Applying Convolutional Neural Networks for Pre-detection of Alzheimer's Disease from Structural MRI data

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***Abstract*—During the recent years, there have been many studies implemented on the automatic diagnosis of Alzheimer's Disease (AD) using different methods. The focus of most of these studies has relied upon the detection of AD from neuroimaging data. However, recognizing symptoms early as much as possible(Pre-detection) is crucial as disease modifying drugs will be most effective if administered early in the course of disease, before the occurrence of irreversible brain damages. Therefore, there is a high importance of utilizing automated techniques for the purpose of pre-detection of AD symptoms from such data. We report an experimental approach to evaluate the best pre-detection method of AD. Our study consists of two main experiments. Those two experiments were implemented using the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset. Prior to our first experiment we have stated an assumption which is, if there is a successful AD detection method that will be successful in AD pre-detection also. Different studies have used different data sets and different diagnosing methods. Therefore we have verified the existing and the most successful detection method which is Support Vector Machine (SVMs) as the first experiment. According to the results obtained from the initial experiment (detection study) the sensitivity is 95.3%, the specificity is 71.4% and the accuracy is 84.4% with use of a SVM. Since those results were not successful, a deep learning based technique (Convolutional Neural Network) was proposed as the second experiment. The proposed Convolutional Neural Network (CNN) model was being tested using different image segmentation methods and different datasets. Finally the best image segmentation method obtained a high accuracy around 96% (sensitivity - 96%, specificity - 98%). And the CNN model remains unbiased to the dataset. Results of those experiments suggest an important role for early diagnosis of Alzheimer's disease using image processing and deep learning techniques.**

***Index Terms*—Alzheimers Disease, Magnetic Resonance Imaging, Image Processing, Pattern Recognition, Support Vector Machine, Convolutional Neural Networks**

I. Introduction

Alzheimer's Disease (AD) is a neurodegenerative disease and the most common type of dementia worldwide [1]. The current prevalence of AD is about 2% at the age of 65 and 35% or higher at the age of 85 [1].As life expectancy increases, the number of people suffering from AD grows rapidly. In 2006, the estimated number of people with AD was 26.6 million [2]. This number is expected to be over 100 million by 2050. Therefore, besides causing a major psychological burden on patients and families. AD is also expected to place large socioeconomic consequences in our societies as well.

Alzheimer's disease is usually diagnosed based upon the person's medical history, behavioural patterns and the medical history of relatives. The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA, now known as the Alzheimer's Association) has established the most commonly used NINCDS-ADRDA Alzheimer's Criteria for diagnosis in 1984 [3]. These criteria require that the presence of cognitive impairment and a suspected dementia syndrome, be confirmed by neuropsychological testing for a clinical diagnosis of possible or probable AD [4]. However diagnosing Alzheimer's requires a careful medical evaluation. Moreover, neuropsychological tests such as the mini-mental state examination (MMSE) are widely used to evaluate the cognitive impairments needed for the diagnosis of the disease [5]. The main disadvantages of the MMSE are, difficulty in identifying mild cognitive impairment and difficulty in recording changes in cases of severe dementia [6]. Alzheimers disease is considered as the loss of neurons and synapses in the cerebral cortex and in certain subcortical regions [7]. This loss of neurons and synapses from the disease leads to clearly visible differences in brain tissues as illustrated in Figure 1. The hippocampal atrophy, ventricle enlargement and cortex shrinkage are sensitive features of Alzheimer's disease. Therefore doctors perform brain scans, such as Computed Tomography (CT), Magnetic Resonance Imaging (MRI), or Positron Emission Tomography (PET), to rule out the other possible causes for the symptom.

Since this is time consuming and less accuracy making the diagnosis of Alzheimer's Disease is often difficult, particularly in the early stages. Moreover the diagnosing accuracy mainly depend on the experience of the radiologists. During the recent years, there have been many studies on the automatic diagnosis of Alzheimer's disease using different methods. Several pattern classifiers have tried for the discrimination of subjects using different neuroimaging data. Different feature extraction methods and classification methods have been used in those recent studies.

The main objective of this study is to overcome the problem of pre-detecting Alzheimer's disease.

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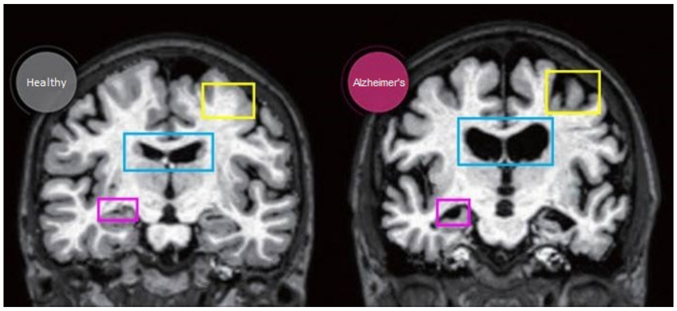

Fig. 1. MRI view of a healthy brain (left) and an Alzheimer's brain (right) [7]. (Yellow - Cortex, Blue - Ventricle, Purple - Hippocampus volume reduced)

II. Related Works

In general, SVM has a lower generalization error than the other classifiers hence SVM has been commonly used to solve pattern classification problems. Kloppel et al. [4] first used the SVM-based criteria to select the most discriminative features, and then applied the SVM-based classifier to diagnose healthy controls and AD patients using MRI brain images. In that study, they have achieved an accuracy of 90.0%, a sensitivity of 91.8% and a specificity of 87.8%. Nir et al. used the fiber-tract modeling method to extract image features and applied SVM to differentiate AD from NC and achieved an accuracy of 86.2%, a sensitivity of 88.0%, and a specificity of 89.2% [8]. According to the recent studies SVM has given the best classification accuracy among the other classifiers.

Bayes classifiers are a family of simple probabilistic classifiers based on Bayes' theorem. Liu et al [9] proposed the multifold Bayesian Kernelization method, which can differentiate AD from NC with a high accuracy, but achieved poor results in diagnosing MCI subjects and non MCI- subjects [10]. Plant et al [11] combined the feature selection with classification using a Bayes classifier for the discrimination between AD and NC on MRI data and reported an accuracy of up to 92%. Lopez et al. [12] applied the multivariate methods, to feature extraction, and then employed the Bayesian framework to classify AD with NC using PET and Single-photon emission computed tomography (SPECT) images.

ANNs have been used to solve a wide variety of tasks that are hard to solve using ordinary rule-based programming. Deng et al. [13] showed that a higher sensitivity and a higher accuracy can be derived using ANN than the traditional discriminant function analysis used in dementia classification using MRI. Moreover Ramirez-Gome et al. [14] employed the artificial neural network technology to build an automaton to assist neurologists during the differential diagnosis of AD and Vascular Dementia (VD).

The focus of most of these studies has been relied upon the detection of AD using neuroimaging data. However, any Alzheimers Disease pre-detection method has not been established yet. Recognizing symptoms early (Pre-detection) is crucial, as disease modifying drugs will be most effective if administered early in the course of disease before any irreversible brain damage occurs. At present, there is no any curative treatment for Alzheimer's disease. The objective of the disease modifying drugs is rather to slow down the progression of the disease, address the behavioral problems and to improve the quality of life. In order to slow down the progression, early diagnosis of the Alzheimer's disease is important. Also, having an early diagnosis helps people with Alzheimer's and their families in different ways such as planning for the future, to be concerned on financial and legal matters and making living arrangements. [15].

Bianchini M and Scarselli F have studied on the complexity between shallow neural networks and deep neural networks in 2014. According to their comparison, deep neural networks perform well than the shallow nets. Also they have emphasized that the deep networks can perform well in classification problems with few resources [16]. Moreover Schindler A, Lidy T and Rauber A compare Shallow versus Deep Neural Network Architectures for Automatic Music Genre Classification. In their comparison, they have indicated that the deep neural networks outperform over shallow neural networks in each dataset that they have used [17].

Convolutional Neural Networks (CNNs) are a category of deep neural networks that have proven very effective in areas such as image recognition and classification [18]. Also, it is a type of feed-forward artificial neural network which learn image features by its own in the convolutional layer. In 2016 Bojarski M, Testa D and et al studied on "End to End Learning for Self-Driving Cars" [19]. In that study, they have trained a CNN to map raw pixels from a single front facing camera directly to steering commands. Finally, they concluded that without any explicit labeling, CNN had the capacity to learn meaningful road features. Krizhevsky A, Sutskever I and Hinton G trained a deep convolutional neural network to classify ImageNet dataset. They have selected only 1.2 million images from the ImageNet dataset [20] which belongs to 100 classes for their study with the use of Graphics Processing Unit (GPU). Finally, they won the top-5 test error rate of 15.3% in ImageNet Large Scale Visual Recognition (ILSVR) Challenge in 2012 [20]. Ren S, He KFigure and et al study on real time object detection in 2015 [21]. They proposed a CNN to classify ImageNet dataset and Microsoft COCO object detection dataset [22]. They achieved the first place In both ILSVR 2015 and Microsoft COCO 2015 competitions. They got the lowest error rate for large scale image classification among the other classification methods. Recent studies on the biomedical domain have used CNN for image classification. Gupta et al. employed 2D CNN for slice-wise feature extraction of MRI scans to classify brain images [23]. Also Havaei M, Davy A et al. achieved successful results for brain tumor segmentation with CNNs [24].

III. Methods

First of all it is assumed that if there is a successful detection method it would definitely generate successful results at the pre-detection too. Further, this study consists of two main parts. It is very complex to compare the recent studies as they have been derived from different datasets and different

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methods. Therefore we have verified the existing and the most successful detection methods which is Support Vector Machine (SVM) as the first experiment. The pre detection is implemented at any successful completion of the verification stage or otherwise any other method will be proposed as the second step. Figure 2 illustrates the basic research methodology of the study.

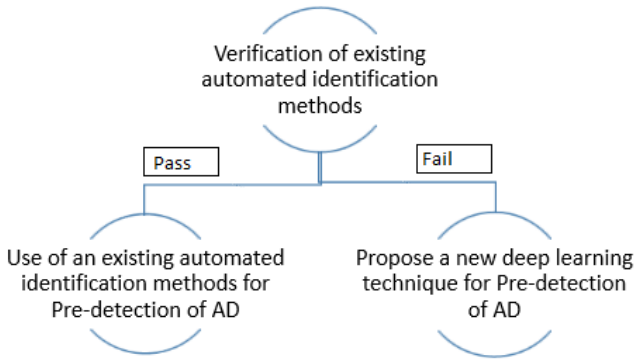

Fig. 2. Basic research methodology

We have selected the structural MRI data because, it is beneficial for the detection of abnormalities in soft tissues and soft organs in the body. Therefore, structural MRI was used to identify the biomarkers of the disease (Figure 1).Data used in the preparation of this article were obtained from the Alzheimers Disease Neuroimaging Initiative database (adni.loni.usc.edu) [25]. The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimers disease (AD). Moreover, The ADNI is a collaborative project that provides reliable clinical data for the research of pathology principle, prevention and treatment of Alzheimers disease [26]. Enrolled subjects were between 55 and 90 years of age. All subjects have a clinical and cognitive assessment and 1.5T structural MRI. ADNI dataset contains 504 subjects where 101 were AD patients, 234 were mild cognitive impairment(MCI) patients and 169 were cognitively healthy subjects(NL). The physicians use laboratory investigations, cognitive testing, physical and historical data to classify the subject's mental status as NL, MCI or AD. The subjects were being followed for about two to three years. Data collection is repeated for every 6 months. Moreover, there are 2428 brain scans in the dataset. For our experiments, we randomly select a subset of MRI scans from the original dataset.

The basic experiment design and the corresponding image processing steps have been illustrated in figure 3.

The MRI scan produces a 3-dimensional (3D) model of the body. Performing image processing techniques in a 3D

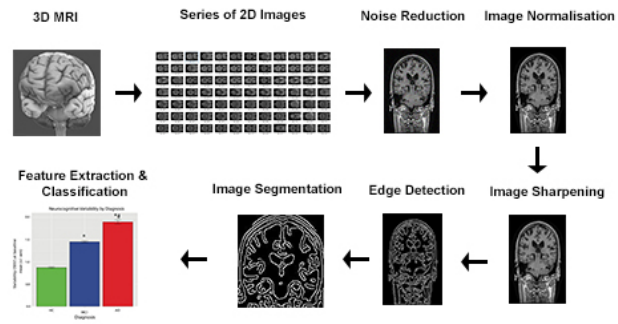

Fig. 3. Basic experiment design and image processing steps

MRI film is hard. Therefore it is necessary to convert those 3D MRI films into a series of 2D images before doing any preprocessing. The two experiments dealt with 2D images which were converted from those 3D MRI scans. Only the Coronal plane of the MRI scan was considered for this study. Because recent studies have emphasized that coronal view of an MRI scan covers the three most important regions which are related to the AD (hippocampal, cortex and ventricle) in the brain [27], [28].

Series of 2D images were pre-processed before feature extraction and classification. Those pre-processing steps were performed using OpenCV library. Recent studies have shown that the median filter has performed well in noise reduction with a small kernel size [29], [30]. Therefore noise removal was performed using the 3x3 median filter. The MRI images have a poor contrast due to glare. Aarthy M and Sumathy P compare different normalization methods and they have emphasized that linear normailization performs well in increasing contrast of a dark image [31]. Therefore images were normalized using the linear normalization method to get a better result. Luft T, Colditz C and et al study on Image Enhancement by Unsharp Masking [32] and they have concluded that the unsharp masking filter has the best sharpening result compared to the other operators. Further, according to the Comparison of Edge Detectors done by Ayaz Akram and Asad Ismail in 2013, Canny algorithm is the optimal solution to the problem of edge detection [33]. Therefore images were sharpened using the unsharp masking filter and edges were detected using the Canny edge detection algorithm. The sharpened image and the edge detected image shown in Figure 4b and Figure 4c respectively. Here the edges were detected since the volume of the ventricles, hippocampal and cortex are considered as features. Moreover, images were segmented using the Region of Interest (ROI) method. A segmented image has been illustrated in Figure 4d

A. Experiment 1: Accuracy testing using SVM

During the recent years, there were many studies on the automatic diagnosis of AD using different methods and different data sets. However, the comparison made between those studies and their results are not practicable since they have used different data sets, different diagnosing methods

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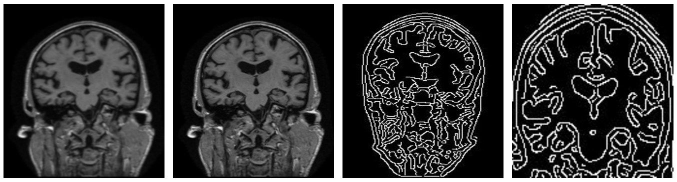

(a) Original Image (b) Sharpened Image (c) Edge detected image (d) Segmented image

Fig. 4. Output of the image pre-processing steps

and different features of the brain. Therefore in this study, the most recent and the common detection methods were tested as the first experiment. This study mainly depends on our main assumption(if there is a successful detection method it would definitely generate successful results at the pre-detection). The Support Vector Machines (SVMs) have been used extensively for the detection studies [4], [8], [11]. An SVM with a Radial Basis Function(RBF) kernel were implemented to verify the recent diagnosing methods since it provides the best classification results when there is small number of features and large number of data. An example of images that were used to train the SVM will be illustrated in Figure 4d. For this experiment, only two classes were used (AD and Healthy - NL) since SVM is binary classifier which doesnt perform well in multiclass classifications [34].

B. Experiment 2: Application of CNN

It is apparent that the previously utilized SVM method is not ideal to detect symptoms of mild to moderate AD cases (Pre-detection stage) from the results obtained from the initial experiment. CNN has the best results when compared to any other image classification method. Therefore, a CNN was implemented to classify brain images. The proposed CNN architecture illustrates in Figure 5 and it consists of two convolutional layers, one pooling layer and a fully connected layer. That CNN model was implemented using Theano[1] and Keras[2] python deep learning libraries and it was used for each sub experiment. Two sub experiments were initiated to select the best segmentation method and to evaluate the robustness of the model.

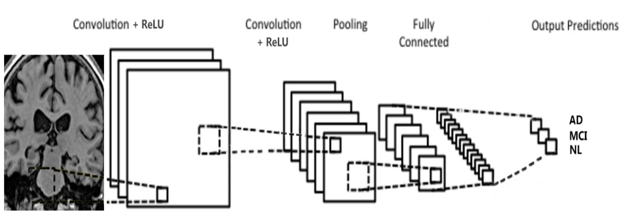

Fig. 5. Architecture of the CNN model

[1]http://deeplearning.net/software/theano/
[2]https://keras.io/

Preprocessed images were further processed in order to achieve the best result. All the images which were to be input to the CNN model were resized into 160 x 160 dimension because different sizes may reduce the accuracy of the classification. Then reformatted images were stored in a matrix in a flattened format. Because the flatten format will merge all the layers of the image into a single layer. After flattering, all the images have the same appearance, but the difference is that image contents are in a single layer.

The data were labeled with the corresponding class (0 - AD, 1 - MCI, 2 - NL). Afterward, the data set was shuffled. Then the data set has been divided(split) into training set and testing set with a ratio of 80/20 (80%for training and 20% for testing).

The Batch size, the number of classes and the number of epochs were defined as 32, 3 and 20 respectively. Batch size defines the number of samples that are going to be propagated through the network. This model takes 32 samples (first 32 images) from the training set and train the network then it takes next 32 samples and train again. An epoch is one forward pass and one backward pass of all the training samples. Here the number of epochs are 20 because a number of epochs should be defined by doing lots of experiments on the same network. The number of epochs shouldn't be either very small or very large. If the number of epochs is small or large, then the network lead to overfitting by itself. Therefore the number of epochs are defined as 20, and it can be changed with future improvements.

Moreover, a number of convolutional filters, the size of the convolutional kernel and the size of the pooling area were declared as 32, 3 and 2 respectively. A number of convolutional kernels define the number of different kernels that model used to learn the features. And the convolutional kernel is 3 x 3 matrix since the size is defined as 3. After and each convolutional operation an additional activation function was used to increase the non-linearity of the network. In here Rectified Linear Unit (ReLU) functions was used as the activation function. Equation 1 illustrates the ReLu function. It applied pixel by pixel and it replaces all the negative pixels by zero and adds non-linearity to the network. Figure 6 illustrates the outputs of different convolutional layers. The subsampling layer may reduce the dimension of each feature map but retain the most important feature maps. Also known as the pooling layer. In here the pooling layer consists of a 2 x 2 matrix. In a CNN fully connected layer act as a classification layer while convolutional layer and subsampling layer act as feature extractors.

$$f(x) = max(0, x) \tag{1}$$

In the first sub experiment, different types of image segmentation methods were used in order to test that accuracy of the network. 1615 images were used to train the CNN model. There were three types (AD, MCI and NL) of images in the dataset. AD images(585), MCI images(460) and NL images(570) in the data set. 1292 images were used to train

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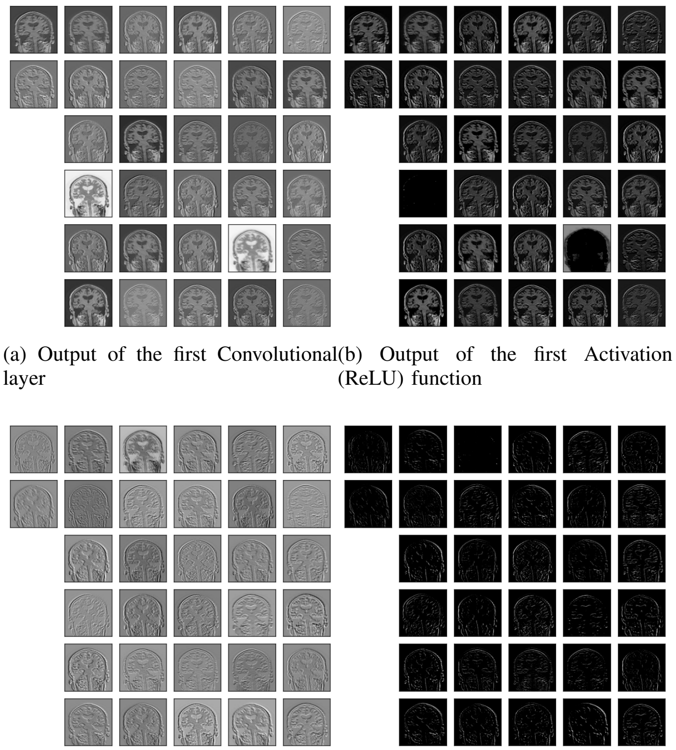

(a) Output of the first Convolutional layer (b) Output of the first Activation (ReLU) function

(c) Output of the second Convolutional layer (d) Output of the second Activation (ReLU) function

Fig. 6. Illustration of different kernel output in different Convolutional layers

the model and 323 images were used to test the model. Under the first sub experiment, six evaluation processes were performed. In the first evaluation, full image was used without detecting any edge (Figure 7a). Also, the second evaluation was performed with use of full images after detecting the edges (Figure 7b). Third (Figure 7c) and fourth (Figure 7d) evaluations were performed with use of an extended ROI with and without detecting edges. The fifth evaluation was performed with use of a limited ROI without detecting edges (Figure 7e). Finally, the last evaluation was performed using a limited ROI with detecting edges (Figure 7f).

After comparing the six evaluation processes in the first sub experiment, the best segmentation method was being selected for the second sub experiment. The second sub experiment helped to prove that the CNN model will not be biased on the dataset. According to the results obtain from the first sub experiment (Table II) it is apparent that the Evaluation 3 (Extended ROI without detecting edges) provides the best classification accuracy (96%) among the other segmentation methods. Therefore, using that segmentation method two different datasets were evaluated in the second sub experiment. The first dataset consists of 36 subjects (AD 7, MCI 14, NL 15). After converting those 3D MRI films into 2D images there were 1615 images. Out of those images, 1292 images were randomly selected to train the CNN model. And 323 images were used to test the model. Another 36 subjects were selected as the second dataset AD 9, MCI 16, NL 11). 1743 2D images were created using those 36 MRI films.

IV. Results

According to the results obtained from the initial experiment, the sensitivity is 95.3%, the specificity is 71.4% and the accuracy is 84.4%. However, those results are very much similar to the results of the previous studies [4], [11] Those results are compared in table I.

TABLE I
Comparison of results in previous studies vs initial experiment

Study	Method	Sensitivity	Specificity
Klppel2008 [4]	SVM(RBF Kernel)	88.8%	87.5%
Plant2010 [11]	SVM(Linear Kernel)	97%	78%
First Experiment [35]	SVM(RBF Kernel)	95.3%	71.4%

The second experiment consists of two sub experiments. In the first sub experiment performance of different image segmentation methods were evaluated. Table II illustrates the sensitivity and specificity of each evaluation process.

TABLE II
Performance Comparison of different image segmentation methods.

Evaluation	Sensitivity	Specificity
Evaluation 1	86%	93%
Evaluation 2	92%	96%
Evaluation 3	**96%**	**98%**
Evaluation 4	93%	96%
Evaluation 5	89%	95%
Evaluation 6	92%	96%

For the second sub experiment two datasets were evaluated and those results were illustrated in Table III. This experiment emphasized that the CNN model will not be biased on the data set.

TABLE III
Performance comparison of two datasets

Dataset	Number of Images	Sensitivity	Specificity
Dataset 1	1615	96%	98%
Dataset 2	1743	95%	98%

V. Conclusion

This paper provides the answer for two research questions. What is the appropriateness of the methods used in previous studies for the diagnosis of Alzheimer's disease such as SVM in the task of early diagnosis and how feasible is it to implement deep learning techniques such as CNNs for the purpose of pre-detection of Alzheimer's symptoms from Neuroimaging data are the two research questions.

According to the first experiment, it is apparent that the previously utilized SVM method is not ideal to detect symptoms of mild to moderate AD cases. Early diagnosis of AD requires to classify images into three classes (AD, MCI and NL). However, SVM does not perform well in multiclass classifications.

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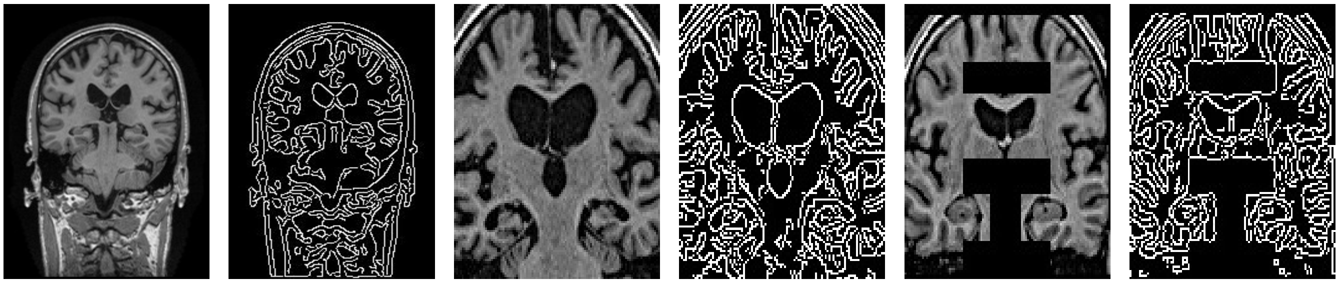

(a) Full image without detection edges (b) Full image with detecting edges (c) Extended ROI selection without edge detection (d) Extended ROI selection with detection edges (e) Limited ROI selection without detecting edges (f) Limited ROI selection with detecting edges

Fig. 7. Illustration of various images used to train and test the CNN model in the first sub experiment.

Therefore, SVM cannot be used for the early diagnosis of AD. Also, the classification accuracy can be further improved by using a deep learning techniques. Moreover, it applies to use deep learning techniques since it is performing well in multiclass classifications.

The second experiment has answered the second research question. It consists of two sub experiments. In the first sub experiment, performance of different image segmentation methods were evaluated. According to the results obtained from the Evaluation 1 and 2, it is obtrusive that the full image does not provide the correct classification. The reason for that is the full image is too complex than the other images and it contains nonbrain regions which are not related to the AD. Subsequently, those nonbrain regions were removed from all the images and evaluate the performance. In the Evaluation 3 and 4 extended ROI were used to extract the features from the brain images. Without detecting any edge extended ROI gives the best result among the six evaluation processes (Sensitivity 96%, Specificity 98%, Accuracy 96%). The purpose of detecting edges is to highlight the volume of ventricles, hippocampus and cortex. However in the extended ROI performance decreases drastically when detecting the edges since the canny edge detection algorithm removes all the white matter and gray matter details from the brain image. But there are many evidence to prove that the white matter and the gray matter have helped to identify the volume of those three features than the boundary detection [14]. Evaluation 5 and 6 based on the limited ROI selection. According to the results, limited ROI without edge detection gives an accuracy of 89% (Sensitivity 89%, Specificity 95%) and with edge detection it is about 92% (Sensitivity 92%, Specificity 96%). According to the assumptions made during the implementation limited ROI should have the best accuracy since it has more focused on three prominent features than the other segmentation methods. When considering the results there was a contradiction in the assumption. The main drawback of the limited ROI is some prominent features are not relaid within the ROI.

For the second sub experiment, two datasets were evaluated and those results were illustrated in Table III. There is no big difference between the results obtained from different datasets. There are enough evidence to prove that the CNN model was not depend on the dataset. Therefore the CNN model remains unbiased to the dataset.

VI. Future Works

Future studies will focus on performance improvement of the CNN model.According to the study done by Karpathy A and et al in 2014 [36] the highest accuracy can be achieved in a CNN by increasing the amount of data used to train the model. Therefore another experiment can be implemented to test the performance of the model by increasing the number of images used to train. Also, CNN model can be further improved by fine tuning. This study mainly focused on the Coronal view of an MRI. As a future enhancement other two views (Axial view and Sagittal view) can be used to identify the landmarks of the disease. Moreover, an autoencoder can be used to extract features from the input image

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