Therefore, pre-processing techniques are generally used to avoid deterioration due to enhancement in the contrast and pixel intensity. We also propose performing the preprocessing operations on the input data available for training and testing the proposed PMCAD-Net. MRI images of the brain are available as Nifti format volumes. These volumes consist of multiple slices captured during the scanning process as shown in Figure 3a. In this Figure, (b) shows the 3D views and (c) shows the axial, sagittal, and coronal views, respectively. As mentioned earlier, the direct use of this 3D volume results in several complications. In general, the physical spacing is considered a consistent parameter for the detection and segmentation tasks. The maintenance of the same resolution is the primary and desirable feature to avoid the center-specific findings. The usual image interpolation along the x -axis, y -axis, and z -axis is based on the frequent physical spacing requirement or number of voxels [42]. Thus, it is important to consider the appropriate, consistent sampling steps because non-uniformity can affect registration and resolution during subsequent processing. Image registration interprets the spatial changes with the reference image and plays a crucial role in medical image processing. Image registration in the target domain can be illustrated as slice-level registration generally performed to handle the capturing motion artifacts. It might give rise to several complications, including random noises and image interpolation [43]. However, it is out of the scope of this work. In our method, we aligned the input images of our training dataset for ease of learning for the associated classification task. Although the proposed PMCAD-Net is robust enough to learn the task without the pre-process registration step, by facilitating the training and limiting the number of false positives, we included registration for our dataset. A pre-processing step is required to convert these images into 2D images. To interpret the useable information from the available volumes, several operations are performed on the MRI scans, including skull stripping, segmentation, and spatial normalization by using SPM12 software. We segment the brain data into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF). It is important to note that the target problem focuses on the early detection of AD and associated dementia, where we consider the GM to describe the early changes in AD. Considering the nature of the target problem, we extracted the information through brain data and regularized it at the rate of 0.0001. The data samples were extracted with the preliminary shape of 256×240 . These images were resized to a size of 224×224 to design the dataset for the proposed PMCAD-Net.

4. Dataset, Experiments and Discussions

4.1. Dataset

In this work, the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset [44] is utilized. ADNI brings together experts and study data to help characterize Alzheimer's disease progression (ADP). MRI and PET imaging, genetics, cognitive tests, CSF, and blood bio-markers are all used by ADNI researchers to gather, validate, and use data as disease predictors. ADNI includes Alzheimer's disease patients, mild cognitive impairment individuals, and older controls, as well as research tools and data from the North American ADNI project. The information of the datasets are present in Table 1. Subjects in this dataset are scanned with respect to different durations of time and visits. Each of the scans in this study is considered a different subject. The overall dataset is divided into 70% as the training dataset, 20% as testing data, and 10% as the validation dataset. In this work, we are handling the complex challenges of multiclass classification for a limited amount of available data. An imbalanced dataset balanced with the augmentation technique is made suitable for the optimal performance of the PMCAD-Net. Multiple categories are available

in the present case, ranging from normal controls (NC) to mild cognitive impairment (MCI) and AD. In comparison, MCI can be classified as early mild cognitive impairment (EMCI) and late mild cognitive impairment (LMCI). It is important to note that the collection of large-scale datasets for MRI imaging is one of the major challenges. A dataset of various patients, including 75 AD, 75 EMCI, and 70 LMCI patients, and 80 NC patients, was obtained from the ADNI database. These images were pre-processed, and augmentation was applied to obtain a uniform and equivalent number of images for multiclass classification. It facilitates handling the major challenge of the early detection of AD.

Table 1. Sample size of the dataset utilized for training and testing the network.

Type	Subjects	Age	MMSE
NC	80	73 ± 8.5	26.5 ± 1.4
EMCI	75	74 ± 7.7	29.5 ± 1.2
LMCI	70	72 ± 7.9	28.5 ± 1.6
AD	75	75 ± 9.5	24.5 ± 1.9

4.2. Experimental Setting

The proposed PMCAD-Net was trained from scratch using the Pytorch framework, Adam optimizer, and backpropagation at a learning rate of 0.0001. The categorical cross entropy loss function was utilized for the optimization of the multiclass classification in the proposed network. The network gets regularized by utilizing only available input samples for training. The network becomes capable of predicting the input data's multiple classes. The overall comparison with the state-of-the-art approaches demonstrated that our method is more practical and suitable in the target domain. We utilized a PC core i7, 6700 K CPU@4 GHZ 32 GB RAM, NVIDIA 2080 Ti GPU to perform the experiments. The comparison with competitor approaches demonstrated that the PMCAD-Net outperformed the state-of-the-art approaches. The preliminary implementation guidelines and data pre-processing strategies are available at our GitHub (<https://www.github.com/imrizvankhan/PMCAD-Net>) repository.

4.3. Experimental Evaluations and Discussions

The proposed PMCAD-Net utilizes a considerably fair amount of available datasets for training. The training proceeded for 100 epochs, with a batch size of 32 and a learning rate of 0.0001. In order to evaluate the efficiency of the proposed framework, we compared PMCAD-Net with several state-of-the-art approaches. The comparison was based on the measurement of the F1-score, specificity (Sp), sensitivity (Se), accuracy (Ac) and precision (Pr) value predictions. These metrics are based on the measures of true positives (TP), true negatives (TN), false positives (FP), and false-negatives (FN) [45].

4.3.1. Positive Predictive Value

The positive predictive value is called the precision and shows the portion of real positive cases.

$$Pr = \frac{TP}{TP + FP} \quad (4)$$

4.3.2. Sensitivity

Sensitivity is the recall value that shows the actual positive and the correctly predicted portion of values. This metric reflects correctly anticipated cases and depicts the coverage of real positive cases, also termed as the true positive rate (TPR).

$$Se = \frac{TP}{TP + FN} \quad (5)$$

4.3.3. Specificity

Specificity is associated with the likelihood of the negative test rate in the absence of the condition and is considered a true negative rate.

$$Sp = \frac{TN}{TN + FP} \quad (6)$$

4.3.4. Accuracy

The classification accuracy is a statistical measurement that evaluates the performance of a classification model by dividing the number of correct predictions by the total number of predictions.

$$Ac = \frac{TP + TN}{TP + FN + TN + FP} \quad (7)$$

4.3.5. F1 Measurement

The F-Metric is a method for combining accuracy and recall into a single measure that encompasses both and is widely utilized in classification tasks.

$$F1 - Measure = \frac{TP}{TP + \frac{1}{2}(FP + FN)} \quad (8)$$

The evaluation results for the classification are shown in Table 2. In this table, we provide the results with a 15% dataset of train-test split. We generalized the comparison and selected several state-of-the-art approaches for comparison, including a CNN-3D model [40], 3D-CNN-PAD [38], NIBR-Net [29], DSMAD-Net [30], DLMCC-Net [31], SCNN [28], and TLEDA-Net [33]. The comparison with all of these methods is shown in Table 3. The comparison was based on multiple modalities, where the distinction of each of the approaches is also shown beside the type of dataset. The comparison in this Table is shown in terms of accuracy, where the proposed method outperformed the state-of-the-art methods. Next, we extended the canvas of experiments and included several other methods and metrics to evaluate the proposed approach. The competitor methods include DEM-Net [35], CNN-AD (VGG-16) [7], and ADTL-Net [34]. The comparison with these methods was based on the F1-score, accuracy, sensitivity, and positive predictive value. The results are shown in Table 4 with a 20% & 80% test and train split, respectively. The comparison of the MRI modality on various datasets demonstrates the overall recall, precision, and prediction score, where our method outperformed the competitor approaches. We also present the graphical representation for the overall sensitivity, accuracy, specificity, and precision in Figure 4. The plots demonstrate the visual analysis for the four classes (i.e., NC, EMCI, LMCI, and AD.) described as four groups (i.e., Group1–Group4). As shown in Figure 4 group 1, group 2, group 3, and group 4 represent the sensitivity, accuracy, specificity, and precision, respectively, for each of the four classes (i.e., NC, EMCI, LMCI, and AD) along-with the average value for these four parameters and classes. The graphical representation is based on the overall performance of the PMCAD-Net, as shown in Table 2. The behavior of these plots is illustrated explicitly in Table 5, where various features of the graphs illustrate the overall performance of the proposed network. The comparison illustrates that our method outperforms several states of the art approaches.

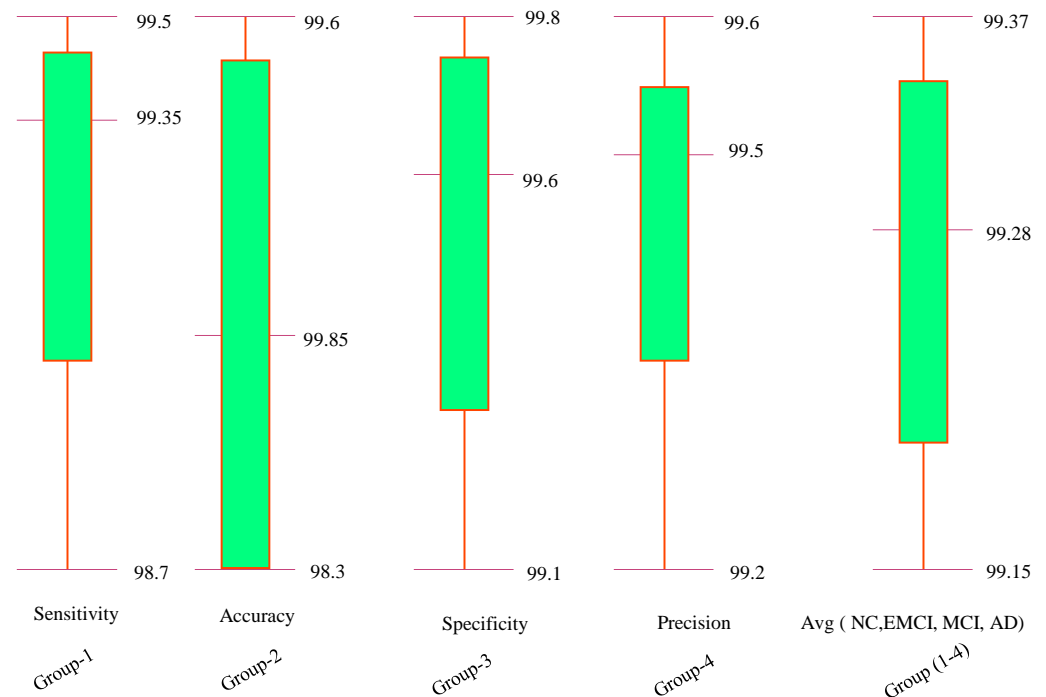


Figure 4. The graphical analysis of the performance of the proposed network. Box plots are shown for the sensitivity, accuracy, specificity and precision for all the four groups (i.e., Group 1–4); each group is comprised of 4 classes (i.e., NC, EMCI, LMCI, and AD). The average is also shown for all groups (i.e., Group 1–4).

Table 2. The comparison of the performance in terms of overall accuracy of the PMCAD-Net on various classes, including normal controls (NC), early mild cognitive impairment (EMCI), late mild cognitive impairment (LMCI), and Alzheimer’s disease (AD).

Classes	Sensitivity	Accuracy	Specificity	Precision	Overall Average
NC	99.3	98.3	99.5	99.5	99.15
EMCI	99.4	99.6	99.1	99.2	99.32
LMCI	98.7	99.4	99.8	99.6	99.37
AD	99.5	98.3	99.7	99.5	99.25
Average per group (Proposed Work)	99.2	98.9	99.5	99.4	99.27

Table 3. Comparison of the accuracy of the various state-of-the-art approaches with the proposed work.

Authors	Methods	Modalities	Distinction	Data	Accuracy
Hossemi et al. [40]	CNN-3D	MRI	NC, MCI, AD	ADNI	94.8
Ayan et al. [38]	3D-CNN-PAD	MRI	NC, MCI, AD	ADNI	85.3
Gupta et al. [29]	NIBR-Net	MRI	NC, MCI, AD	ADNI	78.2
Suk et al. [30]	DSMAD-Net	MRI+PET	NC, MCI, AD	ADNI	62.9
Farooq et al. [31]	DLMCC-Net	MRI	AD, MCI, LMCI, NC 4-way classification	ADNI	98.6
Mehmood et al. [28]	SCNN	MRI	Stages of Dementia 4 way classification	OASIS	99.05
Atif et al. [33]	TLEDA-Net	MRI	AD, MCI, LMCI, NC 2 way classification	ADNI	83.64
Proposed Work	PMCAD-Net (This Work)	(This MRI)	AD, MCI, LMCI, NC 4 way classification	ADNI	99.25

Table 4. Comparison of the proposed work with various state-of-the-art approaches in terms of evaluation metrics.

Authors	Methods	Modalities	Distinction	Dataset	F1 Measure	Accuracy	Sensitivity Recall	Positive Prediction Precision
Murugun et al. [35]	DEMNET	MRI	AD, MCI, LMCI, NC	Kaggle	95.2	95.2	95	95.2
Jian et al. [7]	CNN-AD (VGG-16)	MRI	AD, CN, MCI	ADNI	95	95.13	96	96.3
Acharya et al. [34]	ADTL-Net	MRI	AD, MCI, LMCI, NC	Kaggle	94.7	95.7	92.3	91.9
Proposed Work	PMCAD-Net (This work)	MRI	AD, MCI, LMCI, NC	ADNI	96.34	99.2	96.3	96.4

Table 5. The parametric representation for the understanding of the boxplots and overall behaviour of the network.

Groups	N	Min	Q1	Median	Q3	Max	Mean	Excess Kurtosis	Skewness Shape	Skewness
Group 1 (Sensitivity)	4	98.7	99	99.35	99.45	99.5	99.225	-1.696387	Potentially symmetrical (pval = 0.094)	3.01436
Group 2 (Accuracy)	4	98.3	98.3	98.85	99.5	99.6	98.9	-5.593263	Potentially symmetrical (pval = 0.944)	0.070691
Group 3 (Specificity)	4	99.1	99.3	99.6	99.75	99.8	99.525	0.757656	Potentially symmetrical (pval = 0.262)	0.757656
Group 4 (Precision)	4	99.2	99.35	99.5	99.55	99.6	99.45	2.888889	Potentially symmetrical (pval=0.129)	-1.539601

4.4. Discussion

The readily available binary classification approaches are hardly suitable for multiple classes and require additional resources and effort. On the other hand, the extant work on multiple-class classification requires a large-scale dataset. Some approaches such as the transfer learning-based methods, DLMCC-Net [31] and TLEDA-Net [33], can somehow resolve the problems, but the layer adjustment challenges and the dataset for pretext tasks and the dataset for the downstream may result in domain mismatch. The pre-trained models may converge, but they will fall in a local minimum. Therefore, the performance in these cases will not be better than training from scratch. The challenges are more comprehensive than transfer learning when it comes to training the network from scratch.

The proposed PMCAD-Net also provides a solution for 4-way classification for detecting and diagnosing various stages of Alzheimer's disease. The comparison to other competing techniques demonstrates that our model is critical in accurately diagnosing AD, EMCI, LMCI and NC in a single model framework. This will aid in determining additional illness severity levels as compared to the binary level of classification in some of the previous methods [33]. The proposed multiclass classification of various stages of Alzheimer's disease outperformed the competitor approaches. Comparison with the state-of-the-art approaches is based on the ADNI, OASIS, and Kaggle datasets. The overall performance is shown in Table 2, where we demonstrate the effectiveness of the system in terms of various evaluation metrics. Our PMCAD-Net achieves a superior numeric score.

The performance is further elaborated in the form of box plots, as shown in Figure 4. In this figure, the average analysis and individual analysis are explicitly shown to illustrate the performance of our method. The generalized comparison with other competitor methods, including the CNN-3D model [40], 3D-CNN-PAD [38], NIBR-Net [29], DSMAD-Net [30], DLMCC-Net [31], SCNN [28], and TLEDA-Net [33] is also shown in Table 3. The generalized comparison of the performance is based on F1-score, accuracy, recall (i.e., sensitivity), and positive prediction (i.e., precision) metrics, which are shown in Table 4.

Our method achieves an F1 score of 96.34, an accuracy of 99.2, a recall rate of 96.3, and a precision value of 96.4. The comparison with other methods demonstrates the superiority of the proposed framework.

The overall analysis in terms of performance evaluation metrics demonstrates that the proposed PMCAD-Net outperformed the extant methods. The general architecture allows the users to train it on their own dataset to obtain the desired results. In this case, we train the network for four classes (i.e., NC, EMCI, LMCI, AD); however, it is suitable for more than four classes. If the number of stages increases, such as the addition of the significant memory concern (SMC) and mild cognitive impairment (MCI) classes, this will raise the complexity of classification to 6 classes (i.e., NC, EMCI, LMCI, MCI, SMC, and AD). However, the proposed network can also handle these classes if it is trained on these six classes without any significant modification in the network architecture. Our PMCAD-Net is simple yet effective and has a clear advantage over the extant binary-class and multiclass classification approaches. This work's overall comparison for multimodalities demonstrates that our method outperformed the competitor approaches in terms of F1-score, accuracy, specificity, sensitivity, and precision metrics. The improvement demonstrates that our method represents a promising performance for detecting various stages of the AD.

5. Conclusions

In this work, a practical multiclass classification network for the diagnosis of Alzheimer's disease (PMCAD-Net) is proposed to predict various stages of AD. A generalized framework is proposed to distinguish NC, EMCI, LMCI, and AD. In the proposed framework, we utilize the MRI volumes from the ADNI database and pre-process them to obtain the 2D images. The data-insufficiency problems are handled using the data augmentation approach, which improves the proposed network's robustness, overall performance, and accuracy. The proposed network can handle the various stages of AD and can be extended to several intermediate stages if required. The overall comparison with the state-of-the-art approaches demonstrates that the proposed method outperformed the others. The findings of this study demonstrate that deep learning-based approaches can contribute significantly to the detection of neurodegenerative disorders. Clinical imaging combined with deep learning algorithms can help to diminish the risk factors and prognostic indicators as well as understand the patterns of functional changes in the brain linked with the progression of Alzheimer's disease.

Author Contributions: Conceptualization, R.K.; Data curation, R.K. and Z.H.Q.; Formal analysis, R.K., T.A., F.A. and L.W.; Funding acquisition, R.K. and F.A.; Investigation, R.K.; Methodology, R.K., Z.H.Q. and A.M.; Project administration, Z.H.Q. and A.M.; Resources, R.K., T.A., F.A. and L.W.; Software, R.K.; Supervision, R.K.; Validation, R.K. and A.M.; Visualization, Z.H.Q., A.M. and G.A.; Writing—original draft, R.K.; Writing—review & editing, A.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Data Availability Statement: Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (<http://adni.loni.usc.edu/>). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis or writing of this report. A complete listing of ADNI investigators can be found at: <http://adni.loni.usc.edu/wp-content/uploads/howtoapply/ADNIAcknowledgementList.pdf>.

Acknowledgments: The researchers would like to thank the Deanship of Scientific Research, Qassim University for funding the publication of this project.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Citron, M. Alzheimer's disease: Treatments in discovery and development. *Nat. Neurosci.* **2002**, *5*, 1055–1057. [[CrossRef](#)] [[PubMed](#)]
2. Masdeu, J.C.; Zubieta, J.L.; Arbizu, J. Neuroimaging as a marker of the onset and progression of Alzheimer's disease. *J. Neurol. Sci.* **2005**, *236*, 55–64. [[CrossRef](#)] [[PubMed](#)]
3. Kumar, A.; Singh, A.; Ekavali. A review on Alzheimer's disease pathophysiology and its management: An update. *Pharmacol. Rep.* **2015**, *67*, 195–203. [[CrossRef](#)] [[PubMed](#)]
4. Tajbakhsh, N.; Shin, J.Y.; Gurudu, S.R.; Hurst, R.T.; Kendall, C.B.; Gotway, M.B.; Liang, J. Convolutional Neural Networks for Medical Image Analysis: Full Training or Fine Tuning? *IEEE Trans. Med. Imaging* **2016**, *35*, 1299–1312. [[CrossRef](#)] [[PubMed](#)]
5. Demetriades, A.K. Functional neuroimaging in Alzheimer's type dementia. *J. Neurol. Sci.* **2002**, *203*, 247–251. [[CrossRef](#)]
6. Zhang, J.; Zheng, B.; Gao, A.; Feng, X.; Liang, D.; Long, X. A 3D densely connected convolution neural network with connection-wise attention mechanism for Alzheimer's disease classification. *Magn. Reson. Imaging* **2021**, *78*, 119–126. [[CrossRef](#)] [[PubMed](#)]
7. Jain, R.; Jain, N.; Aggarwal, A.; Hemanth, D.J. Convolutional neural network based Alzheimer's disease classification from magnetic resonance brain images. *Cogn. Syst. Res.* **2019**, *57*, 147–159. [[CrossRef](#)]
8. Wen, J.; Thibeau-Sutre, E.; Diaz-Melo, M.; Samper-González, J.; Routier, A.; Bottani, S.; Dormont, D.; Durrleman, S.; Burgos, N.; Colliot, O.; et al. Convolutional neural networks for classification of Alzheimer's disease: Overview and reproducible evaluation. *Med. Image Anal.* **2020**, *63*, 101694. [[CrossRef](#)] [[PubMed](#)]
9. Khan, R.; Yang, Y.; Liu, Q.; Qaisar, Z.H. Divide and Conquer: Ill-Light Image Enhancement via Hybrid Deep Network. *Expert Syst. Appl.* **2021**, *182*, 115034. [[CrossRef](#)]
10. Nayak, D.R.; Dash, R.; Majhi, B. Automated diagnosis of multi-class brain abnormalities using MRI images: A deep convolutional neural network based method. *Pattern Recognit. Lett.* **2020**, *138*, 385–391. [[CrossRef](#)]
11. Tong, T.; Gray, K.; Gao, Q.; Chen, L.; Rueckert, D.; The Alzheimer's Disease Neuroimaging Initiative. Multi-modal classification of Alzheimer's disease using nonlinear graph fusion. *Pattern Recognit.* **2017**, *63*, 171–181. [[CrossRef](#)]
12. Zhang, D.; Wang, Y.; Zhou, L.; Yuan, H.; Shen, D.; The Alzheimer's Disease Neuroimaging Initiative. Multimodal classification of Alzheimer's disease and mild cognitive impairment. *Neuroimage* **2011**, *55*, 856–867. [[CrossRef](#)]
13. Sørensen, L.; Igel, C.; Pai, A.; Balas, I.; Anker, C.; Lillholm, M.; Nielsen, M.; The Alzheimer's Disease Neuroimaging Initiative. Differential diagnosis of mild cognitive impairment and Alzheimer's disease using structural MRI cortical thickness, hippocampal shape, hippocampal texture, and volumetry. *Neuroimage Clin.* **2017**, *13*, 470–482. [[CrossRef](#)] [[PubMed](#)]
14. Petot, G.J.; Friedland, R.P. Lipids, diet and Alzheimer disease: An extended summary. *J. Neurol. Sci.* **2004**, *226*, 31–33. [[CrossRef](#)] [[PubMed](#)]
15. Jo, T.; Nho, K.; Saykin, A.J. Deep learning in Alzheimer's disease: Diagnostic classification and prognostic prediction using neuroimaging data. *Front. Aging Neurosci.* **2019**, *11*, 220. [[CrossRef](#)] [[PubMed](#)]
16. Talo, M.; Yildirim, O.; Baloglu, U.B.; Aydin, G.; Acharya, U.R. Convolutional neural networks for multi-class brain disease detection using MRI images. *Comput. Med. Imaging Graph.* **2019**, *78*, 101673. [[CrossRef](#)] [[PubMed](#)]
17. Murthy, V.N.; Singh, V.; Chen, T.; Manmatha, R.; Comaniciu, D. Deep decision network for multi-class image classification. In Proceedings of the IEEE Conference on Computer Vision and Pattern Recognition, Las Vegas, NV, USA, 27–30 June 2016; pp. 2240–2248.
18. Prince, M.J.; Wimo, A.; Guerchet, M.; Ali, G.C.; Wu, Y.T.; Prina, M.A. *World Alzheimer Report 2015—The Global Impact of Dementia: An Analysis of Prevalence, Incidence, Cost and Trends*; Alzheimer's Disease International: London, UK, 2015.
19. Ramzan, F.; Khan, M.U.G.; Rehmat, A.; Iqbal, S.; Saba, T.; Rehman, A.; Mehmood, Z. A deep learning approach for automated diagnosis and multi-class classification of Alzheimer's disease stages using resting-state fMRI and residual neural networks. *J. Med. Syst.* **2020**, *44*, 37. [[CrossRef](#)] [[PubMed](#)]
20. Khan, R.; Akram, A.; Mehmood, A. Multiview Ghost-Free Image Enhancement for In-the-Wild Images With Unknown Exposure and Geometry. *IEEE Access* **2021**, *9*, 24205–24220. [[CrossRef](#)]
21. Khan, R.; Yang, Y.; Liu, Q.; Shen, J.; Li, B. Deep image enhancement for ill light imaging. *JOSA A* **2021**, *38*, 827–839. [[CrossRef](#)] [[PubMed](#)]
22. Khan, R.; Yang, Y.; Liu, Q.; Qaisar, Z.H. A ghostfree contrast enhancement method for multiview images without depth information. *J. Vis. Commun. Image Represent.* **2021**, *78*, 103175. [[CrossRef](#)]
23. Khan, R.; Liu, Q.; Yang, Y. A deep hybrid few shot divide and glow method for ill-light image enhancement. *IEEE Access* **2021**, *9*, 17767–17778. [[CrossRef](#)]
24. Shams, M.Y.; Elzeki, O.M.; Abouelmagd, L.M.; Hassani, A.E.; Abd Elfattah, M.; Salem, H. HANA: A healthy artificial nutrition analysis model during COVID-19 pandemic. *Comput. Biol. Med.* **2021**, *135*, 104606. [[CrossRef](#)]
25. El-Hasnony, I.M.; Elzeki, O.M.; Alshehri, A.; Salem, H. Multi-label active learning-based machine learning model for heart disease prediction. *Sensors* **2022**, *22*, 1184. [[CrossRef](#)] [[PubMed](#)]
26. Afzal, S.; Maqsood, M.; Khan, U.; Mehmood, I.; Nawaz, H.; Aadil, F.; Song, O.Y.; Nam, Y. Alzheimer Disease Detection Techniques and Methods: A Review. *Int. J. Interact. Multimed. Artif. Intell.* **2021**, *6*. [[CrossRef](#)]
27. Hao, X.; Bao, Y.; Guo, Y.; Yu, M.; Zhang, D.; Risacher, S.L.; Saykin, A.J.; Yao, X.; Shen, L.; Initiative, A.D.N.; et al. Multi-modal neuroimaging feature selection with consistent metric constraint for diagnosis of Alzheimer's disease. *Med. Image Anal.* **2020**, *60*, 101625. [[CrossRef](#)] [[PubMed](#)]

28. Mehmood, A.; Maqsood, M.; Bashir, M.; Shuyuan, Y. A Deep Siamese Convolution Neural Network for Multi-Class Classification of Alzheimer Disease. *Brain Sci.* **2020**, *10*, 84. [[CrossRef](#)] [[PubMed](#)]
29. Gupta, A.; Ayhan, M.; Maida, A. Natural image bases to represent neuroimaging data. In Proceedings of the International Conference on Machine Learning, Atlanta, GA, USA, 16–21 June 2013, pp. 987–994.
30. Suk, H.I.; Lee, S.W.; Shen, D. Deep sparse multi-task learning for feature selection in Alzheimer’s disease diagnosis. *Brain Struct. Funct.* **2016**, *221*, 2569–2587. [[CrossRef](#)] [[PubMed](#)]
31. Farooq, A.; Anwar, S.; Awais, M.; Rehman, S. A deep CNN based multi-class classification of Alzheimer’s disease using MRI. In Proceedings of the 2017 IEEE International Conference on Imaging Systems and Techniques (IST), Beijing, China, 18–20 October 2017; pp. 1–6.
32. Szegedy, C.; Liu, W.; Jia, Y.; Sermanet, P.; Reed, S.; Anguelov, D.; Erhan, D.; Vanhoucke, V.; Rabinovich, A. Going deeper with convolutions. In Proceedings of the IEEE Conference on Computer Vision and Pattern Recognition, Boston, MA, USA, 7–12 June 2015; pp. 1–9.
33. Mehmood, A.; Yang, S.; Feng, Z.; Wang, M.; Ahmad, A.S.; Khan, R.; Maqsood, M.; Yaqub, M. A transfer learning approach for early diagnosis of alzheimer’s disease on MRI images. *Neuroscience* **2021**, *460*, 43–52. [[CrossRef](#)]
34. Acharya, H.; Mehta, R.; Singh, D.K. Alzheimer Disease Classification Using Transfer Learning. In Proceedings of the 2021 5th International Conference on Computing Methodologies and Communication (ICCMC), Erode, India, 8–10 April 2021; pp. 1503–1508.
35. Murugan, S.; Venkatesan, C.; Sumithra, M.; Gao, X.Z.; Elakkiya, B.; Akila, M.; Manoharan, S. DEMNET: A deep learning model for early diagnosis of Alzheimer diseases and dementia from MR images. *IEEE Access* **2021**, *9*, 90319–90329. [[CrossRef](#)]
36. Islam, J.; Zhang, Y. Brain MRI analysis for Alzheimer’s disease diagnosis using an ensemble system of deep convolutional neural networks. *Brain Inform.* **2018**, *5*, 2. [[CrossRef](#)]
37. Goceri, E. Diagnosis of Alzheimer’s disease with Sobolev gradient-based optimization and 3D convolutional neural network. *Int. J. Numer. Methods Biomed. Eng.* **2019**, *35*, e3225. [[CrossRef](#)] [[PubMed](#)]
38. Payan, A.; Montana, G. Predicting Alzheimer’s Disease—A Neuroimaging Study with 3D Convolutional Neural Networks. *arXiv* **2015**, arXiv:1502.02506.
39. Khan, N.M.; Abraham, N.; Hon, M. Transfer learning with intelligent training data selection for prediction of Alzheimer’s disease. *IEEE Access* **2019**, *7*, 72726–72735. [[CrossRef](#)]
40. Hosseini-Asl, E.; Ghazal, M.; Mahmoud, A.H.; Aslantas, A.; Shalaby, A.M.; Casanova, M.F.; Barnes, G.N.; Gimel’farb, G.L.; Keynton, R.S.; El-Baz, A.S. Alzheimer’s disease diagnostics by a 3D deeply supervised adaptable convolutional network. *Front. Biosci.* **2018**, *23*, 584–596.
41. Lundervold, A.S.; Lundervold, A. An overview of deep learning in medical imaging focusing on MRI. *Z. Für Med. Phys.* **2019**, *29*, 102–127. [[CrossRef](#)]
42. Ji, J.X.; Pan, H.; Liang, Z.P. Further analysis of interpolation effects in mutual information-based image registration. *IEEE Trans. Med. Imaging* **2003**, *22*, 1131–1140. [[PubMed](#)]
43. Florkow, M.C.; Zijlstra, F.; Kerkmeijer, L.G.; Maspero, M.; van den Berg, C.A.; van Stralen, M.; Seevinck, P.R. The impact of MRI-CT registration errors on deep learning-based synthetic CT generation. In Proceedings of the Medical Imaging 2019: Image Processing, San Diego, CA, USA, 16–21 February 2019; Volume 10949, p. 1094938.
44. Jack, C.R., Jr.; Bernstein, M.A.; Fox, N.C.; Thompson, P.; Alexander, G.; Harvey, D.; Borowski, B.; Britson, P.J.; L. Whitwell, J.; Ward, C.; et al. The Alzheimer’s disease neuroimaging initiative (ADNI): MRI methods. *J. Magn. Reson. Imaging Off. J. Int. Soc. Magn. Reson. Med.* **2008**, *27*, 685–691. [[CrossRef](#)]
45. Witten, I.H.; Frank, E. Data mining: Practical machine learning tools and techniques with Java implementations. *ACM Sigmod Rec.* **2002**, *31*, 76–77. [[CrossRef](#)]