DETECTION OF MULTISTAGE ALZHEIMER FROM 4D FMRI DATA USING DEEP LEARNING

A THESIS SUBMITTED TO

THE GRADUATE SCHOOL OF

ENGINEERING AND NATURAL SCIENCES

OF ISTANBUL MEDIPOL UNIVERSITY

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR

THE DEGREE OF

MASTER OF SCIENCE

IN

ELECTRICAL, ELECTRONICS ENGINEERING AND CYBER SYSTEMS

By

Nawazish Ali

September, 2022

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30 September 2022

We certify that we have read this dissertation and that in our opinion it is fully adequate, in scope and quality, as a dissertation for the degree of Master of Science.

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ACKNOWLEDGEMENT

I would like to thank my advisor Prof. Dr. Reda Alhajj has been a constant source of inspiration, direction, motivation, and support for me throughout this process. Working with him was an incredible privilege that I am looking forward to working under his supervision in the future.

I also want to thank my jury members who give time to my defense from their precious time. Especially I would like to thank all the professors and faculty members who give me the knowledge and their support and guidance during my master’s degree.

I would like to thank Istanbul Medipol University which allows me to excel my knowledge to further limits. It was a nice experience working here as Research Assistant and Teaching Assistant. I also want to thank my friends here in Medipol who always motivate me to do my best in my study.

I want to dedicate this thesis, especially to my parents, and I am eternally grateful for their constant support and encouragement throughout my academic and personal journeys, no matter how far we have traveled apart. To be honest, I'm never quite sure how to convey my thanks for their help. Regardless, I know I couldn't have done all of this without them.

Nawazish Ali

September, 2022

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LIST OF SYMBOLS

λ : Learning rate
β : Weight Decay

ABBREVIATIONS

AI : Artificial Intelligence
ML : Machine Learning
DL : Deep Learning
CNN : Convolutional Neural Network
LSTM : Long Short-Term Memory Network
AUC : Area Under Curve
TP : True Positive
TN : True Negative
FP : False positive
FN : False Negative
ROC : Receiver operator characteristic
GPU : Graphical Processing unit
2D : 2 Dimensional
3D : 3 Dimensional
OASIS : Open Access series of imaging studies

4D FMRI'DAN MULTISTAGE ALZHEIMER'İN TESPİTİ

DERİN ÖĞRENMEYİ KULLANAN VERİLER

ÖZET

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İlaç dağıtım sistemleri ve tıbbi görüntüleme gibi biyomedikal verilerdeki kalıpların tanınmasını önemli ölçüde iyileştiren makine öğrenimi tekniklerinin uygulanması, araştırmacıların karmaşık tıbbi sorunları daha iyi anlamalarına ve çözmelerine yardımcı olmak için en önemli yöntemlerden biri olarak ortaya çıkmıştır. Son birkaç yıl. Bu, son yıllarda tıbbi araştırma alanındaki en önemli gelişmelerden biri olmuştur. Derin öğrenme, verilerden düşük seviyeden üst seviyeye kadar özellikler çıkaran sınıflandırmalar için güçlü bir tekniktir. Alzheimer hastalığını teşhis etmek için bir dizi derin ve makine öğrenimi öğrenme algoritmasının kullanılması olağanüstü sonuçlar göstermiştir. Alzheimer hastalığı, zamanla kötüleşen ilerleyici, ölümcül bir hastalıktır; bu nedenle, hastalığın etkisini azaltmak için mümkün olduğunca erken keşfetmek önemlidir. Alzheimer hastalığını teşhis etmek için derin öğrenme algoritmaları, MRI görüntüleme verilerini kullanan makine öğrenimi algoritmalarından önemli ölçüde daha iyi performans gösterir. MRG verilerini doktorlar için analiz etmek bile zor. Literatürde Alzheimer teşhisi için iki teknik kullanılmıştır: ya görüntüyü 2D/3D'ye bölerek ya da fonksiyonel bağlantıya çevirerek ya da ön işlemeden sonra 4D görüntü verilerini kullanarak. Bu araştırmada, ön işlemeden sonra Alzheimer teşhisi için 4D fonksiyonel MRI verileri kullanılmıştır. Dilim zamanlama, kafa hareketi düzeltme, dilim normalleştirme, beyin çıkarma, yumuşatma ve görüntü normalleştirmeyi içeren farklı ön işleme teknikleri uygulanır. 3D evrişimli sinir ağı (CNN) modeli, OASIS verileri üzerinde uygulanmış ve eğitilmiştir. 3D CNN modelinde transfer öğrenme tekniği kullanılmış ve buna uzun-kısa süreli bellek (LSTM) katmanları eklenerek verilerden zamansal bilgilerin öğrenilmesi sağlanmıştır. Genişletilmiş algoritmaya Conv3d-lstm adı verildi ve önceden işlenmiş ADNI verileri üzerinde yeniden eğitildi. Algoritmayı yeni veriler için genellemek için bu çalışmada iki farklı veri seti kullanılmıştır. Önerilen modelin performansını değerlendirmek için farklı 2D CNN modelleri de eğitilmiş ve test edilmiştir. Son olarak, önerilen modelin diğer eğitilmiş algoritmalar ve daha önceki çalışmalarla karşılaştırılabilir en iyi sonuçları verdiği sonucuna varılmıştır. Algoritma, %96 AUC ve %91.06 doğruluk ile en yüksek doğruluğa ve AUC'ye sahiptir. Önerilen algoritma iyi sonuçlar elde ediyor, ancak yine de performansta iyileştirme için alan var.

Anahtar sözcükler: Alzheimer tespiti, Alzheimer sınıflandırması, fMRI, Derin Öğrenme, CNN, LSTM, ADNI, OASIS.

DETECTION OF MULTISTAGE ALZHEIMER FROM 4D FMRI DATA USING DEEP LEARNING

ABSTRACT

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September, 2022

The application of machine learning techniques, which significantly improve the recognition of patterns in biomedical data, such as drug delivery systems and medical imaging, has emerged as one of the most important methods for assisting researchers in gaining a better understanding and resolving complex medical issues over the past few years. This has been one of the most significant developments in medical research in recent years. Deep learning is an effective technique for the classifications that extract low-level to high-level features from data. Utilizing a range of machine learning and deep learning algorithms to identify Alzheimer's disease has shown outstanding results. Alzheimer's dementia is progressive, a fatal disorder that turns out to be worse over time; therefore, it is important to diagnose it as early as possible to lessen its impact. To diagnose Alzheimer's disease, deep learning techniques perform significantly better than machine learning techniques by using MRI imaging data. MRI data is even hard to analyze for the physicians. In the literature, two techniques have been used for the identification of Alzheimer's: either by splitting the image into 2D/3D or translating it into functional connectivity or by using the 4D image data after the preprocessing. In this research, the 4D functional MRI data is used for the detection of Alzheimer's after preprocessing. Different preprocessing techniques are applied which include head motion correction, slice timing, slice normalizing, brain extraction, image smoothing, and normalization. The 3-dimensional (CNN) model is implemented and taught on the OASIS data. The transfer learning technique is used on the 3D CNN model and bidirectional long-short-term memory (LSTM) layers are added to understand the temporal information from data. The extended algorithm was named Conv3d-lstm and retrained on the preprocessed ADNI data. Two different datasets are used in this study to generalize the algorithm for the new data. Different 2D CNN models are also trained and tested to assess the performance of the proposed model. Finally, it is concluded that the suggested algorithm provides the finest results comparable to those of other trained algorithms and earlier studies. The algorithm has the highest accuracy and AUC with an AUC of 96% and 91.06% accuracy. The proposed algorithm achieves good results but still, there is space for improvement in the performance.

Keywords: Alzheimer detection, Alzheimer's classification, fMRI, Deep Learning, CNN, LSTM, ADNI, OASIS.

CHAPTER 1

1. INTRODUCTION

1.1. Problem definition

Alzheimer's dementia (AD) is a degenerative brain illness that is distinguished by gradually progressing functional and mental deficiencies as well as changes in behavior. AD is also linked to the formation of amyloid as well as tau protein in the brain. Shortfalls in short attention span, executive dysfunction, visual-spatial disorder, and praxis are the most common cognitive symptoms associated with Alzheimer's disease (AD). Several forms of Alzheimer's disease have been identified, some of which preserve memory more than others. **Figure 1.1** demonstrates the structural change in the early and advanced stages of Alzheimer's dementia. Even though recent improvements in amyloid image analysis and genetic factors show great promise for enabling and Presymptomatic diagnosis of Alzheimer's disease and differentiating it from other neurodegenerative disorders, clinical assessment, which includes cognitive testing, remains an important part of diagnosing and staging Alzheimer's illness.

In the United States, Alzheimer's illness (AD) is the most widespread form of neurodegenerative disease and the sixth primary cause of death on the whole [1]. Even though there is mounting evidence that the pathology of Alzheimer's disease begins to deposit in the brain during the middle years of life, the typical onset of clinical symptoms does not occur before the age of 65 [2], [3].

The number of people aged 65 and up is growing faster than any other age group in the world, contributing to the exponential rise in the prevalence of Alzheimer's illness. In 2050, the amount of people old 65 and up is expected to rise from 63 million in the Americas to 137 million, 18 million people in Africa compared to 38 million people in Europe, and Asia saw a rise in disease from 172 million to 435 million. [4]. According to data from the Getting Older, Demography, and Cognitive Study (ADAMS), 14 percent of Americans aged 71 and up have dementia. In this group, AD dementia was responsible for 70% of all dementia cases across all ages [5]. Later, ADAMS researchers published findings indicating that 22% of individuals elderly 71 and up in the US have mental loss without overt dementia. This amounts to approximately 5.4 million people [6].

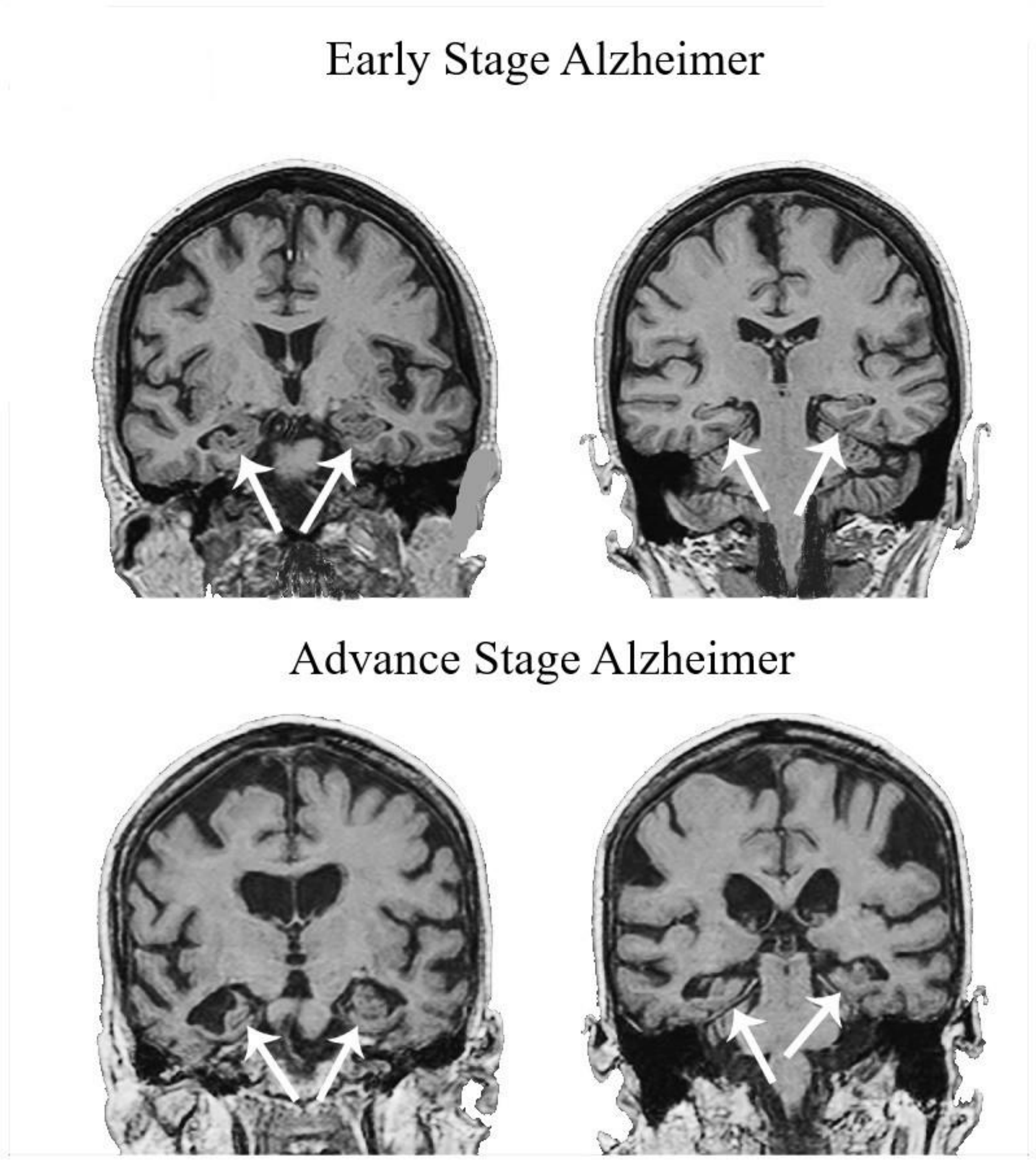

Figure 1.1: Demonstrate the early and advanced stages of Alzheimer's dementia.

Despite the fact that age is one of the most important consequence causes of developing Alzheimer's disease, simply being old is not enough to cause the disease. The most significant consequence factors include the presence of multiple E4 gene alleles (APOE4), low occupational, and educational ability, intimate history of Alzheimer's illness, mild or severe traumatic brain injury, and vascular threat issues. Another major cause is the presence of cardiovascular risk factors.

The rate of occurrence of AD varies according to sex. Women make up nearly two-thirds of the Alzheimer's disease patient population [7]. According to ADAMS, after the age of 71, 16% of women and 11% of men are diagnosed with dementia [5]. Although women tend to outlive men, this fact alone cannot account for the gender gap in mortality rates. There are probably many factors at play, including genetics, hormones, and social norms (such as the fact that women in their 70s and 80s today have a lower rate of education and employment than men).

It has also been reported that there are racial differences in the prevalence of AD. In comparison to older Caucasians, older Hispanics, and African Americans have a higher prevalence of Alzheimer's dementia (AD). This is due to lower education levels as well as a higher prevalence of cardiovascular comorbidities [8], [9]. However, it is likely that other genetic and societal factors also play a role.

The burden on society is extremely significant. It is estimated that in 2012, the total expanse for healthcare and enduring care of people with Alzheimer's illness and additional types of dementia amounted to $200 billion in the United States. It is important to recognize the contributions made by unpaid caregivers in addition to this. An estimated 15 million Americans, the majority of whom are family caregivers, offering 17.4 billion times of care to people living with Alzheimer's and other dementias in 2011, a total that had a value of nearly $210 billion in terms of their time [10].

1.2. Detection Techniques

In its later stages, Alzheimer's disease is an extremely dangerous condition for which there is no treatment or cure. Although there has lately been an upsurge in studies towards the diagnosis of AD at early developmental stages, the early identification of AD is complicated by brain alterations and their complexity for fMRI (functional magnetic resonance imaging). The characteristics of Alzheimer's dementia (AD) are possibly evaluated to build tools that are more efficient and accurate based on modern technologies that are both inexpensive and readily accessible to the public right now. Neuroimaging techniques [11], [12], [13] behavior and emotion analysis [14], [15] as well as cognitive approaches and cognitive testing, are some examples of the many techniques that are developed and applied to diagnose Alzheimer's disease in its early stages. These methods have been often highlighted. The installation of sensors in the patient's house is one of the behavioral analytic approaches that may be used to assist in the detection of unpredictable reactions to typical difficulties encountered in the activities of daily life. Because it requires the cooperation of the patient, this technique has many restrictions, which is one of the most significant drawbacks of the approach. Put the sensors in place inside your home.

A decline in social cognition is one main symptom of Alzheimer's illness (AD), and some studies have focused on patients' ability to interpret emotions using a variety of methods, including eye-tracking data [16], voice/speech recordings [17], facial expressions [18], and electroencephalograms (EEG) [19], [20]. One of the symptoms of AD is a decline in social cognition. Imaging methods for the brain include MRI (structural magnetic resonance imaging) [21], [22], fMRI (functional magnetic resonance imaging) [23], fluorodeoxyglucose positron radiation imaging (FDG-PET) [24], amyloid positron radiation imaging (PET) [11], and diffusion tensor imaging (DTI) [25] . These neuroimaging techniques continue to be used mostly at more advanced facilities because they are promising tools for detecting aberrant brain changes associated with Alzheimer's disease (AD). The patient receives an injection of a tracer that binds to the protein as part of the amyloid PET procedure. This procedure uses the presence of diffuse amyloid deposits in the cortex as a measure of neurodegeneration. Both quantitative information and qualitative information on the topography of a deposition in the brain may be gleaned from an amyloid PET scan. This quantitative information may be on a regional basis. The evaluation of variations in blood movement and blood oxygen substance is how fMRI (functional magnetic resonance imaging) determines the metabolic procedures of the brain [26]. The degree of shrinkage in the lower brain areas, particularly the hippocampus, provides more evidence of the structural alterations that have occurred in the brain [26]. Quantitative measurements of the metabolic activity of the brain may be obtained by FDG-PET [27].

1.2.1. AI detection techniques

Magnetic resonance imaging (MRI) is an emerging technique for studying the nervous system's structure and function, known as fMRI (functional magnetic resonance imaging). fMRI measures variations in blood movement and oxygen content in the brain to identify metabolic activity. The use of fMRI in the research of Alzheimer's illness detection is critical [28]. Towards building functional networks, fMRI data has been employed in the existing methodologies [29]. Graph theory, ML, and DL techniques would be employed to study functional brain networks to determine the features of AD [30]. Below we explained the ML and DL techniques mentioned in the literature for the detection of Alzheimer's.

1.2.2. Machine learning (ML) techniques for alzheimer's detection

The utilization of computational resources in healthcare organizations is constantly growing, and it is becoming increasingly common to record patient information online instead of on paper-based forms. Although access to several electronic medical records (EHRs) has improved as a result, 80% of the data is unstructured. Because of this, processing unstructured data using database management systems and other conventional techniques is tough. These EHRs can be equipped with data mining (DM) and machine learning (ML) tools and techniques to raise the requirement of care and productivity in healthcare facilities (Alonso et al., 2018). Finding previously unidentified and practical patterns in a large number of current datasets is called data mining or information retrieval. These patterns are employed to comprehend the historical dataset, categorize fresh data, and produce data summaries. Sumathi and Sivanandam (2006) say that data mining can classify, or group records based on how similar or different they are. This makes it possible to find deeper patterns in data.

However, ML approaches can be used to get over the obstacles that different technologies have revealed. A quick and effective diagnostic procedure is necessary for AD. ML classifiers can be used to facilitate this easily. These classifiers use strong and efficient algorithms that operate on the idea of learning. Unlike other technologies, ML helps treat AD while being simple to use and guaranteeing accurate results. These outcomes are trustworthy and secure. The application of ML approaches to AD treatment and diagnosis removes the main obstacle to patient security and privacy that exists in the utilization of other technologies.

The use of ML classifiers like SVM, KNN, and Naive Bayes classifiers in combination with neurofunctional and neurostructural scans like PET, MRI, cerebrospinal fluid (CSF), and SPECT studies can yield superior AD diagnosis findings.

In Zhou et al. [31], they proposed combining MRI, cognitive testing, and the MMSE in SVM AD classification. Among 59 AD patients, 127 normal subjects (CN) people, 67 amnestic MCI patients, and 56 non-amnestic MCI patients participated. MMSE values distinguish AD from normal patients. Free Surfer image analysis produces volumetric variables. The study had two parts: training and testing. To restrict the percent error in detecting the proposed method's accuracy, it was implemented 50 times and the average accuracy was calculated. A decision boundary classifier was built using an SVM classifier and a kernel function. The structural MR images improve accuracy by 10%, to 92.4%. In this work, the MMSE rating that was chosen rank-wise along with variables impacting classification and SVM were employed for classification. However, not every potential combination of factors was chosen, and as a result, a combination that may have produced better results may have been overlooked.

In Zhou et al. [32] study they suggested utilizing the Naive Bayes algorithm and wavelet entropy to classify AD from HCs based on MR images. Wavelet transform filters initial MR images and represents them in x and y orientation to depict the image at many scales. Each dimension uses the wavelet transform to get MR image details. T2 MRI was used to classify 64 people (18 HCs, 46 AD sufferers). Thus, AD and HC detection rates were 92.6%. Multi-disease identification could be improved, despite the model's problematic wavelet entropy interpretation. Together, the Naive Bayes classifier and the wavelet entropy transform were utilized to make the determination. When compared to the study by Zhou et al. [31], this one turned out to be a little more accurate and simpler. However, due to the complexity of the wavelet transform and the assumption that abnormalities in several regions of the brain are manifestations of a single abnormality, it was not useful for multi-disease classification.

In Belmokhtar and Benamrane's [33] research they wanted to differentiate between AD, MCI, and CS by integrating various binary classifier models based on the whole voxel-based morphological coupled to MR pictures in the OASIS dataset. The VBM [34] and the MMSE and CDR tests are used to identify features to improve AD detection rates. The Java Agent Framework reduces categorization time. 5-fold validation was used to determine the effectiveness of each binary SVM model; test data were collected from five subjects, while training data were collected from the remaining 25 subjects. The mean of all SVM models resulted in 100% accuracy for classifying AD patients. To examine the classification procedure and save processing time, they employed a binary SVM coupled with voxel-based image data and the Java Agent Development Framework. Thus, the achieved accuracy was 100%; nevertheless, it changed with the amount of MRI datasets.

In Ali et al. [35] research they proposed a unique MRI classification system, TANNN, based on filtration and content-based image retrieval. Feature extraction analyzes the threshold and illness categorization to detect the AD shape in MRI as well as classification time and accuracy. The OASIS dataset, consisting of 416 photos of 18-year-olds, was used for estimation and comparison. The decision tree seemed to have the highest accuracy (96.19%), but the KNN was better for detection accuracy and classification time. This study suggests that TANNN's excellent accuracy makes it useful for real-time categorization. They suggested TANNN for locating classification patterns at the microscopic level. The higher execution speed made this a better option, but it would be much stronger if it could mine the image for its many components, such as shape and texture.

In Rueda et al. [36] work they developed an image processing technique that classifies significant brain patterns. This classification isn't about salient places, but the full region. This image analysis can map any brain region associated with brain disorders, as shown by OASIS and MIRIAD in 4 AD patient groups. The algorithm can be understood by mapping patterns onto brain scans and using them to classify AD and HC patients. Salient brain patterns performed better than traditional feature-based morphometry in the classification technique. Such a technique has not been examined in describing and categorizing AD patients based on MR images. The output of G1, G2, G3, and G4 had 86.05, 80.16, 76.47, and 70.2% accuracy. The information was gleaned using both the bottom-up and top-down methods. However, this method could only reveal differences on a small scale and could not reveal the intricate web of relationships between these differences.

Machine learning is used to implement a significant number of distinct methods, but each of these methods is plagued by a unique set of challenges. The classification of Alzheimer's dementia by some of them simply makes use of structured data, and the number of participants in their datasets is extremely small. A few of them suffer from the issue of having low accuracy. Although it is a challenging process, machine learning is an efficient method for completing categorized tasks. To train machine learning algorithms, you must first extract features from the data and then feed those characteristics that have been extracted to the algorithms. The classification of

Alzheimer's illness is accomplished by researchers using a type of machine learning method. However, each model has both advantages and disadvantages. Some researchers merely record a section of the brain and then use machine learning algorithms; nevertheless, there is a possibility that these researchers will miss the area of the brain that has Alzheimer's disease; despite this, their predictions are accurate. The vast majority of the research relies solely on MRI information for its detection methods. However, MRIs provide only anatomical details of the brain, and the researchers do not take into account the functional connections of the brain. It is necessary to use fMRI data since this type of data provides both structural and functional information. Only then can a functional connection be identified. It is difficult to extract features from the data to classify the fMRI data using machine learning since the fMRI data is quite complicated and it is difficult to extract features from this type of data. CNN (Convolutional Neural Network) is a type of (DL) deep learning that will be utilized to solve this problem because it can automatically extract features from picture data and can be fed complex data.

1.2.3. Deep learning (DL) techniques for alzheimer's detection

A subtype of machine learning method known as "deep learning" involves the learning process being carried out through a deep and hierarchical structure. DL techniques have attracted a lot of consideration recently and have been utilized extensively in a variety of brain studies, including the classification of Parkinson's illness through 3-dimensional fissile imaging data, the detection of seizures, the diagnosis of childhood epilepsy, and the identification of Alzheimer's disease.

Deep belief networks, stack autoencoders, CNN(convolutional neural networks), RNN(recurrent neural networks), and combinations of DL(deep learning) are a few examples of the several types of DL(deep learning) algorithms that have been shown. Robotics, NLP(natural language processing), medical imaging, online data brook identification, routing in swarming luggage handling, neurological interface for cortex visual prosthetic device, and additional fields have all demonstrated great success with Convolutional Neural Networks (CNN) in solving detection and classification problems. Additionally, it has attracted plenty of attention in the early identification and diagnosis of AD. A CNN has a complex design that includes layers of fully linked, max/average pooling, and convolutional algorithms. Varied architectures have different layer depths, but typically they start with a pooling layer, move through different convolutional neural layers, and end with completely connected layers.

The arithmetic convolutional operator, which glides one function over another and calculates a summation of their multiplication pointwise, is a foundation of convolutional layers. Convolutional layers connect neurons to a set amount of pixels inside their responsive field rather than all of the pixels in the input image. Convolutional layers are designed to take low-level information from the top levels and combine them to create features of an image in the subsequent layers. To downsample the data, the convolutions are typically placed after one or more convolutional layers. The average pooling and pooling layers are the two most prevalent pooling layers, and they both focus on each receptive field. While average pooling sends the arithmetic mean to the next layer, max pooling sends the benefit that is most valuable to the region of interest to the next layer.

Figure 1.2 demonstrate the example of a CNN(convolution neural network). In CNN architecture, the input picture is fed to the layers called the Convolutional layer which applies different convolution filters to the image and extracts the features from the image. The initial layer captures low-level features while the later layer extracts top-level features from the pictures data. Next to the CNN(convolution layer), the pooling layers are used to reduce the dimensionality of the feature. After several combinations of CNN layers and pooling layers, the extracted features are fed to the fully connected layer and output layers which helps to make decisions from the data.

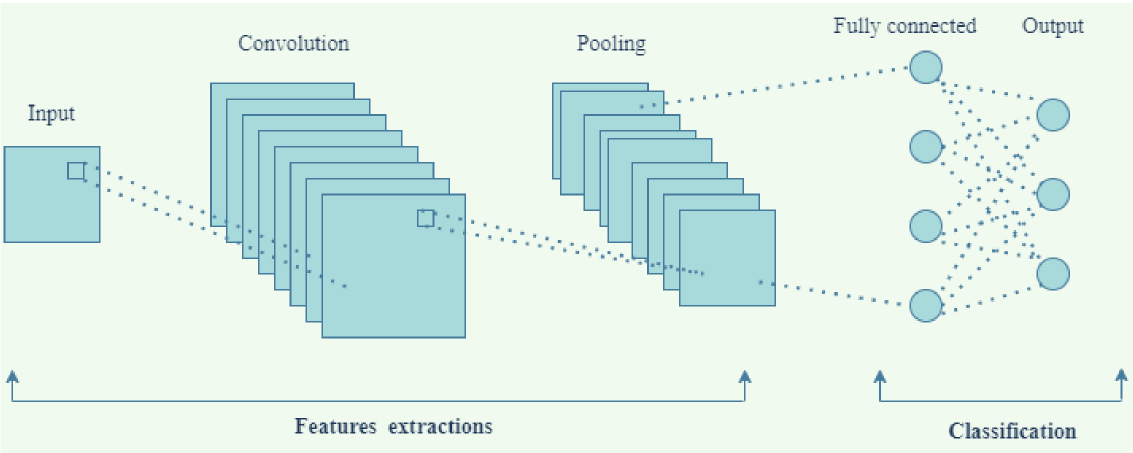

Figure 1.2: Demonstrate the general data flow architecture of CNN.

Numerous studies used DL(deep learning) algorithms for the recognition and categorization of Alzheimer's. For example, To predict the course of AD, Lee et al. [37] created multi-modal recurrent neural networks (RNN) employing various biomarkers, including MRI images, demographic information, knowledge experience, and CSF biomarkers. RNNs are a subset of deep learning algorithms that take temporal sequences into account. They use the ADNI dataset without the preprocessing and achieve an accuracy of 81 percent. Their predicted accuracy is almost near to baseline accuracy. They don't achieve high improvements in terms of accuracy, and they didn't calculate the other performance matrices.

In the research carried out from Wada et al. [38], a CNN is constructed from the ground up. This CNN has a total of six layers, three of which are convolutional layers, while the remaining three are fully linked layers. Research on AD has often employed either a two-dimensional or a three-dimensional CNN. In a two-dimensional CNN model, the inputs are 2-dimensional pictures, and each picture represents one piece from the stack. In 3-dimensional CNNs, on the other hand, the input nodes are either voxels or regions of interest (ROI). They achieve an accuracy of 72% but they didn't mention the detail of the dataset and preprocessing. They use CNN on the MRI data, but their accuracy is low as compared to other existing work.

Both ternary and binary AD classification were accomplished by Feng et al. [39] using SoftMax with two-dimensional CNN, 3-dimensional CNN, and 3-dimensional CNN with SVM respectively. and reported a greater level of performance when the 3-dimensional CNN and SVM were coupled. They used ADNI data for the classification of Alzheimer's. They perform some preprocessing tasks on the data which are normalization, skull striping, tissue segmentation, and non-linear affine transformation. They achieve 82.57% accuracy in 2D CNN and 89% in the case of 3D CNN. They only computed accuracies but did not consider other performance matrices.

Two-dimensional convolutional neural networks were used by Farooq et al. [40] for the four classes of categorization of MRI images into Alzheimer's dementia, mild mental impairment, normal intellectual aging, and late mental impairment (LMCI). Transfer learning applied to models from Google Net, ResNet-18, and ResNet-152. They used the ADNI dataset for the classification and adopt three classes from ADNI which are AD (Alzheimer's dementia patients), NC(normal control patients), and MCI(mild cognitive impairment patients). They apply different preprocessing steps to the data which are skull striping, GM segmentation, bias correction, and modulation. They extracted two-dimensional images from the data and achieved an accuracy of 98%.

CNN has the benefit of requiring no image segmentation for feature extraction. This benefit was utilized by Silva et al. [41] who created a CNN(Convolutional Neural Network) to obtain features from MRI imaging data for the identification of AD. With three-dimensional convolutional layers, 32 neurons in the initial layer, 64 neurons in the second layer, and 128 neurons in the third layer, they designed CNN. They also utilized the Relu activation function, drop out, and max pooling on every layer. For categorization, the final layers are coupled to a fully linked layer. They use feature maps map for several classifiers, such as KNN(K nearest neighbor), SVM(Support vector machine), RF(Random Forest), and CNN(Convolutional Neural Network). They compared the performance of different models (CNN + K - nearest neighbors and CNN + RF), and the hybrid method (CNN + SVM) produced a greater classification rate. They used Minimal Interval Resonance Imaging in Alzheimer's (MIRIA) data for this study. They perform normalization on the data and achieved an accuracy of 96%. They used two-dimensional data and excluded temporal information from the data.

Jain et al. [42] employed the extracted features of CNN that were VGG-16 that had been pre-trained on the ImageNet dataset to detect Alzheimer's disease using MRI imaging. They also used the very popular dataset ADNI for this research and consider the tree classes which are AD, NC, and MCI. They performed motion correction and Non-Uniform Intensity normalization (NU) as preprocessing of the data. They used only two-dimensional data but did not consider the temporal information from the data and achieved 95% accuracy.

Utilizing MRI image scans, So et al. recommended a supervised neural network MLP(Multi-layer perceptron) for a regimen of Alzheimer's phases based on the texture of the hippocampus [43]. They employed the 3-dimensional (GLCM) gray level concurrence technique to assess the textural characteristics, and then they selected the features with the highest quality by using Fisher's coefficient. They used the ADNI dataset for this study. They performed image registration, cropping, and texture analysis on the obtained data. They obtained subjects of three different categories which are AD, NC, and MCI. They performed binary classification on the data and achieved 72% accuracy for MCI vs AD, 85% for NC vs AD, and 75% for NC vs MCI.

Ortiz-Garcia et al. [44] employed MRI scans and PET scans images in DBN (deep belief network) AD categorization. From PET and MRI data, they chose 70 AD, 68 NC, 26 late MCI, and 111 MCI individuals. Preprocessing comprises registering and shrinking MRI and PET images to 1.5 mm in axial, coronal, and sagittal perspectives. They used MRI to separate white matter (WM) from grey matter (GM). Normalizing PET scans using mean cerebellar activation level. Using Welch's t-test, they picked relevant coordinates from each modality and separated the brain into 116 areas, excluding the cerebellum. The classification was accomplished utilizing DBN using 4 polling systems: weighted voting, voting, SVM(Support vector machine) based data transformation, and DBN-based data fusion. DBN(Deep belief Network) and SVM(Support Vector Machine) based voting for AD and NC patients is 90% accurate. They used ADNI data for this research and perform voxel segmentation and brain parcellation. They combine the two different datasets in this study but only consider the structural information from the data.

Using clinical information from the Hachinski ischemia score, geriatric depression scale, neuropsychiatric inventory questionnaire, and cerebrovascular illness, Ann et al. [45] constructed a collection of DBNs(Deep Belief Networks) for AD(Alzheimer’s dementia) categorization. To lessen attribute correlation and broaden the base classifiers, they used two dense autoencoders developed for feature learning at the voting layer. They used the data provided by the National Alzheimer’s Coordinating Center (NACC) and the data is MRI(Magnetic Resonance Imaging). They achieved an accuracy of 78%.

For AD diagnosis and MCI, Ding et al. [11] developed a DL(deep learning) method built on brain PET scans. By creating a CNN premised on Inception V3 that had been trained on ImageNet, they used transfer learning. By including a dropout before layers were fully connected at the network's end, they improved CNN. The data is extracted from the ADNI and perform image sampling, thresholding, and extraction of relevant images volume using connected component analysis. Their performance matrix is not clear how much accurate their modality is.

Using PET imaging, Shakarami et al. [152] used two-dimensional CNN premised upon SVM and Alex Net to classify participants into AD(Alzheimer’s dementia) and NC(normal control) patient’s groups. By deleting the final three levels of the design, adding 22 more layers with a fully linked layer, and an SVM(Support Vector Machine) classifier to categorize the slice into NC and AD groups, they were able to fine-tune the Alex Net. They used ADNI data for this study and achieved a comparable result which is 96 percent. They used the preprocessed mages extracted from the ADNI website. They consider only the structural information and do not consider the functional information.

Weei et al. suggested Linking biomarkers with functional and structural brain networks to detect MCI(Mild Cognitive Impairment) and AD(Alzheimer's dementia) patients [46]. To eliminate the potential loss of information in modeling, Chein et al. created NN(neural networks) that can get together high-order and low-order characteristics to categorize [47]. These researchers faced inevitable info loss in modeling while turning 4-dimensional functional MRI data into the brain power networks since the brain power network aims at the depiction of cooperation among areas of the intellectual cortex.

Parmar et al. make use of the 3-dimensional CNN(convolutional neural network) for the categorization of Alzheimer's [48]. They used ADNI fMRI data for the training of the model and achieve 93% accuracy but did not consider the sequential information in the voxels. They only design a CNN which considers the temporal information of the data.

Wei et al. use a combined 3-dimensional CNN(convolutional neural network) and LSTM(long short-term memory network) for the classification of different stages of Alzheimer's [49]. They used the sequential information from the data and achieve 90% accuracy. They use a different approach from all other approaches that exist in the literature but their area under the curve (AUC) and accuracy for multi-class classification is low.

Odusami et al. use the pre-trained Renet18 paradigm for the categorization of Alzheimer's dementia [50]. They classify different stages of Alzheimer's using 2D CNN(convolutional neural network) from fMRI data. They reported very high results which are 99% without the consideration of time information from the data. They used only the two dimensions of data, but actual fMRI data is 4 dimensional.

Jia et al. used fMRI data for the classification of different stages of Alzheimer's [51]. They preprocessed the data and used 3DPCANet for the extraction of features from the data. They used the extracted features for the classification of Alzheimer's by using the SVM traditional machine learning technique. They achieve 95% accuracy for the MCI, 92% for the normal control, and 91% for Alzheimer's dementia.

Kazemi et al. used fMRI data gathered from the ADNI website for the classification of 4 different stages of Alzheimer's and normal control patients [52]. They used the pre-trained network called Alex Net for the classification which only considers the two dimensions of the data. By Ignoring the other dimensions, it is not convincing that the model performs well on all the dimensions of the data. They achieve a 97% average accuracy.

Puranik et al. use data from the ADNI website and perform preprocessing on the data for the classification of Alzheimer's disease [53]. They used Inception Resnet V2 model pre-trained neural network architecture to convert 3d images to 2D and trained the model. They used only the structural information from the data and did not consider the time information from the data. They achieve an average accuracy of 87%.

Many scientists have tried to apply deep learning techniques to the domain of fMRI data processing. For example, Sarraf et al. [54] utilized 2-dimensional fMRI image segments to train a CNN(Convolutional Neural Network) for the categorization of individuals who had Alzheimer's disease and were healthy. A Principal component analysis 3D CNN was trained by Kam et al. [55] utilizing 3-dimensional fMRI image slices. This research all tried to use deep convolutional networks to directly extract features using 3D or 2D picture slices from the original 4D fMRI data. By converting 4D fMRI data to intrinsically correlation [56] or dividing it into 3D or 2D pictures, and so feeding the features obtained into a classification algorithm. The majority of research to date has used this data to identify Alzheimer's disease. The latter method inevitably lost quite a significant amount of data on the time information of the 4-dimensional fMRI data, whereas coarse-grained modeling left out a lot of longitudinal structure information and time information from data. They did not fully exploit the information contained within 4D fMRI data. Directly using 4D fMRI, in my opinion, can keep all time-varying and functional information, which may be crucial for AD diagnosis. However, this presumption has never been proven in the past in terms of algorithmic restrictions.

1.3. Scope Of Work

The utmost vital biomarkers for the finding of AD have been made possible by considerable advancements in neuroimaging techniques over the past few decades, including structural MRI, positron emission tomography (PET), and functional MRI [57], [58]. Furthermore, a novel paradigm of utilizing computer-based ML(machine learning) techniques in the sense of categorization and programmed finding of AD has emerged as a result of ongoing advancements in the simulation influence of computers and the accessibility of datasets associated with AD, including the OASIS(Open Access Series of Imaging Studies) and the ADNI(Alzheimer's Disease Neuroimaging Initiative) [27].

Traditional machine learning systems are built on guided or partially-automatic feature understanding methods, which often entail a large number of difficult preprocessing stages that call for specialized knowledge [59], [60]. Deep learning (DL) methods are relatively new to the field of machine learning, but they have quickly emerged as a viable alternative to traditional approaches to machine learning's limitations [59], [60]. These methods offer significantly improved outcomes in CV(computer vision), object finding, classification, and medical imaging analysis. This study intended to assess the modern state of the art concerning the use of DL(deep learning) algorithms for the analysis of Alzheimer's illness by utilizing neuroimaging data.

The purpose of our research is to diagnose the early stage of Alzheimer’s illness by utilizing AI(Artificial Intelligence) techniques. This study analyzes the performance parameters of multiple DL techniques over two different neuroimaging datasets to identify Alzheimer's disease at an earlier stage. In this study, two independent datasets were employed to identify Alzheimer's illness using the DL(deep learning) algorithms CNN(Convolutional Neural Network) and LSTM(Long Short-Term Memory). There were two distinct datasets utilized in the process of generalizing the model's findings from its training on those datasets. The objective of this work is to accurately classify Alzheimer's disease by developing an algorithm based on deep learning that makes use of a variety of various methods. The newly implemented algorithm is now capable of classifying various Alzheimer's disease stages based on a variety of datasets.

1.4. Overview Of Proposed Solution

Artificial intelligence(AI) also performs an essential role in the detection of Alzheimer's. The general architecture of Alzheimer's classification using AI is presented in **Figure 1.3**. Two techniques use ML(machine learning) and DL(deep learning) to identify Alzheimer's. We will explain machine learning and deep learning in Chapter 2. Nowadays, most researchers use DL(Deep Learning) for the recognition and categorization of Alzheimer's because of advancements in DL, specifically after the invention of the Convolutional Neural Network(CNN), which makes feature extraction very easy. Even CNN can classify complex data. LSTM networks are also very helpful for the classification of sequential data.

We used fMRI data for this research, and it contains a sequence of voxels. To enhance the classification performance of our algorithm, we employed LSTM. For the recognition of Alzheimer's, CNN is used with LSTM(Long-Short-Term Memory) in this study. A deep learning-based model named Conv3d-lstm is implemented in this research. It's made up of 3D CNN layers, batch normalization, maximum pooling, and LSTM(Long-Short-Term Memory). A set of 3-dimensional CNNs(Convolutional Neural Networks) was utilized to get spatial information from every part of a 3-dimensional stationary picture from a functional MRI image series. It uses 3-dimensional CNN for getting spatial structural info and CNN for analyzing features from the data. The extracted features are fed to LSTM to preserve the information from each voxel in the image. It can directly deal with 4-dimensional functional MRI data and use both the time information and the structural information from functional MRI to find AD.

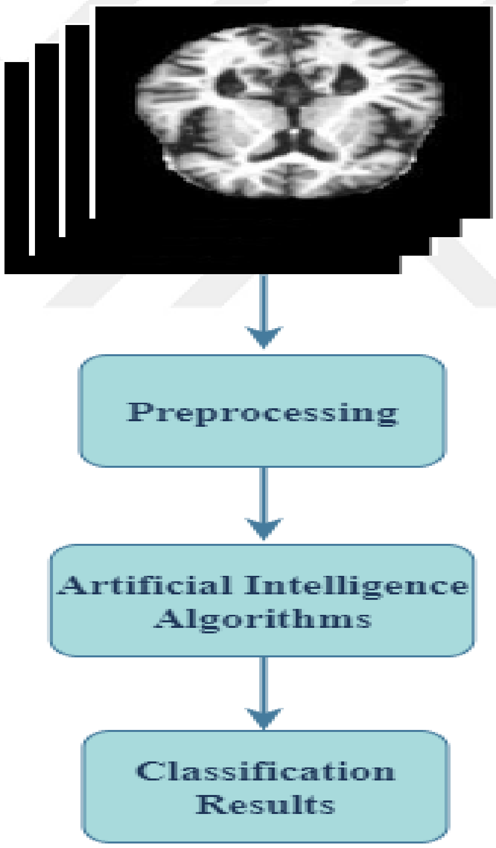

Figure 1.3: Demonstrates the classification step involved in the detection of Alzheimer's using AI.

1.4.1. Originality

In the present investigation, a unique deep learning method known as Conv3d-lstm was established through the use of the deep learning algorithms 3-dimensional CNN [61] and

LSTM [62]. The LSTM layers are connected to the CNN layers in a hierarchical fashion. The CNN layers are responsible for the extraction of the features from the three-dimensional data, and the LSTM layers assist the CNN in the classification of those features by taking into account the sequence of voxels that exist in the fourth dimension of the data. The unique algorithm that has been proposed is capable of handling fMRI data in all four dimensions. Before the researcher extracted the structural information from the functional MRI data in order to concentrate just on the three-dimensional data.

For the purpose of Alzheimer's disease classification, the aforementioned algorithm takes into account the four-dimensional data. The proposed algorithm was trained on multiple datasets, the first of which was the neuroimaging dataset from ADNI (adni.loni.usc.edu), and the second of which was the neuroimage data from the OASIS data repository(https://www.oasis-brains.org/#data). The model is trained on two distinct sets of data to generalize the features it has learned and make it easier for the algorithm to make predictions based on newly available data.

1.4.2. Contributions

Several other deep learning algorithms are developed in this study so that the performance of the suggested algorithm can be compared to that of the other techniques. The first two-dimensional CNN models were developed with the help of the transferred learning methodology and the pre-trained networks ResNet-18, VGG, and Dense Net. These networks were utilized in the implementation procedure. The performance of these 2-dimensional CNN models is good when compared to other methods that are described in the research literature compared to that of the other techniques. The first two-dimensional CNN models were developed with the help of the transferred learning methodology and the pre-trained networks ResNet-18, VGG, and Dense Net. These networks were used in the implementation process. The performance of these 2D CNN models is good when compared to other methods that are described in the research literature, but these results did not meet our expectations. We did not take into account the voxel information when developing a 2D convolutional model because the model can only receive data in a two-dimensional space and the derived features are not sufficient for accurate classification. The accuracy of the 2D CNN model is significantly lower than 80%.

The 3D CNN model is also trained to classify the data relating to Alzheimer's disease. The 3D CNN model was trained on the OASIS data, and then it was used for classification using transferred learning. The previously trained parameters were kept for subsequent preparation of the 3-dimensional CNN model with ADNI data. The outcomes obtained by the 2-dimensional CNN models, and the 3-dimensional CNN model produces superior outcomes. It is determined that the 3-dimensional CNN model has a correctness of 85.76%. Additionally, bidirectional LSTM layers are added to the 3D CNN model before the fully linked model, and then the model is trained once again utilizing the data. By including the LSTM layers in our suggested model, we can get improved results. The addition of the LSTM layers allows for the acquisition of the voxel information that exists in the fourth dimension, which assists the model in the classification process and leads to an improvement in its overall performance. Our revised model has an accuracy of 91.06%, which is higher than the accuracy found in the prior studies. The main contributions of this study are mentioned below.

- Implemented a novel deep learning algorithm using CNN and LSTM called Conv3d-lstm for the classification of Alzheimer's
- Used different convolutional neural network base algorithms to validate the performance of the proposed algorithm.
- Preprocessing of the raw data collected from the ADNI database to extract meaningful information.
- Apply the image normalization technique to the data for smooth training.
- Different hyperparameters are tuned during the training of the proposed algorithm.

1.5. Thesis Structure

In **Chapter 1**, we highlight the introduction and background on Alzheimer's disease. We also describe literature review, scope of work, an overview of the proposed solution, and Contributions. In **Chapter 2**, we provided an explanation of the technique as well as other essential components of the area of study that we were conducting. In **Chapter 3**, we describe the findings of our research work in the form of practical implementation. In **Chapter 4**, we give a comparison of our research to the many methodologies that are already in use, as well as an explanation of the findings of our research. In **Chapter 5**, we'll talk about the conclusion and future plans.

CHAPTER 2

2. THEORETICAL PART

This chapter will describe some important component which is related to our research work. We will describe the details of those components that are involved in this research.

2.1. Artificial Intelligence (AI)

Artificial intelligence (AI) is indeed the ability of a modern computer or computer-aided robot to carry out tasks that are frequently performed by intelligent people. The aim of designing a system that can reason, deduce meaning, extrapolate, or learn from experience is described by the expression often. Computers can do very complicated tasks, such as deducing authentication of the arithmetic hypotheses or playing chess, as the design of the modern computer in the 1940s. Nevertheless, even though computer processing speed and memory have continued to develop. To create an AI system, developers must carefully reverse-engineer human features and skills in a computer and then use the machine's computing power to outperform humans. One must go deeply into the subfields of Artificial Intelligence and comprehend how those domains may be applied to the various industries of business to grasp how AI truly works.

Artificial intelligence (AI) has recently considerably altered the analysis and application of digital data. Now, AI is used for simple tasks, including image or voice recognition, and it often outperforms human talents in these areas. The promise of rapid, low-cost, and precise automation, such as the analysis of image data by AI algorithms, makes this a very attractive prospect for transfer to the medical field. To better understand complicated multifactorial disorders like AD, numerous studies have been conducted. With the help of AI, brain imaging, biochemical parameters, clinical, and neuropsychiatric (NPS) datasets from patients and controls may be integrated and processed to create methods that can be employed in the biomedical and clinical fields for the categorization and stratification of patients. Computer-Assisted Diagnosis is a major area of use for artificial intelligence in the biomedical industry (CAD). Data analysis is automated in this type of app with the hope that it would aid in making an initial and correct diagnosis of Alzheimer's illness and other types of dementia. In this research different AI techniques are used for the categorization of Alzheimer’s. Deep learning as well as its techniques which are transferred learning, CNN(convolutional neural network), and LSTM(long short-term memory) networks are used. By using different AI algorithms, we achieve improved results compared to existing studies in the literature. **Figure 2.1** explains the overall procedure for the detection of Alzheimer’s using Artificial Intelligence.

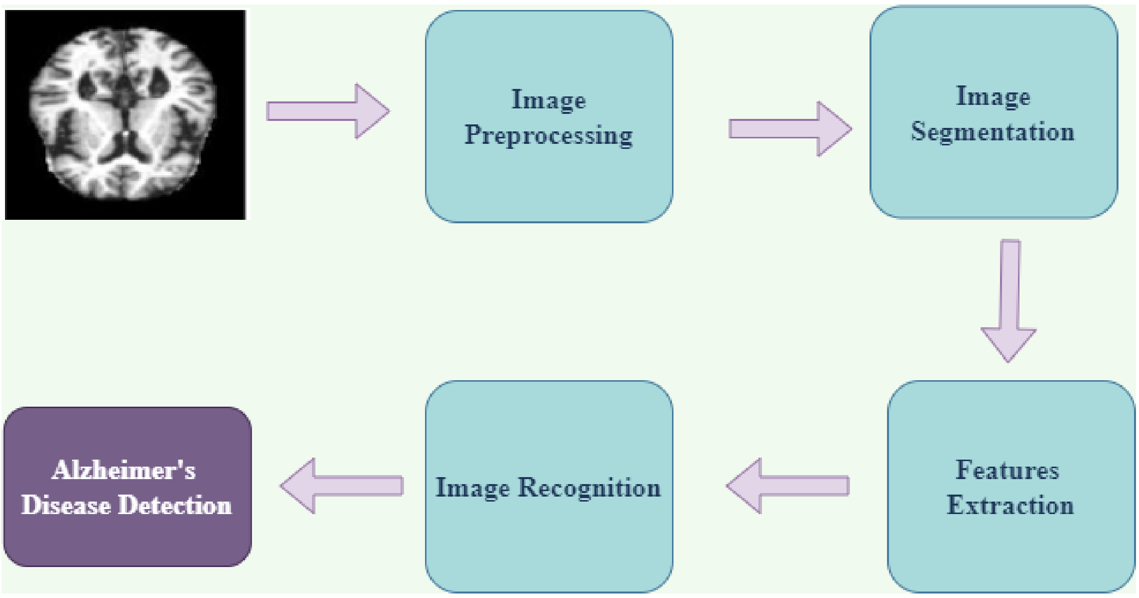

Figure 2.1: Explains the detailed procedure involved in the detection of Alzheimer's by employing AI.

2.1.1. Machine learning

ML teaches a computer how to draw conclusions and make choices based on its previous experiences and data. It does this by recognizing patterns and analyzing data from the past to infer the meaning of individual data points and arrive at a plausible conclusion without the need for human experience to be involved. Businesses can make better decisions and save time because of the automation of the process of coming to conclusions via the evaluation of data. ML(Machine learning) techniques are utilized in a vast array of application areas, including email filtering, medicine, computer vision, and voice identification[63]. These applications are utilized in areas where it is challenging or not possible to design conventional algorithms to perform the required tasks.

ML(Machine learning) includes different applications e.g., UML(Unsupervised Machine Learning), RL(Reinforcement Learning), and SML(Supervised Machine Learning). Several methods are used for the identification of Alzheimer's dementia. In Section 1.2 we explained all the methods available in the literature for the detection of AD. Several ML(machine learning) techniques are used for the identification and SVM(Support Vector Machine) is the most used method. In this study, the deep learning subtype of machine learning is used for the categorization of Alzheimer’s. SML is applied for the identification of Alzheimer’s.

2.1.1.1. Supervised machine learning (SML)

Supervised machine learning(SML) is one of the categories of ML in which computers are taught using training data that has been appropriately "labeled," and then, using that data as a foundation, machines anticipate the output. Data that has been labeled implies that a portion of the input data has previously been tagged with the proper label. An SML algorithm's goal is to find a mapping function that maps the input data (x) to the output data (y). Classification is one of the primary categories that fall under the umbrella of supervised learning.

The classification of Alzheimer's disease can benefit greatly from the application of this method. Both ML(machine learning) and DL(deep learning) can be applied during the classification process. Thanks to classification, we are able to quickly identify the patient as having Alzheimer's disease, as having normal dementia, or as having any other stage of Alzheimer's disease. The Supervised learning technique called supervised learning is used for the classification of dementia. The data having a label is fed to a classification algorithm to classify the data for having different stages of Alzheimer's.

2.1.1.2. Unsupervised machine learning (UML)

Unsupervised learning(UML) is a kind of ML(machine learning) in which the individual doesn't have to look over the algorithm. As an alternative, it facilitates the algorithm to function autonomously and discover formerly unnoticed patterns and knowledge. It mainly focuses on unlabeled data. The goal of SML(supervised machine learning) is to detect the find the pattern in the unstructured data. clustering, associating, and reducing the dimensionality of the data are the three most common applications for unsupervised learning models. In addition to being a subtype of ML and DL, UML(unsupervised learning) is also a form of conventional learning.

Clustering is a prime example of one of the most common types of unsupervised learning. We can discriminate between patients who are at various phases of Alzheimer's disorder with the use of clustering. There are many kinds of clustering, and each form has a unique set of benefits and drawbacks. It is dependent on the requirements of the problem as well as the type suitable for the problem domain. For this research, we are planning to apply an unsupervised learning technique which is online learning for this study. We also want to extend this approach and want to apply clustering to it for future studies. The proposed online learning and clustering techniques are explained in sections 5.2.2 and 5.2.3.

2.1.1.3. Clustering

Data are unsupervised and classified, or clusters, by the clustering process. This information can be observations, feature vectors, or data elements. Each cluster contains grouped data that are like one another and distinct from other clusters. Clustering is a common practice, and its effectiveness is crucial because many applications consider it to be a fundamental step. Information extraction, biology, compression, climate, physiology, medicine, and business can all benefit from clustering.

For image clustering, a given image database is sorted into clusters using any available clustering method. Every image in the dataset is assigned a class label following clustering, with photos that share a class label being conceptually comparable. Clustering has been used as a categorization tool in several recent AD studies. These methods use a clustering methodology to extract features, which are then input into an algorithm to categorize the data. Clustering is used to divide the image of the brain into various segments, such as white substance volume, gray substance volume, and rational fluid. This is done for brain segments. We are planning to apply to cluster several areas of the brain. Clustering different brain areas can guide the classification process for the better categorization of Alzheimer’s illness

2.1.1.4. Reinforcement machine learning (RL)

Reinforcement learning (RL), a subfield of ML(machine learning), examines how smart objects should act in a given circumstance to maximize the idea of cumulative reward. One of the three primary machine learning paradigms is reinforcement learning, along with supervised and unsupervised machine learning. RL is also helpful for patients with Alzheimer's. By using RL, the model can assist in daily tasks for the patients. For example, A reminder system that sends notifications to guide Alzheimer's patients while they are performing everyday life tasks has been proposed by Jarray et al. [9]. Indeed, anytime the activity identification system can recognize the patient's action, the prompt system established by Jarray et al. [9] evaluates the latter and delivers an alarm to the patient, if necessary. This occurs when the activity identification system can recognize the patient's movement. **Figure 2.2** explains the methodology of reinforcement learning.

Future research on this subject will employ a reinforcement learning method. For the classification of Alzheimer's, the online learning technique will be used, which is an RL(reinforcement learning) technique. The proposed online learning method is explained in Section 5.2.2.

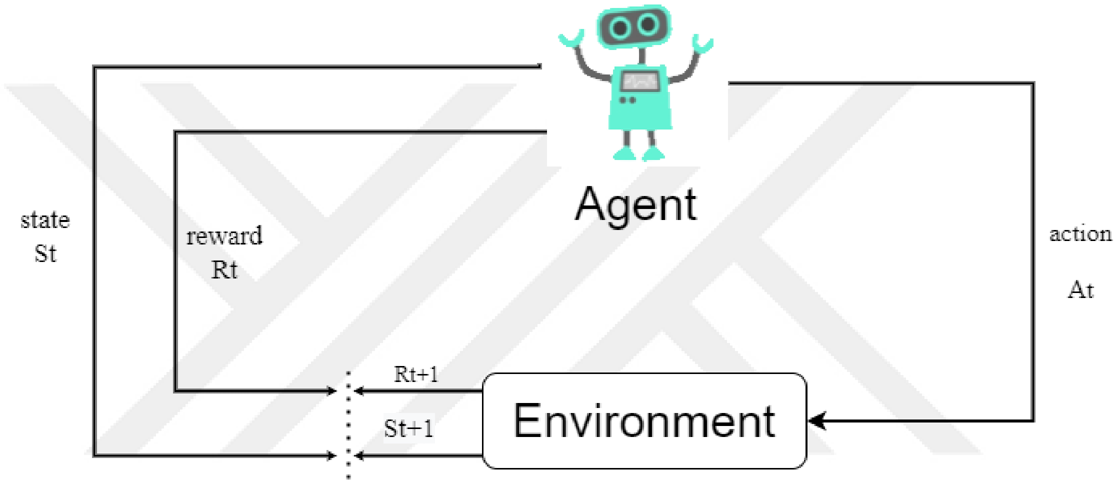

Figure 2.2: Demonstrate the methodology of reinforcement learning.

2.1.2. Deep learning (DL)

Deep Learning(DL) often referred to as SDL(Structure deep learning) is a subtype of ML(Machine learning) that utilize ANN(Artificial Neural Network) as well as representation learning to perform intelligent tasks. There are three different ways to learn: supervised, semi-supervised, and unsupervised [64]. The information analysis and distributed transmission nodes seen in biological structures served as an inspiration for ANN(artificial neural networks). ANNs have been prominent in a variety of ways from biological brains. ANNs, to be more specific, tend to be symbolic and static, while biological brains are dynamic and analog [65], [66].

Data pre-processing is often not required with deep learning, which simplifies the machine learning process. By ingesting and processing unstructured data like text and pictures, these algorithms reduce reliance on human specialists by automating feature extraction. While in traditional machine learning algorithms first, we need to extract features from unstructured data then we start training for making automated systems. **Figure 2.3** shows the comparison between ML(machine learning) and DL(deep learning). Below we will describe some of the tasks which can be done using DL(deep learning) which includes CV(Computer Vision) and NLP(Natural Language Processing).

For CV, most people use CNN(Convolutional Neural Network) while for natural language processing they use an RNN(Recurrent Neural Network) or LSTM(Long Short-Term Memory). They can be used together. Below we will explain these terms as well. DL(Deep Learning) performs an essential role in the identification of Alzheimer's illness and in assisting the patient with their daily tasks by using RL(Reinforcement learning).

Different deep learning algorithms are used in this research for the categorization of Alzheimer's disorder. The main component is computer vision in which we used CNN(Convolutional Neural Network) and LSTM(long short-term Memory network) is used. The computer vision is to obtain the structural knowledge from the data and LSTM is used to keep track of time information in the data.

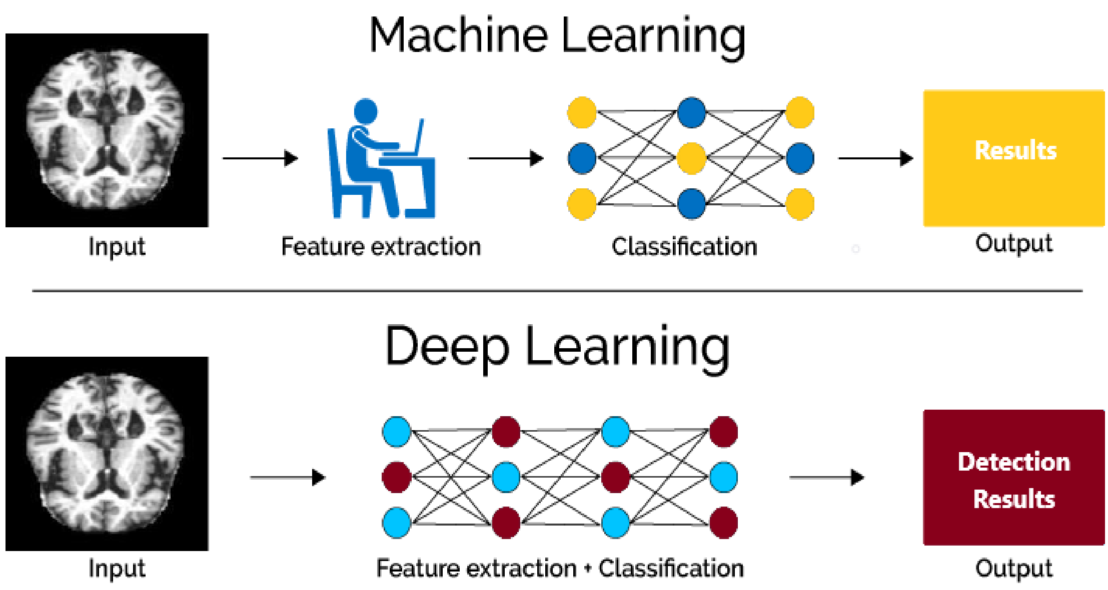

Figure 2.3: Demonstrate the difference between ML(Machine Learning) and DL(Deep Learning).

2.1.2.1. Computer vision (CV)

Modern computers and intelligent systems may now employ computer vision (CV) to gather valuable information from images, video recordings, and other visible inputs and to take actions or make recommendations in response to that knowledge. While CV offers computers the capability to perceive, observe, and interpret the world, AI allows them to think intelligently. Computer vision trains machines to perform similar tasks without the need for retinas, optic nerves, or a visual brain. Instead, it uses a camera, data, and algorithms. As a result, the process can be finished in a lot less time. A machine that has been trained to inspect products or monitor a production asset may quickly outperform people since it can evaluate hundreds of things in an image per minute and find defects or problems that are invisible to the human eye. CV shows an important role in extracting information from medical images. Extracting, evaluating, and visually depicting the structural and functional features of biological tissues is made possible with the help of computer vision technologies that have been specifically suited to multi-dimensional and multi-spectral MR data. This can significantly improve the analysis.

The method of machine learning known as computer vision is utilized in the process of extracting usable information or, to use another term, features from images. These features are then put to use for various purposes, such as categorization. In this study, computer vision was used to obtain meaningful features from images of the brain. Those features were then used to classify the various phases of Alzheimer's disease.

2.1.2.2. Convolutional neural networks (CNN)

A CNN(Convolutional Neural Network) is a DL(Deep Learning) technique that can take in a picture as input, assign various objects and elements in the picture significance (learnable weights and biases), and be able to discern between them. In comparison to other classification methods, CNN requires significantly less preprocessing. Contrary to fundamental approaches, where filters must be hand-engineered, CNN can gain knowledge of these filters and their attributes. The Visual cortex's organizational structure, which resembles the connections in the human brain's neuron network, influenced how Conv Nets were created. Individual neurons can only respond to stimuli in this restricted region of the field of vision, called the receptive field. Several overlapping fields like this make up the entire visual field. Most researchers use two techniques for the detection of Alzheimer’s by employing CNN. Learning from scratch and transfer learning[66], [21]are the two main learning methods used in CNN for AD research. Transfer learning is the process of employing a previously trained algorithm and fine-tuning it to address a new dilemma, as opposed to starting from scratch and train with randomly initialized weights. Pretrained networks are often chosen based on the results of earlier studies. Due to its effectiveness throughout the training process, transfer learning is widely used to solve picture classification challenges. It drastically reduces the amount of training data needed and speeds up training. This is crucial for data from medical imaging since there are typically few training images available.

The most well-known method that is utilized these days for the extraction of various degrees of characteristics from images is called convolutional neural networks. In this particular work, we used CNN to analyze the brain image and extract meaningful information from the data collected from the brain to categorize Alzheimer's disease. **Figure 2.4** shows the combination of convolution layers with an activation function.

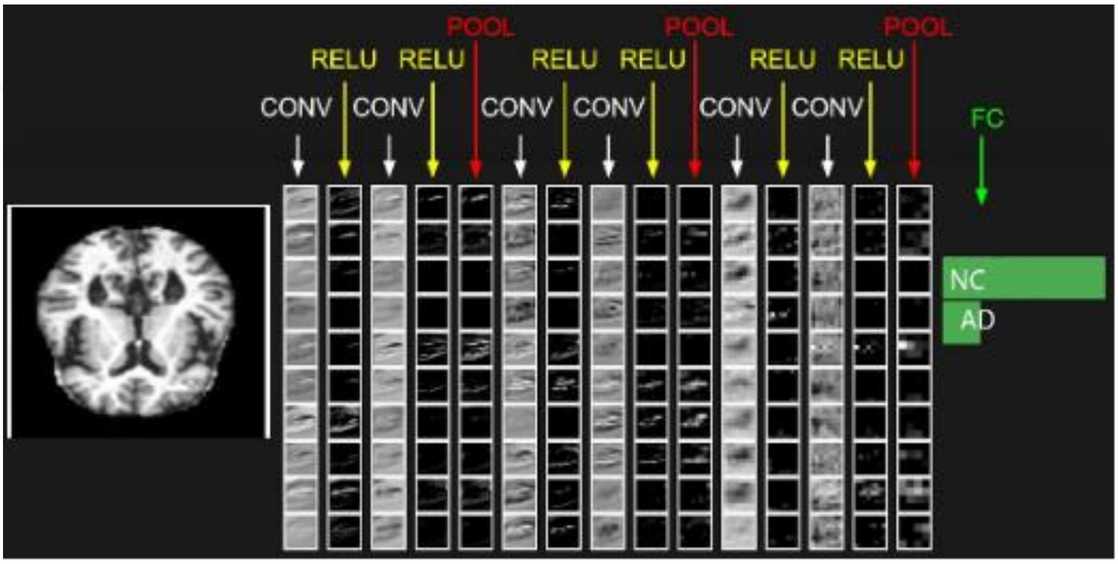

Figure 2.4: This shows that CNN architecture in which the initial layers obtain subordinate features and later layers extracts complex features.

2.1.2.3. Recurrent neural network (RNN)

An RNN(recurrent neural network), is a subtype of the ANN(artificial neural network). In RNN, the relations between the nodes may form either a targeted or untargeted graph alongside a temporal chronological sequence. Because of this, it can display temporally vigorous behavior. RNNs are a descendant of FFNN(feedforward neural networks) and can utilize their inner state memory to handle input structures of varying lengths. RNN is also beneficial for the detection of Alzheimer’s. In both cross-sectional and longitudinal investigations, RNNs can help detect AD. RNNs are used in cross-sectional studies to assess a subject at a particular point in time. RNNs are used in general cross-sectional approaches to extract features from brain scan image slices and determine their relationships. RNNs track participants over time in longitudinal studies to assess the course of AD. RNNs are used in general longitudinal approaches to understanding the illness progression among brain scans that were collected over time and extracting features from them.

RNN is another method of deep learning that may be used to the data to process sequential information. We processed the series of voxels in the brain image data using RNN, however, this did not preserve a record of the memory of the information contained in the prior voxels. We decided to employ LSTM for this work because RNN did not generate satisfactory results for the Alzheimer's classification task.

2.1.2.4. Long short-term memory networks (LSTM)

A type of RNN(recurrent neural network) recognized as an LSTM(Long Short-Term Memory) network is able of learning order dependency in sequence prediction challenges. This is a behavior that is necessary for complicated problem areas like voice recognition, machine translation, and other similar problems. Intentionally, LSTMs are created to prevent the long-term reliance issue. They don't strive to learn; in fact, remembering knowledge for a long time is their default behavior. Alzheimer's disease can be better diagnosed with the use of an LSTM neural network. Because the AD data consists of voxel sequences, for the most part, LSTM is well-suited to storing the information derived from these sequences, which in turn helps to enhance classification accuracy.

Figure 2.5 demonstrate the architecture of the LSTM neural network. First, the forget gate $\mathbf{F_t}$ multiplies the state of the final cell $\mathbf{C_{t-1}}$. The candidate state $\hat{\mathbf{C}}_\mathbf{t}$ of the cell is then added to the input gate value $\mathbf{I_t}$ which is then multiplied with $\hat{\mathbf{C}}_\mathbf{t}$ to produce the cell state $\mathbf{C_t}$ of this unit, and the value is updated. The hidden state $\mathbf{h_t}$ and output gate $\mathbf{o_t}$ are then calculated. To determine the output of the value gate, the input $\mathbf{X_t}$ as well as the final hidden state $\mathbf{h_{t-1}}$ first were determined by sigmoid. The hidden unit state of the cell is obtained by multiplying the cell $\mathbf{C_t}$ by the output gate following a **tanh** operation.

In this study, fMRI voxel sequences are processed by employing LSTM for Alzheimer's disorder categorization. Long short-term memory (LSTM) excels in analyzing data sequences. In our work with CNN, we made use of LSTM, which uses four dimensions consisting of a sequence of voxels to help the fully connected layers in classifying data, whereas CNN pulls characteristics from a three-dimensional image.

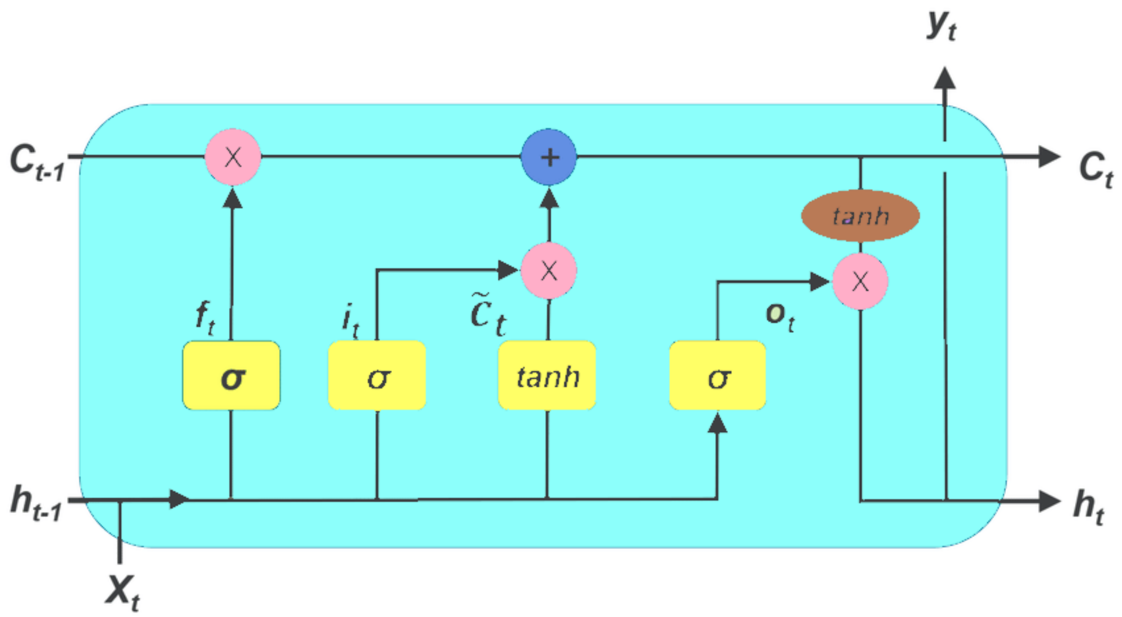

Figure 2.5: Demonstrate the architecture of LSTM for the processing of sequential data.

CHAPTER 3

3. EXPERIMENTAL PART

3.1. Datasets

In this step, we research the available datasets for the finding of Alzheimer's disorder. We selected two datasets for the recognition of Alzheimer's. The first data we found that the ADNI(Alzheimer's Disease Neuroimaging Initiative) dataset which is a highly used database for Alzheimer's. We collect the resting state Functional MRI data from the ADNI database (adni.loni.usc.edu). Because patients will not be doing any tasks and there will be no simulation, the process will be more pleasant than a standard fMRI. Second, rest-fMRI data may be collected during a clinical scan. Scientists are interested in studying and extracting brain networks from rest-fMRI data to better understand the brain. For starters, since patients will not be asked to complete any tasks and there will be no simulation, the process will be more pleasant than a standard fMRI [67].

To categorize fMRI data and, more crucially, to distinguish brain disease data from data on healthy people, physicians have long had an interest in the creation of an assistance tool or algorithm. Alzheimer's disease is a difficult brain ailment to identify, but any machine learning method that can categorize it would be helpful. The acquisition was carried out from a Philips MRI digital scanner made by PMHS(Philips Medical Healthcare Systems). The experimental data's imaging constraints were as follows: 48 slices, a voxel volume of 3.31 mm, a TR/TE of 3000/30 ms, an 80° spin angle, and a 64-by-64 imaging matrix. There were 140 voxels in each series. To identify Alzheimer's disease brains from healthy brains and to generate a trained and predictive model, this study makes use of a CNN and LSTM, one of the DL(Deep Learning) network architectures.

The second dataset we utilized for this experiment is the OASIS-2(Open Access series of Imaging Studies) data which we collected from the OASIS database (https://www.oasis-brains.org/#data). A total of 150 participants, varying in age from 60 to 96 years old, participated in this longitudinal study. For 373 scanning sessions, everyone underwent scanning at 2 or more visits, with each visit being spaced for a minimum of one year. There are 3 or 4 distinct T1-weighted MRI tests acquired for each person during a single scanning session. These scans are included. All the individuals are right-handed, and they are a mixed group of males and females. Throughout the research, 72 of the participants were evaluated as having no signs of dementia. Sixty-four of the subjects who participated in the research were categorized as having dementia during the period of their earliest visits, and this diagnosis was retained for all future scans; among these were 51 individuals with minor to mild Alzheimer's disease. A further 14 members were categorized as having no signs of dementia during the period of their first visit but were later classified as having dementia during a second examination.

3.2. Image Preprocessing

In this research, 157 individuals' medical records were analyzed to determine whether they had Alzheimer's disease. According to the statistics, four distinct groups cover a variety of age ranges. The information on the patients' ages, the number of patients falling into each age group, and their genders are shown in **Table 3.1**. The first group is Alzheimer's Dementia (AD), which consists of 34 participants with a mean age of 74.9 years. It contains 19 female participants and 15 male participants. The second group is referred to as early moderate cognitive impairment (EMCI), and it has a total of 46 participants with an average age of 72.95 years. In EMCI there are 27 female participants and 19 male participants. The third group is known as late mild cognitive impairment (LMCI), and it is comprised of 32 participants of which 18 are female patients while only 14 are male patients and their mean average is 74.7 years. The normal control (NC) group is the last one to be discussed, and it consists of 45 individuals of which 25 patients are female while 20 patients are male, and their average mean age is 76.6 years.

Table 3.1: Shows the detail of the subject involve in the study, their age, and gender as well.

Group	Subjects	Male	Female	Age Mean years
AD	34	15	19	74.9
EMCI	46	19	27	72.95
LMCI	32	14	18	74.7
NC	45	20	25	76.6

There are different operations involved in the preprocessing of ADNI data. For the preprocessing, we used the preprocessing pipeline known as DPARSF(Data Processing Assistant for Resting-State fMRI) [68]. The initial ten voxels of each sequence were eliminated for motion calibration because in beginning the patient tries to adjust himself and those voxels have the problem, so we remove the first ten voxels from the data of each subject. After that, we perform the ST(Slice timing) corrections, HM(head movement), stabilization to an EPI pattern, BET(brain extraction), a GK(Gaussian kernel) with six mm full width at partial maximum (FWHM) spatial smoothing, and filtering within the 0.01 to 0.08 Hz frequency range were all part of the post-processing. Finally, nuisance signals were regressed out, which included 6 head motion correction constraints, a comprehensive average signal, a white substance signal, and a cerebrospinal liquid symbol. The data with a considerable HM were omitted from the study, and the linear tendencies of time information were deleted from resting state fMRI.

The preprocessing steps involved in this study are explained below. The dimensions of the data received once all data processing work was done were (64, 64, 48, and 130), with the fourth dimension being the time information. **Figure 3.1** shows the sample of raw data converted from Dicom to nifty format before the preprocessing. The OASIS data is already in MRI data in 3D shape. We use this data without preprocessing. For the OASIS data, we only perform data normalization and data registration. By data normalization, our models give us improved results. **Table 3.2** shows the detail of the OASIS data involved in this study.

Table 3.2: Details of participants in the OASIS-2 study.

Group	Subjects	Male	Female	Age Mean years
Demented	78	50	28	75
Nondemented	72	42	30	77

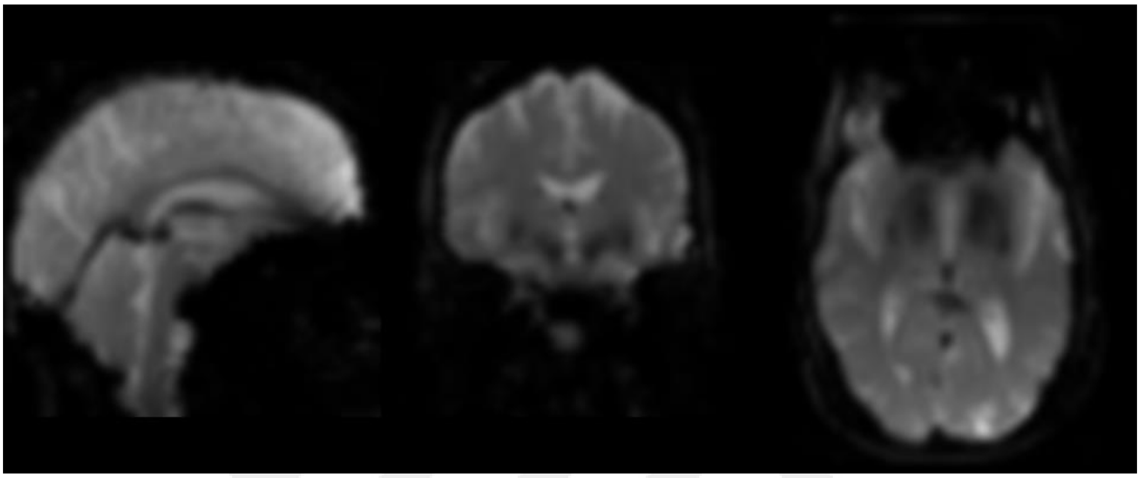

Figure 3.1: Sample raw data obtained from ADNI data repository.

3.2.1. Slice timing

Most functional magnetic resonance imaging (fMRI) data is collected utilizing 2-dimensional pulse sequences which acquire pictures one slice at a time, so all slices are recorded at various times within a repeat time (TR). When dealing with longer TR, timing discrepancies become increasingly troublesome. The time it takes to acquire each successive slice of an MRI picture varies, hence this variation must be compensated for. Once the set of slices, slice order, and reference slice have been set, DPARSF will time the slices by invoking SPM routines. **Figure 3.2** shows the slice timing performed on the raw images. The slices in the images are corrected.

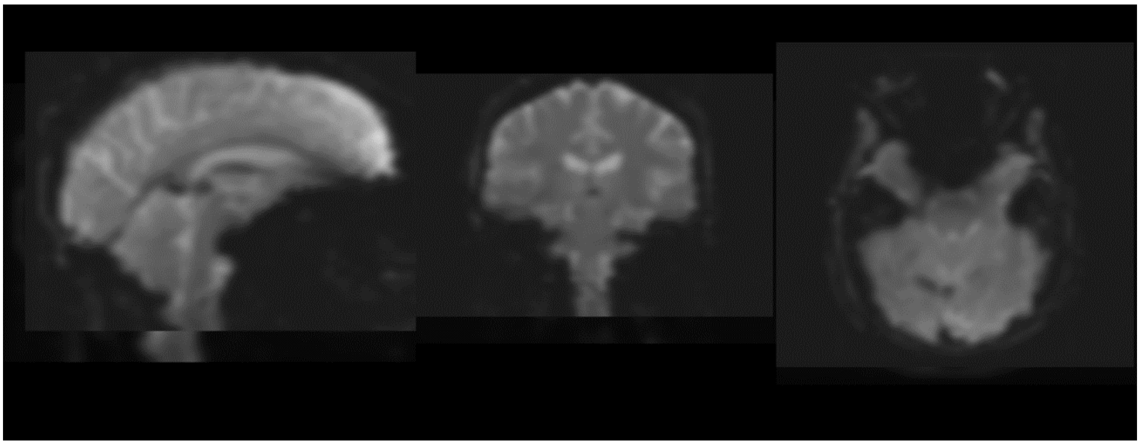

Figure 3.2: Slice timing applied to the raw data to correct the slices.

3.2.2. Head motion correction

The purpose of movement correction is to alter the photos taken over a period so that the position of the brain is consistent throughout all the pictures. Participants who had considerable head motion should not be included for further analysis since this kind of motion can cause a significant number of artifacts to be introduced into an fMRI time series. **Figure 3.3** represent the head motion correction performed on the raw data.

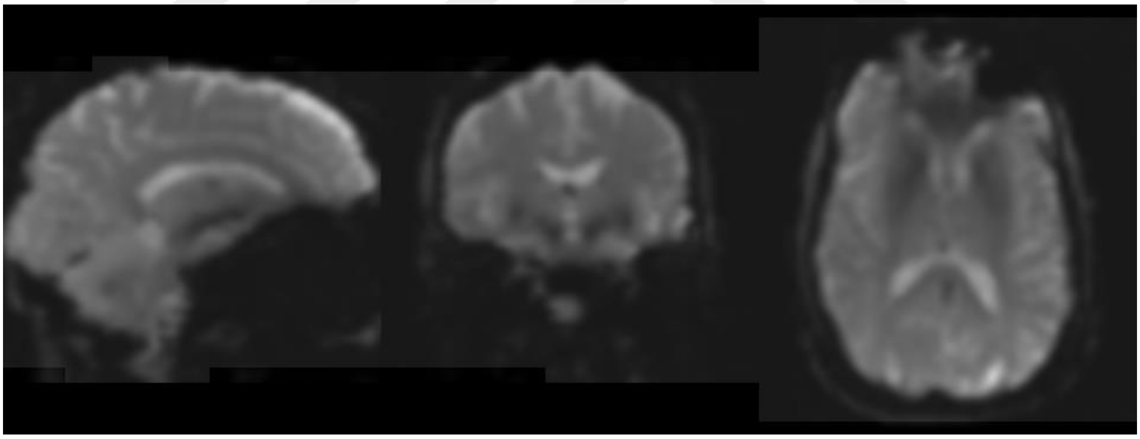

Figure 3.3: Head motion correction and realignment of the raw data.

3.2.3. Skull striping

Because fMRI research focuses on brain tissue, the first thing we do is crop out the skull and any other parts of the image that aren't related to the brain. The DPARSF uses FSL at the backend for the extraction of the brain. FSL is also MRI preprocessing tool and they built DPARSF on top of FSL. To extract the brain, we need to set some threshold values to range from 1 to 5. We try different values for brain extraction and finally we set the threshold to 4 which gives us good image results. **Figure 3.4** shows the skull stripped from the brain image and the skull is not shown in the figure.

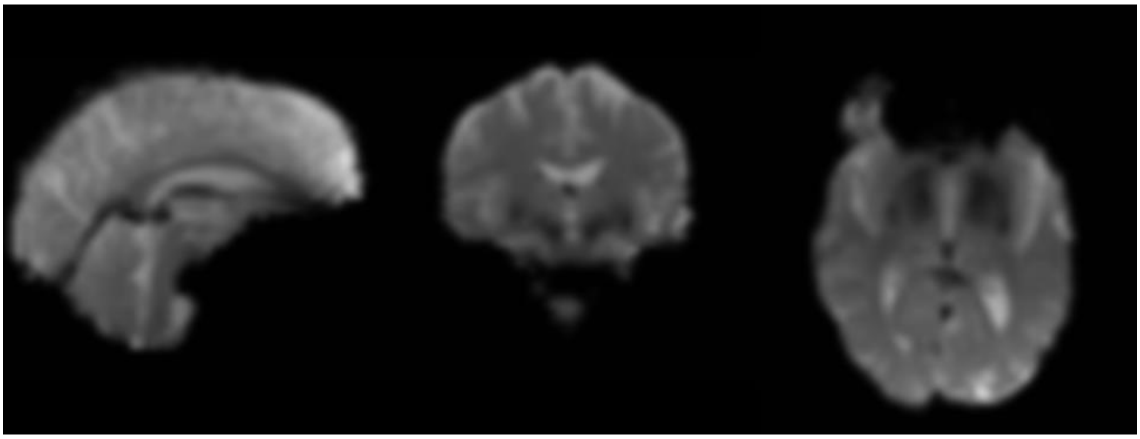

Figure 3.4: Skull striping performed on the raw data to extract the information for classification.

3.2.4. Normalization

The size, shape, and direction of the brain, as well as the gyral structure, might vary greatly amongst participants. The individual brain is often either digitally reconstructed or physically normalized into a uniform template to make it possible to conduct inter-subject comparisons. SPM gives the user the option of using either the echo-planar imaging (EPI) framework (Ashburner and Friston, 1999) or the unified segmentation of T1 image to normalize the functional pictures into (MNI) Montreal Neurological Institute space. Both methods are described below (Ashburner and Friston, 2005). **Figure 3.5** shows the normalized images from the raw data for further processing.

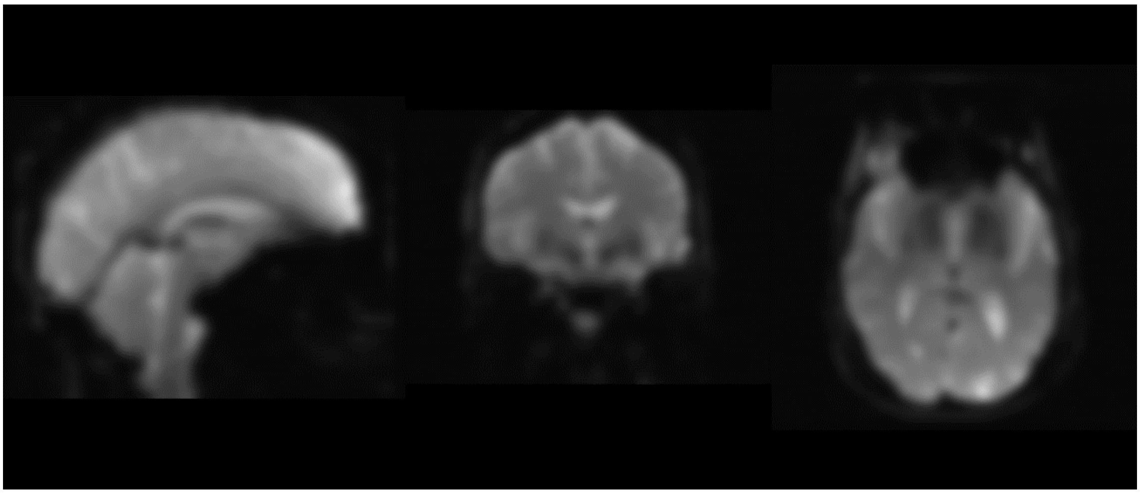

Figure 3.5: Normalization performed on the raw data.

3.2.5. Smoothing

During the inter-subject averaging procedure, smoothing is a preprocessing step that is utilized to decrease noise as well as effects caused by remaining variations in functional as well as structural. The Gaussian filter, which takes the form of a normal distribution, is the smoothing method that is utilized the most frequently. **Figure 3.6** shows the smoothing performed on the data for further preprocessing.

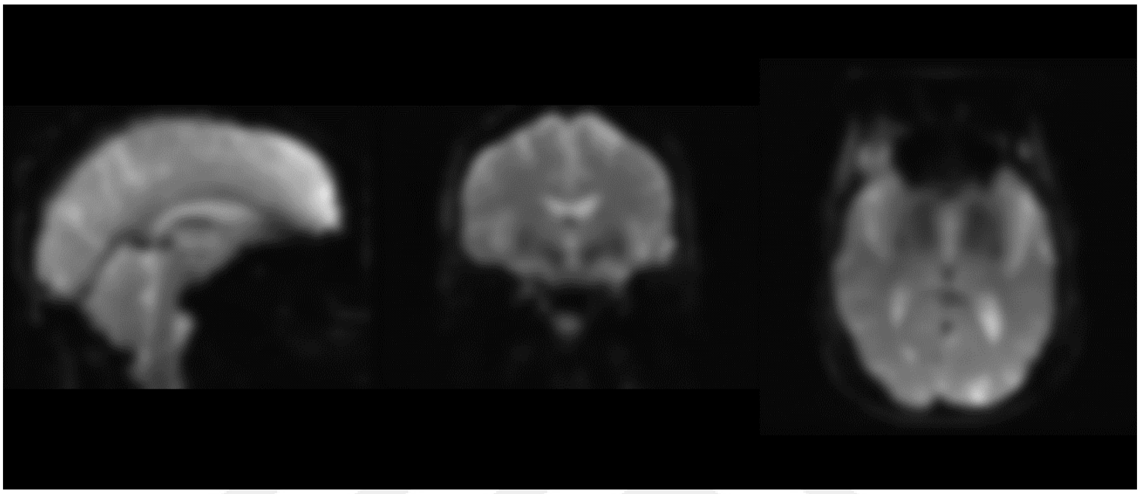

Figure 3.6: Smoothing performed on the data for the classification of Alzheimer's.

3.2.6. Filtering

To lessen the impact with very lower frequencies and high-frequency neurobiological noise, the data are often bandpass filtered (for example, between 0.01 and 0.08 Hz). It is important to highlight that the dataset should not be filtered while calculating fALFF, as fALFF is a proportion of the amplitude at low frequency to the amplitude across the complete band. **Figure 3.7** shows the applied filter on the raw data for a clear understanding of the features of the data.

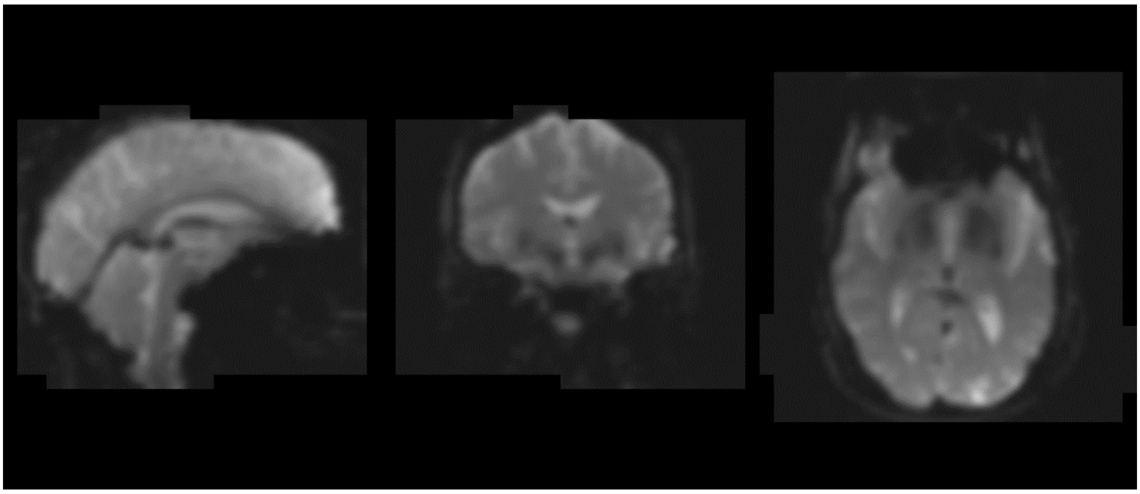

Figure 3.7: Represent the filtering operation performed on the raw data to make data clear for the classifier to classify data for Alzheimer's classification.

After the preprocessing of data, converted the images from nifty to NumPy format and after that applied data normalization on all the images. Image normalization is the image preprocessing technique that is used to normalize the pixel intensity value. It normalizes the pixel intensity in the image by calculating min and max pixel values and taking their average. Image normalization helps in the smoothing of the images and hence images give a clear representation of objects in it. Image normalization also helps in the smooth training of deep learning models. Because of normalization, the loss of model didn't increase or decrease abruptly meanwhile it changes gradually. In our case image normalization helps us to train an effective algorithm. Before applying the image normalization our training accuracy was 80% but after applying the normalization and regularization our accuracy goes to 91%. **Figure 3.9** represent some sample images of data after applying the normalization. We also apply image normalization to the OASIS dataset and **Figure 3.8** shows the sample picture taken from the normalized OASIS dataset.

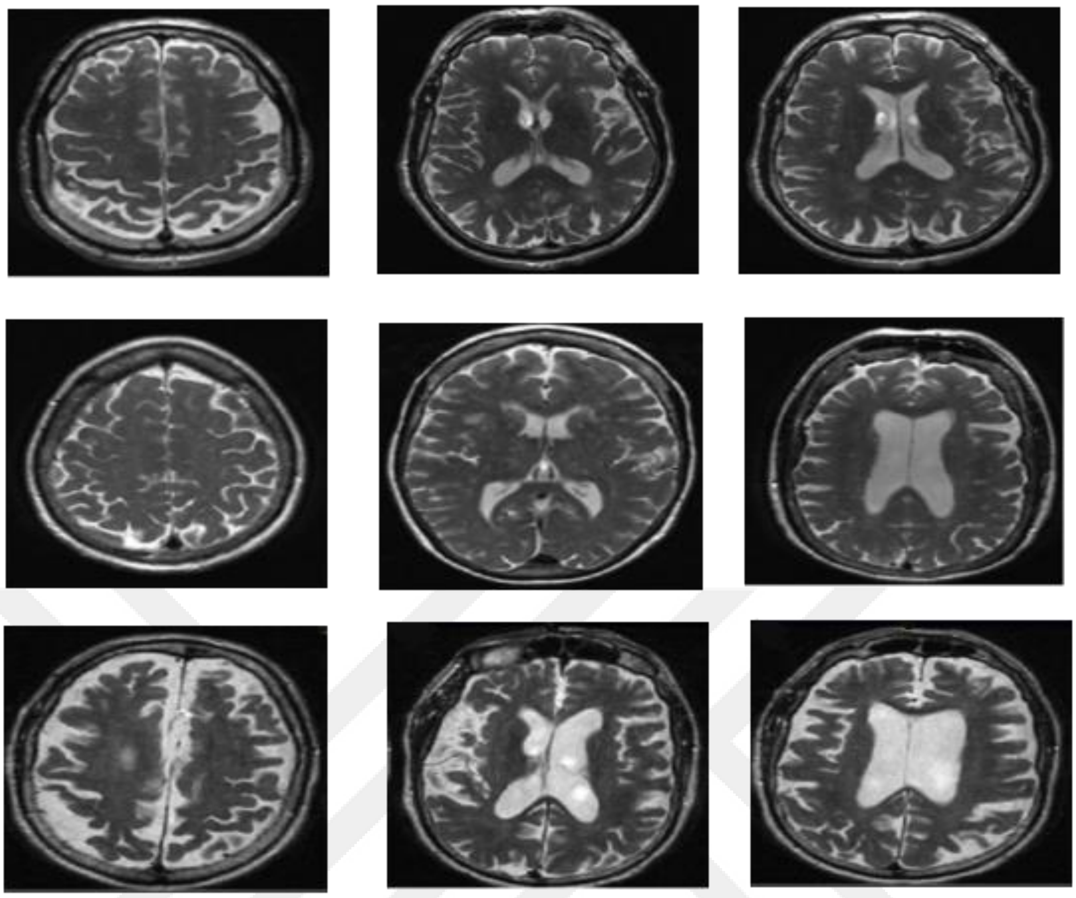

Figure 3.8: Shows the sample images obtained from OASIS dataset after the preprocessing.

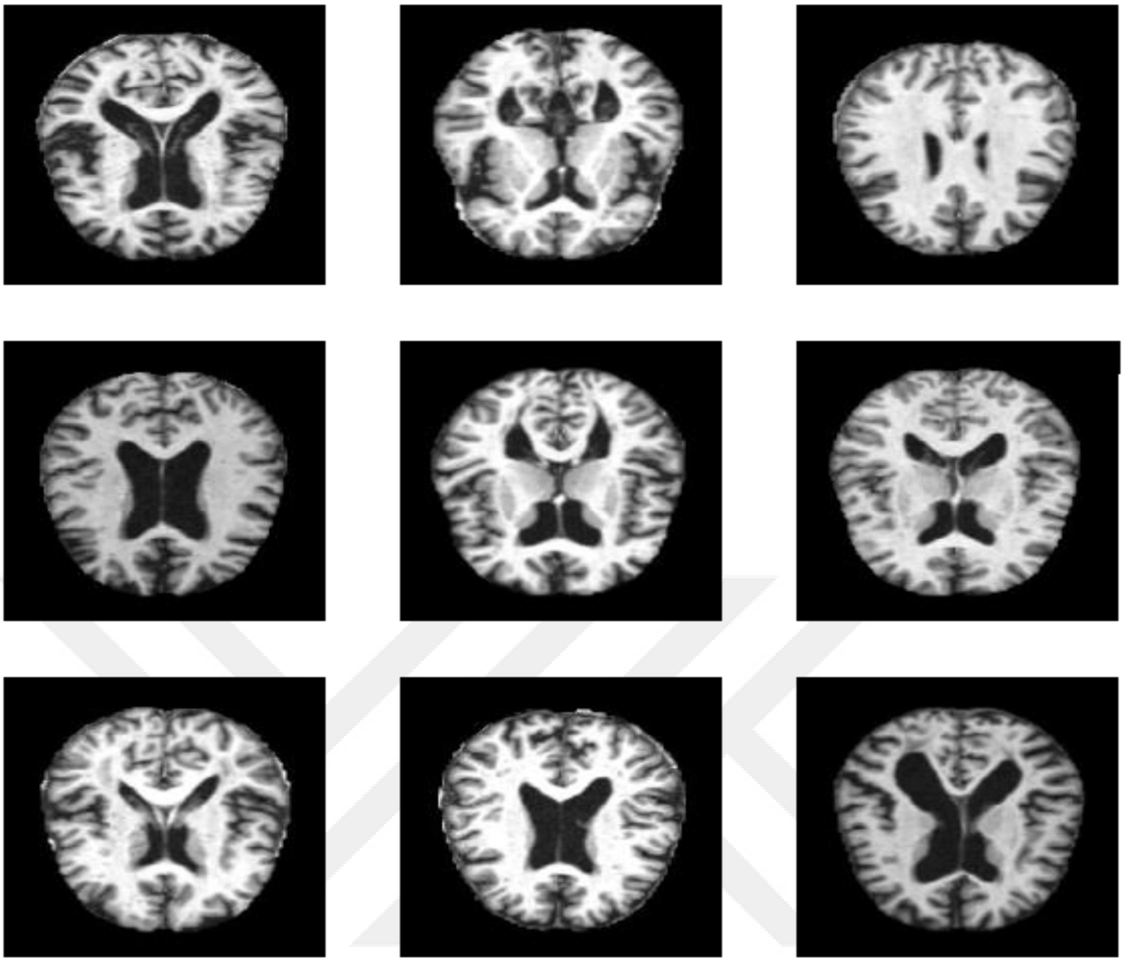

Figure 3.9: Shows the images after applying the normalization feature obtained from ADNI data. It gives a very clear representation.

3.3. Implementations

Most recent research in computer-based diagnosis of AD has shown that, under identical settings, deep learning algorithms consistently outperform more conventional, hand-crafted feature design approaches [69]. We performed many controlled experiments to compare the outcomes of trials using various data utilization strategies. We first performed standardized 2D fMRI scans using the most well-known 2D CNN models, which are Resnet [70], VGG19 [71], and Dense Net [72]. We also trained the 3D CNN model for comparison. Finally, we trained our proposed model which is composed of 3D CNN and LSTM we called this Conv3d-lstm. It is a similar structure to 3D CNN and at end of CNN layers, we add LSTM layers just before the fully connected layer.

The Keras [73] framework was utilized to develop all of the deep learning models in this investigation, and TensorFlow [74] was used as the backend for all of them. Cross-validation was used to train the models, and the data was split 70%-10%-20% across a training, validation, and test set. By keeping an eye on the validation set's precision throughout training, we used early stopping [75] and weight decay, and we ultimately retained just the models that performed best there. We change the learning rate during the training process.

Figure 3.10 shows how the learning rate change with the number of iterations. Initially, we set the learning rate at 0.1 which is changed during training. Adam optimizer was used to fine-tune the model's parameters using categorical cross-entropy loss [76] to calculate and reduce loss while training to map the difference between the model's prediction and the ground-truth value. A learning rate of 0.0001 was found to be optimal for training the Conv3d-lstm model. Weight decay is also performed to reduce the overfitting from the model and here are some parameters for weight decay $\beta 1 = 0.5$, $\beta 2 = 0.9$, and $\varepsilon = 1e^{08}$.

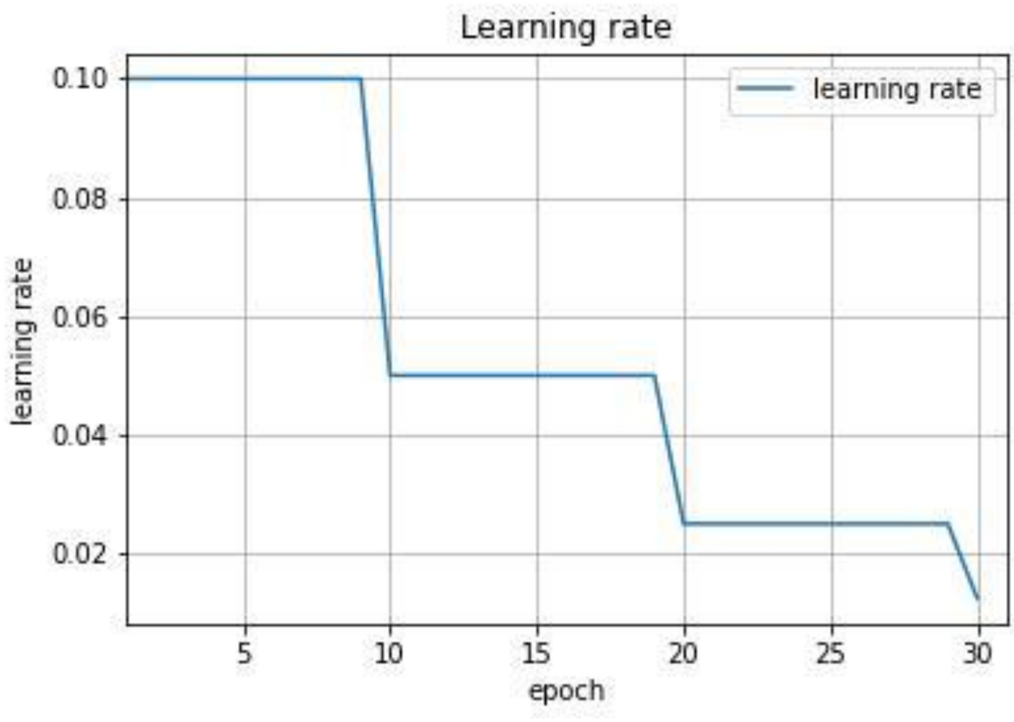

Figure 3.10: Shows the gradually decreasing learning rate while training.

3.3.1. 2D CNN models

For this approach, we use the most used pre-trained algorithms which are Resnet, VGG19, and Dense Net. We utilize a technique called transfer learning for training and validating the algorithm for chosen datasets. We pick the already existing models and utilize their trained weights for the training. These algorithms perform quite well as compared to the existing studies but not as much was expected. We experiment different hyper-parameters during training which are learning rate, batch size, and weight decay. We choose the best hyperparameters which give us the highest performance. When making predictions for a single slice, 2D CNNs rely on convolutional kernels with the same number of dimensions. Forecasts for a whole volume are made by accumulating results from many smaller predictions. When making predictions, the two-dimensional convolutional kernels can draw on information from the entire slice's height and width. However, 2D CNNs are limited in their ability to extract information from adjacent slices because they only accept one image slice as input. The prediction could benefit from voxel information from neighboring slices. **Figure 3.11** demonstrate the functionality of 2D CNN.

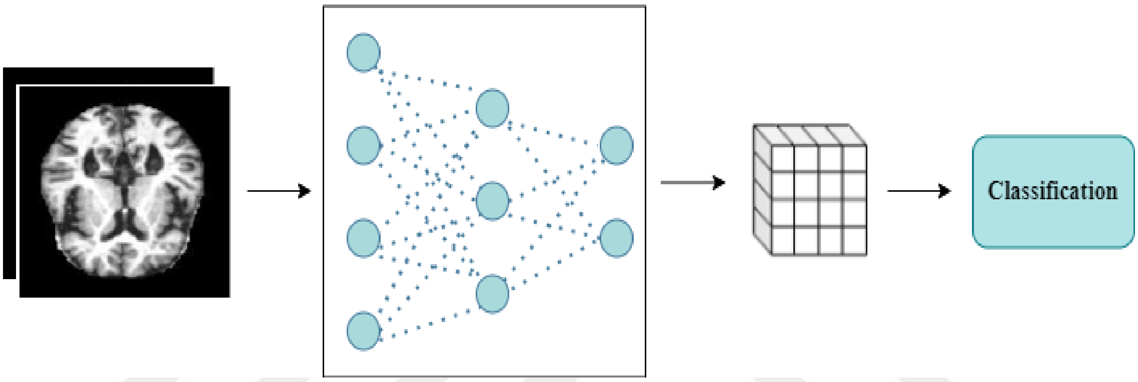

Figure 3.11: Demonstrates the functionality of two-dimensional CNN.

3.3.2. 3D CNN

The problem of utilizing one slice at a time solve with the help of using 3-dimensional CNNs. Because of the increased amount of parameters that are employed by these CNNs, the ability to utilize interslice context can result in higher performance; however, this comes at a computational cost. For the development of the 3D CNN model, we use 16 3D convolutional Neural layers each with max pooling and batch normalization. Max pooling helps CNN to reduce the dimensionality of data by applying different filters during training. While Batch normalization helps the model to normalize the data batches and reduce the chances of overfitting. We also use the regularization parameters which are used during training for the regularization of training parameters. For regularization, we used the L1 and L2 regulations to reduce the overfitting of the model. We use the weight decay technique to change the learning rate of our model during training so that model can obtain the optimal learning rate. Initially, the learning rate was 0.1 which was later reduced after every 10 epochs during training.

The number of trainable parameters of our model was 2 million. We set the batch size of 4 because it was obtained as the optimal size. The Adam optimizer was used for the optimization of the loss function. The categorical cross-entropy loss was used. The activation function Relu is utilized for the activation of the neurons in the CNN(convolutional layers). At the output layer SoftMax activation function was used to predict the probability of having each class for the classification of Alzheimer's. The model is trained on the OASIS data. After training the model on the test data the best model is adopted for the further training of the model on ADNI data. After training the model by updating different hyperparameters and choosing of best hyperparameters testing of the model on the test data is done. The model achieves promising results which are explained in the results section. **Figure 3.12** explains the overall methodology of the 3D CNN model.

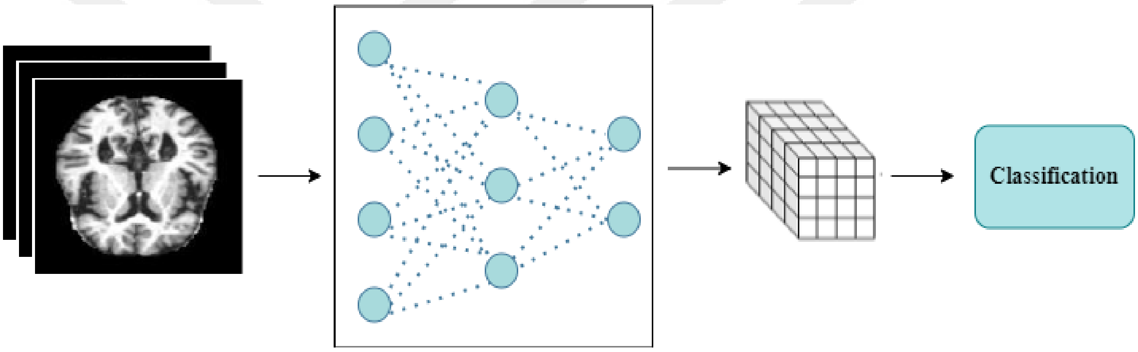

Figure 3.12: 3D structure of CNN algorithm for the processing of neuroimaging.

3.3.3. Conv3d-lstm

The Conv3d-lstm model is made up of a 3-dimensional CNN(convolutional neural network) [77] and LSTM(long short-term memory) network [62]. The 3-dimensional CNN is a broad view of conventional CNNs for processing three-dimensional images. The highly prominent difference makes the model more suited for extracting features from 3-dimensional pictures by changing convolution kernels from 2-dimensional to 3-dimensional. Appropriately, 3D CNN may be able to deal with the spatial and structure information from the fMRI data. To address the gradient-waning issue of time series [78] data, the LSTM was developed as an enhanced recurrent neural network (RNN). Its intrinsic complex gate structure allows it to construct time series information and association information in time-series data, making it useful in a variety of fields including NLP(natural language processing) and audio signal processing. LSTMs are nowadays very popular for sequence processing. It can help in enhancing the features extracted by CNN and result in high performance. **Figure 3.13** Demonstrate the architecture of the NN(neural network) layers of our proposed algorithm.

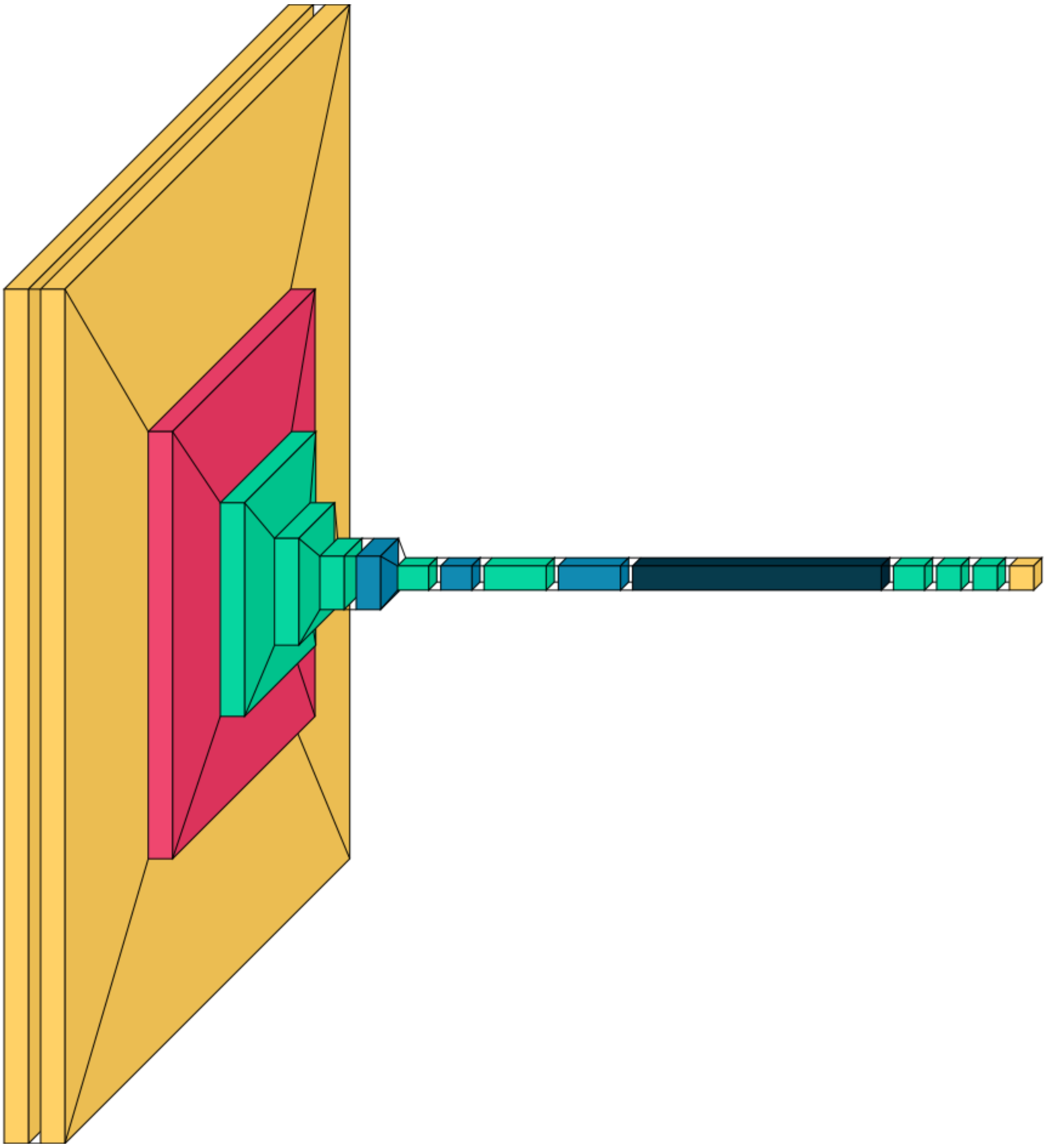

Figure 3.13: Demonstrate the architecture of the NN(neural network) layers of our proposed model.

Since 4D fMRI data is not the same as regular 2D time series data, LSTM networks cannot be utilized directly to process it. To develop the Conv3d-lstm deep learning model, a 3D CNN and an LSTM network were fused. The Conv3d-lstm model may be directly applied to the raw fMRI data without any preprocessing into functional brain images. In addition, this might reduce the amount of information that is lost when utilizing an fMRI scanner. Consequently, the Conv3d-lstm was an easier-to-implement, more general-purpose method. The expert's expertise was not required on any prior information. While using a proposed algorithm doesn't need to change the dimensionality of the images from 4-dimensional to 3-dimensional or 2-dimensional. In this way, the time information and functional connectivity in the brain will be preserved and hence it helps to train an effective classification model. **Figure 3.14** demonstrates the generalized structure of our proposed algorithm.

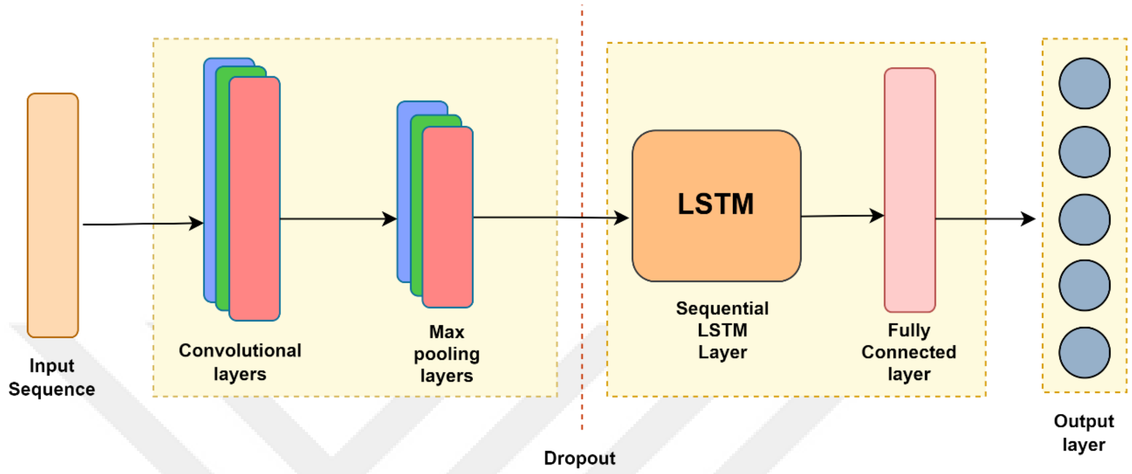

Figure 3.14: Demonstrate the generalized structure of our suggested algorithm.

Various hyperparameters were utilized throughout the training process of the 3D CNN using the OASIS dataset. We were able to obtain the 3D CNN algorithm with the highest performance and then train it using the ADNI data set. The CNN architecture of the model is obtained from the three-dimensional CNN model. It comprises 16 CNN(convolutional layers) in three-dimensional, with MP(max pooling) and batch normalization occurring after each convolution block. Every block is composed of three layers of convolutional data. The weight decay approach is utilized to adjust the weight being trained to get the optimum rate of learning. The loss of weight helps to prevent overfitting. The Adam optimizer was utilized to accomplish the optimization. When it came time to activation of neurons in the convolutional layer, the Relu activation function was utilized. On the other hand, the activation function SoftMax was employed in the output layers, where it was employed for classification. In addition, regularization techniques L1 and L2 are utilized to minimize the probability of overfitting the algorithm. During the process of training the Conv3d-lstm model, we tried out several different batch sizes using a range of different iterations, but we made sure to take into consideration the memory limits because the amount of data is too large. Following the selection of multiple dropout values for the deactivation of neurons within the convolution layers and the LSTM, the final value selected is the one that yields the most beneficial outcomes for our purpose.

Early stopping is implemented into the 3D CNN model after it has been trained on the OASIS data for a total of 200 epochs. After training the model on the OASIS dataset, the model was obtained for additional training on the ADNI dataset by adding the LSTM layers to it, which gives it the name Conv3d-lstm. This was done so that the model could be used for further training on the ADNI dataset. The transfer learning method is utilized to complete the training on the ADNI data, and the proposed algorithm is performed admirably on both sets of information. Now, the more generalized algorithm is the one that can forecast Alzheimer's disease for a variety of datasets. The produced model, which incorporates transfer learning as well as the addition of LSTM layers, results in a more generic method. This model is trained for the same hyperparameters for a total of 200 iterations and produces excellent output. Because LSTM is good at processing sequential information, and because fMRI data contains the order of voxels and LSTM helps classify them more efficiently, using transfer learning and LSTM network together is meant to achieve the goal that LSTM is good at processing sequential information. **Figure 3.15** shows the overall methodology of our proposed system.

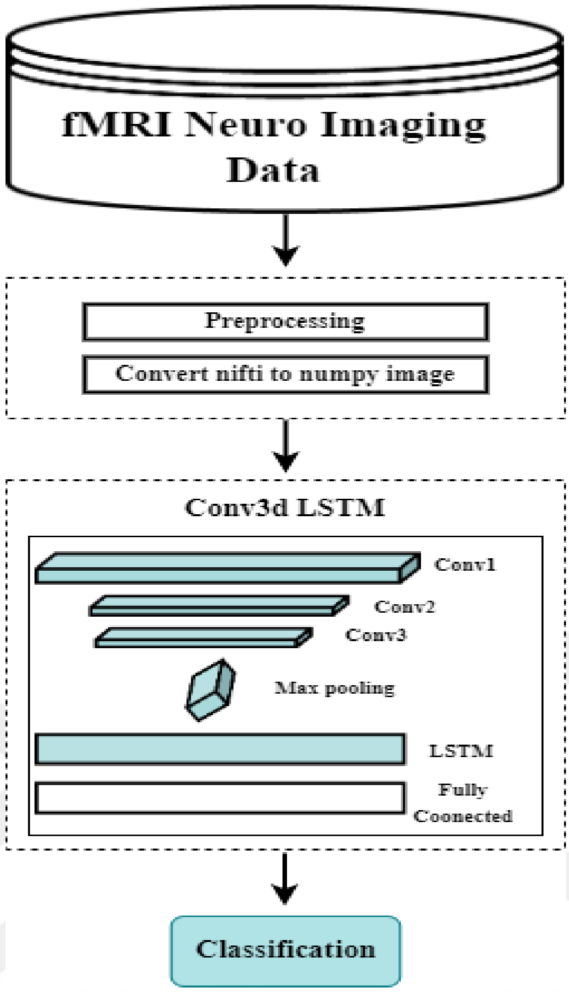

Figure 3.15: Methodology of our proposed works.

CHAPTER 4

4. RESULTS AND DISCUSSION

4.1. Results

Convolutional neural networks, which model their architecture on the human visual system, are conceptually like more conventional human neural networks. Compared to typical feed-forward back propagation training, the CNN topology is preferable because it makes use of spatial connections to reduce the number of parameters. Small portions of the image—referred to as local receptive fields—are employed as inputs by CNNs at the base of the hierarchical form of images. The complicated architecture of CNN allows a degree of invariance to shift, scale, and rotation since the local receptive field gives the neurons in the neural network or processing unit access to basic information like aligned edges or corners. This is one of the most significant qualities of CNN. There are different algorithms implemented for this work to compare their performance. Below, we detail each way implemented to solve the challenge of Alzheimer's detection.

The VGG19, Resnet, and Dense Net models utilize a transfer learning strategy that initializes their models with model weights that have been trained on images from the dataset. This strategy is used for 2D fMRI experiments. After being preprocessed, the data that are utilized are two-dimensional data without the time slices from fMRI data. This is necessary since the neural network in question is only two dimensions. These slices are extracted from the 4D brain picture at the origin plane from the axial plane or transverse plane, and they correspond to each time point in the time portion. Network architecture includes various network components including the Pooling Layer, Normalization Layer, and Fully Connected Layer are also included. To calculate the output of neurons related to local areas in the input, the Convolutional Layer (or so-called CONV) is used. Each one calculates the dot product of its weight and the input volume area to which it belongs. Downsampling in the spatial dimensions is accomplished via the

Pooling Layer, abbreviated POOL. To normalize the data, the RELU layer uses a threshold activation function on each layer in the network. The picture volume is not altered by this layer. We utilized the activation function SoftMax function in the fully connected layer. The FC layer calculates class scores, which in turn increases the class count.

Following the completion of the preprocessing steps, the 3D data needed for the experiment on the 3D convolutional neural network was recovered from the 4D FMRI data that was originally collected from OASIS. The data is sliced in such a manner that it is possible to segment 4D data from time series data, and then extract 3D corresponds to each time slice and preserve them in a 3D matrix. An essential part of this network is a Convolutional Layer made up of neurons with trainable weights and biases. The 3D model is trained On OASIS data with different hyperparameters. After the training of the 3D model, the best model is obtained, and apply transfer learning on this model. The LSTM layer is added to this model to keep track of time information in the fMRI data. The model is retrained on the ADNI data which was collected from the ADNI database to make the model more generalized with other datasets as well. The performance of the 3D convolutional network model is presented below. **Figure 4.1** explains the training accuracy and validation accuracy of the three-dimensional algorithm trained on the OASIS data and further this model trained on the ADNI data using transfer learning. The accuracy of the model was 88.05% on OASIS data.

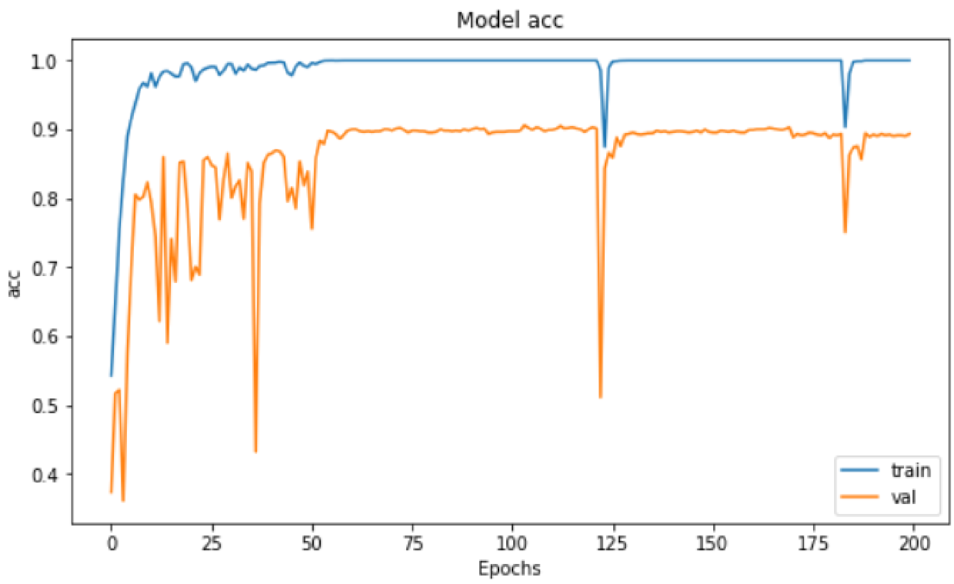

Figure 4.1: Accuracy graph of 3D CNN model.

The AUC(area under the curve) and loss of the 3D CNN method are also computed to demonstrate the algorithm's performance. **Figure 4.2** depicts the training AUC and the validation AUC. **Figure 4.3** depicts the calculated training and validation loss while training.

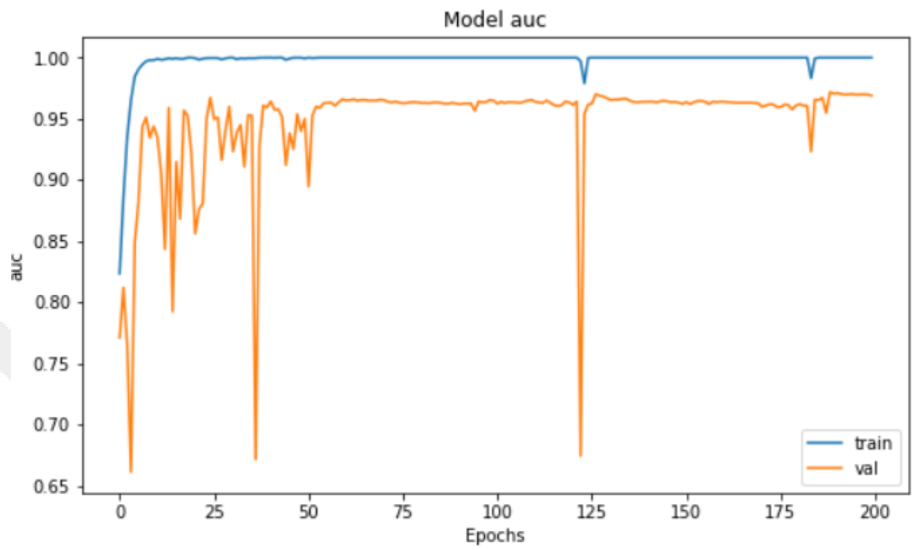

Figure 4.2: Training and validation area under the curve(AUC) of 3D CNN algorithm.

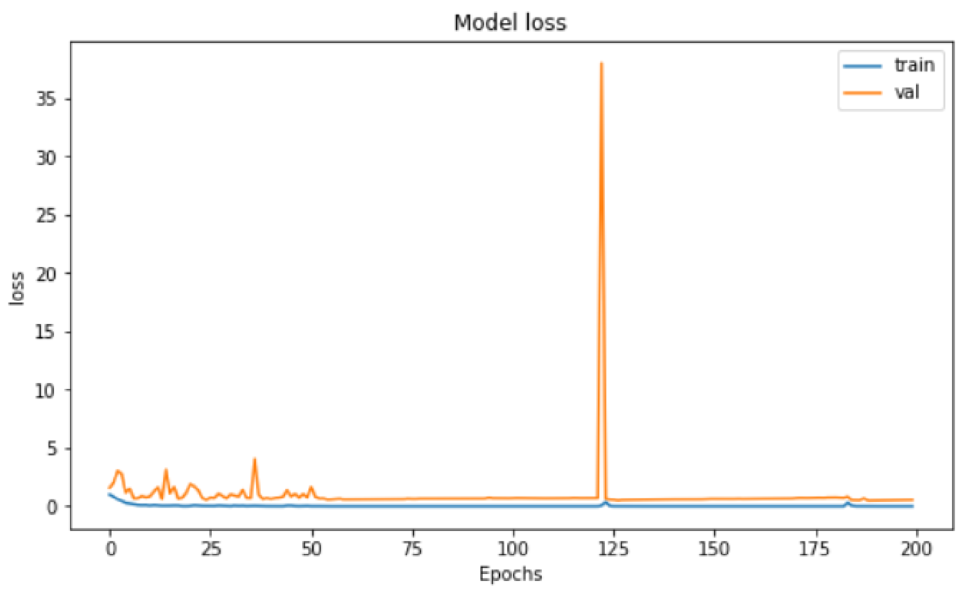

Figure 4.3: Training and validation loss of 3D CNN algorithm.

The preprocessed functional MRI four-dimensional data is input directly to our proposed Conv3d-lstm network model. For every experiment, the total number of participants from the group with the fewest data was used as a benchmark, and data from the other classes were drawn at random to make up for the difference. This was done to eliminate the potentially negative impacts of misclassification on the experiment outcomes.

All the classification findings from the control trials were double-checked using cross-validation, with the final value being the average of the results from all experiments. Accuracy (ACC), defined as the proportion of correctly labeled samples, was used as the measure of performance.

To check the implementation of the proposed algorithm for AD, NC, EMCI, and LMCI, a binary class and multiclass classification study were performed. The C3d-LSTM [70] model, which got the greatest results out of all the prior studies in the literature that used 4D fMRI data, is compared to the results of the proposed algorithm in **Table 4.1**. Implemented 2D and 3D convolutional neural network models are less accurate than the present model. Our proposed 3D Convolutional Neural Network with LSTM model has the highest accuracy as compared to 2D and 3D models and with the implemented algorithm in the literature. The accuracy of our model's multiclass classification and binary class classification is higher than the claimed accuracy of existing models, as shown in **Table 4.1**.

While the C3d-LSTM [70] achieves an accuracy of 89.47% in multiclass classification, our model achieves an accuracy of 91.06%. Our 3D convolutional model's multiclass classification accuracy is 85.76%. Because we concentrated primarily on the structural information of the image while slicing the data from 4D fMRI to 2D, temporal information was not considered, making it challenging to classify the data into numerous categories. As a result, our 2D approaches did not produce the intended results. When compared to 2D and 3D models, accuracy is higher when using 3D images since we slice each time as a single image. We fed the time information when training the 4D data on the proposed model, and the LSTM layers are used in the model to keep track of changes in the time information. We also use techniques for "image normalization" on the 4D data, and the results are improved than what has been reported in the literature.

Figure 4.4 shows the training accuracy and validation classification accuracy of our proposed model. In the figure, it is shown that there is a gradual change in the training accuracy and validation accuracy because in the data there is too much variation. Data vary from one patient to another patient and there might be a change in the settings of the fMRI scanner machine as well. Most of the time graph is smooth but, in some subjects, there is variation in the data, so the accuracy changes are not smooth all the time. **Figure 4.5** demonstrates the training loss and validation loss of the trained algorithm.

Table 4.1: Demonstrate the comparison of accuracies between our trained model and the literature that reported the highest results.

Models	AD/EMCI	AD/LMCI	AD/NC	EMCI/LMCI	EMCI/NC	LMCI/NC	Multiclass Classification
VGG	75.12	74.68	78.67	77.86	79.63	80.34	76.85
ResNet 18	82.34	77.94	86.78	88.40	78.32	82.57	79.37
Brain Network Model	74.63	70.24	78.35	71.46	76.83	80.43	75.72
DenseNet	82.75	76.59	77.95	77.98	69.72	84.32	80.34
C3d-LSTM [70]	92.11	88.12	97.37	88.12	88.12	88.12	89.47
Conv3D	88.65	86.76	68.62	77.82	91.12	89.37	85.76
Conv3d-lstm	**92.45**	**89.68**	**96.85**	**91.75**	**89.23**	**90.56**	**91.06**

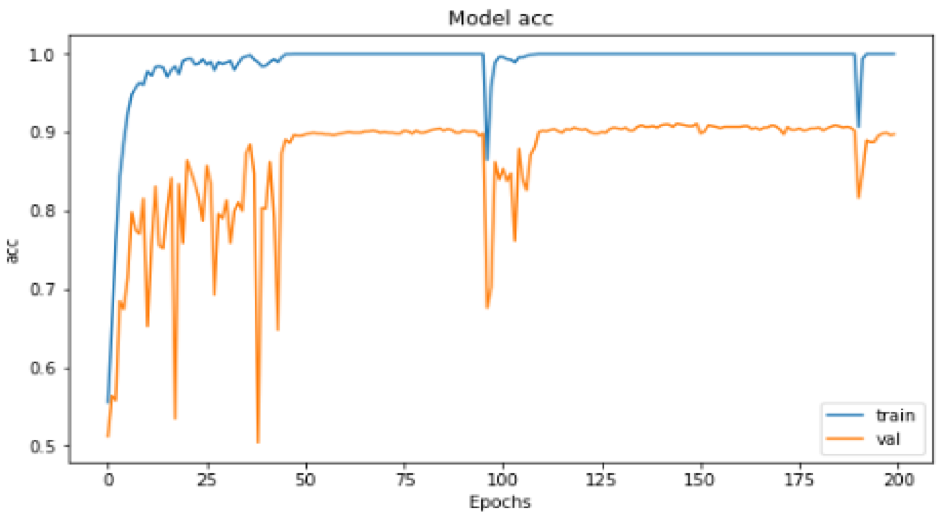

Figure 4.4: Present the training accuracy and validation accuracy of our proposed model.

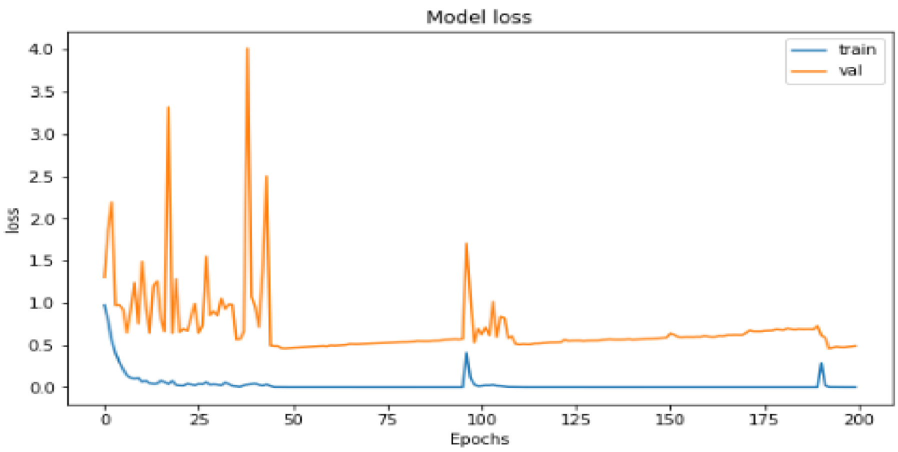

Figure 4.5: Demonstrates the training and validation loss of our proposed model.

The classification outcomes of several deep learning models are compared in **Tables 4.2** and **Figure. 4.6**, using the AUC(area under the curve) [79], [80], and ROC(receiver operating characteristic) curve metrics, correspondingly. **Table 4.2** shows the comparison of our trained algorithm with the existing one in the literature using ROC matrices. **Figure 4.3** represent the training and validation AUC of our proposed model.

Table 4.2: Demonstrate the AUC assessment between our trained model and the already existing algorithm in the literature.

Models	AD/EMCI	AD/LMCI	AD/NC	EMCI/LMCI	EMCI/NC	LMCI/NC	Multiclass Classification
VGG	0.84	0.84	0.95	0.87	0.86	0.88	0.87
ResNet 18	0.85	0.85	0.95	0.86	0.78	0.78	0.83
DenseNet	0.84	0.87	0.96	0.85	0.80	0.81	0.85
C3d-LSTM [70]	0.92	0.92	1.00	0.90	0.86	0.86	0.92
Conv3D	0.88	0.86	0.94	0.84	0.91	0.90	0.91
Conv3d-lstm	**0.97**	**0.97**	**0.99**	**0.94**	**0.95**	**0.94**	**0.96**

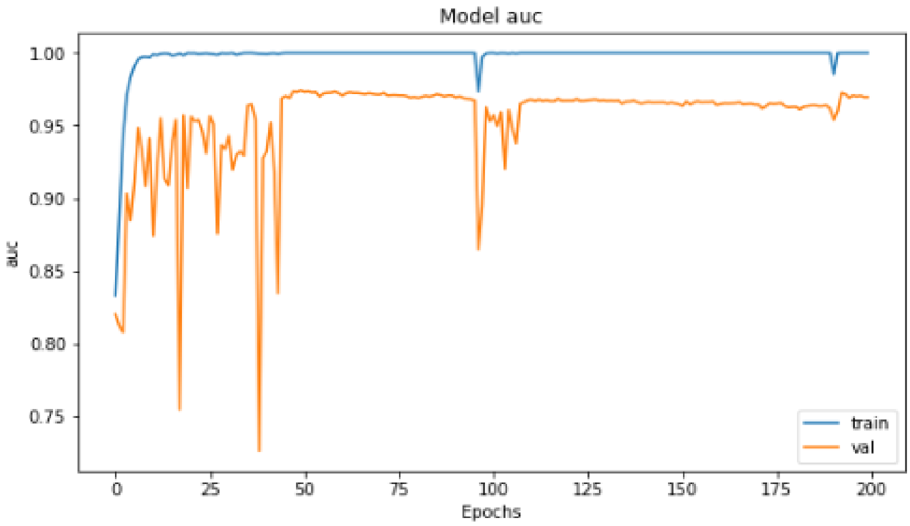

Figure 4.6: Shows the training and validation area under the curve of our proposed algorithm.

Testing the model on the test data that allows us to provide clear and persuasive proof of the efficacy of our proposed technique. On the test data, we found that our algorithm did well. Although several studies have reported high validation accuracy rates, none have shown high test accuracy rates for their algorithms. Test accuracy of 88.13 percent is achieved by our model. Since present methods do not take test accuracy into account, so we cannot make a fair comparison. Our algorithm's confusion matrix, calculated from the test data split during preprocessing, is shown in **Figure 4.7.** The confusion matrix shows that in the case of the NC(normal control patients) 160 images out of 201 are detected as true positive and 41 of them are predicted as a false negative. 33 images are predicted as EMCI(early mild cognitive impairment) because this is the early stage of Alzheimer's and NC is normal control in both cases data is much similar, so the model is confused while predicting. In the case of LMCI(late mild cognitive Impairment) there are only 6 images and out of 6 five are predicted as true positive and only one image is predicted as a false negative. In the case of AD(Alzheimer's dementia), there are 643 images, and 601 are predicted as a true positive, and only 34 are predicted as false negative. In the case of EMCI, there is a total of 430 images and 362 of them are predicted as true positive, and 58 are predicted as a false negative. In the case of AD and EMCI, the ratio of false negative prediction is high because patients of these two classes have Alzheimer's disease. The fMRI data is very complex and sometimes it is hard to differentiate between its classes.

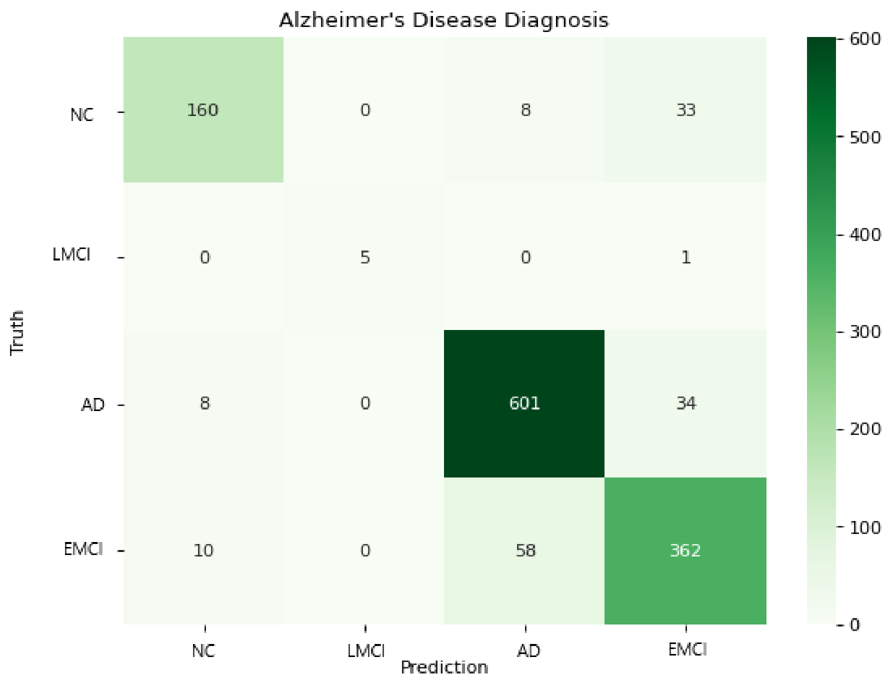

Figure 4.7: Represent the confusion matrix that we calculated on the test data.

Other performance matrices are also calculated to show the performance of the proposed algorithm. The calculated matrices are precision, recall, and f1-score, and it shows very promising results. **Table 4.3** shows the precision matrices which are calculated for each class. Hence it shows very convincing results. These metrics help to better understand the efficiency algorithm. These precision matrices are defined below.

4.1.1. Precision

When we talk about precision, what we mean is the ratio of correctly anticipated positive observations to the total of expected positive observations. Accuracy is inversely correlated with the false positive rate. The formula for computing the precision from the confusion matrix that is carried out on the test is provided in Equation 4.1.

$$\boldsymbol{Precision} = \frac{\boldsymbol{TP}}{\boldsymbol{TP+FP}} \qquad \textbf{(4.1)}$$

4.1.2. Recall (Sensitivity)

The percentage of correctly predicted positive observations to the overall number of observations in the correct class is referred to as "recall." Recall should ideally be 1 for a classifier to be judged successful (high). Recall only becomes 1 when the denominator and the numerator are equal, or even when TP = TP + FN, which also shows that FN is 0. The value of the denominator will inevitably rise above the value of the numerator as FN increases, which will lead to a reduced recall value—the exact opposite of what we want. The formula for calculating the recall from the prediction results is shown in Equation 2.

$$\boldsymbol{Recall} = \frac{\boldsymbol{TP}}{\boldsymbol{TP+FN}} \tag{4.2}$$

4.1.3. F1 Score

The F1 Score is calculated by averaging precision and recall. As a result, this score takes into account the potential for both false positives and false negatives. Although it is more difficult to understand, F1 is usually more beneficial than accuracy, especially when there is an unbalanced class distribution. Accuracy is greatest when the cost of a false negative and a false positive is almost equal. If the expenses associated with false positives and false negatives differ significantly, it is advised to incorporate both Recall and Precision.

$$\boldsymbol{F1\ Score} = \frac{\boldsymbol{2*(Recall*Precision)}}{\boldsymbol{(Recall+Precision)}} \tag{4.3}$$

Table 4.3: Demonstrates the efficiency matrices of our proposed algorithm.

Classes	Precision	Recall	F1 Score	Support
NC	0.90	0.80	0.84	201
LMCI	1.00	0.83	0.91	6
AD	0.90	0.93	0.92	643
EMCI	0.84	0.84	0.84	430

4.2. Discussions

The network architecture is what sets this method apart from others. In recent years, 3D convolutional neural networks (CNNs) equipped with spatial feature extraction have been put to use in video processing and categorization. However, when properties extracted from images are applied to functional brain data, the relevance attributes change slightly. While 3D convolutions have recently been applied to the classification of neurological illnesses, this method differs in a few key aspects. CNN's architecture is the most critical component. The temporal feature map, spatial and spectral collector, and classifier are its three primary components. Without any input from spatial structure, the first 2 convolutional layers' retrieve dimension is measured only in temporal shifts. To do this, a kernel of size 3 x 3 x 3 x N is used, where N is the total number of channels. The most common applications for kernels with filter size 3 x 3 x 3 x N are depth reduction and the blending of the outputs of many kernels.

On the contrary, here we employ the 3 x 3 x 3 x N filters to pull temporal information out of the raw data. For temporal feature extraction, 3 x 3 x 3 x N kernels are unusual in 3D CNN. First-layer output is based entirely on how a voxel has changed over time. This means that the convolutions will have a comparable effect on voxels with similar time series. Extracted ROIs are simply low-level temporal characteristics, and the output at various channels can be thought of as such. High spatial features, which can be thought of as a complex combination of ROIs, are generated by combining these minimal temporal features in the 2nd temporal convolutional layer. Again, there is no impact from spatial structure because the kernel size is 3 x 3 x 3 x N. By using a custom kernel in the initial two layers, we guarantee that the network will never be able to learn any in-subject anatomical correlations. Because of these voxel-wise temporal variations, the temporal response of individual samples of the same fMRI series data may vary. In addition, the inputs to the network include Important characteristics that change the volume without any anatomical intensity information as a result of preprocessing techniques such as regional signals and temporal drift removal.

The 3-dimensional convolutional neural networks with LSTM are used in this study for the categorization of Alzheimer’s disorder. The proposed algorithm achieves promising results. The performance of the proposed algorithm is shown in section 4.1, where the accuracy of the suggested algorithm is higher than all the current studies in the literature. The accuracy of our proposed algorithm is higher than the work that exists in the literature, for example, Wei et al. Alzheimer’s [49]uses the temporal information from the data for the categorization of Alzheimer’s and achieves the highest results. They achieve correctness of 89% for multi-stage categorization. The proposed algorithm also uses the temporal information from the data, and the accuracy is improved. They also consider different performance matrices to evaluate the implementation of their suggested algorithm with previous studies, and they compare the area under the curve (AUC) of the algorithm with previous studies. They reported that the AUC of their algorithm was 92% for the multi-class classification of diseases. They also compare the AUC of individual classes. They reported 100% AUC in the case of NC vs AD, 92% for MCI vs AD, and

86% for NC vs MCI. Our proposed algorithm outbounds their results. We have achieved an AUC for multiclass classification of 96%. We also compare the AUC for the individual classes. We achieve the AUC for NC vs AD at 99%, MCI vs AD at 97%, and NC vs MCI at 95%. For comparing the performance of the proposed algorithm different state-of-the-art algorithms are also trained on the data and the proposed model achieves higher results as compared to those algorithms.

To compare the performance of our proposed algorithm we also consider other performance matrices which are precision, recall, and f1 score. Our proposed algorithm shows promising results in other performance matrices as well. We calculated the performance of each class and achieve good results. The precision, recall, and f1-score of our proposed algorithm in the case of normal control (NC) patients are 90%, 80%, and 84% respectively. In the case of EMCI, the results are 84%, 84%, and 84 respectively. For the case of LMCI patients, the results are 100%, 83%, and 91%. The results for Alzheimer's dementia patients (AD) are 90%, 93%, and 92%. All the performance matrices are presented in **Table 4.3**.

CHAPTER 5

5. CONCLUSIONS AND FUTURE WORK

5.1. Conclusions

The following are the two most significant contributions to this research: To begin with, most of the image data has been fed into classifiers to detect Alzheimer's disease from two-dimensional or three-dimensional images. Though some brain imaging methods, such as functional MRI, produce four-dimensional data that includes together structural and functional information of the brain. Most researchers used 4-dimensional data by morphing them in the brain networks or splitting them into two-dimensional or three-dimensional images. This is because these 4D data offer both spatial and temporal information about the brain. Our working hypothesis is that this method will cause data loss throughout the categorizing phase. This study provided evidence to support our hypothesis that optimizing the use of natural structural and functional information retained in 4-dimensional functional MRI data is important for detecting Alzheimer's disease and can improve the overall classification performance of classifiers when used without slicing. This hypothesis was founded on the premise that improving the utilization of the natural temporal and spatial information retained in 4-dimensional functional MRI data is critical for Alzheimer's categorization. The second contribution of this research was the creation of a four-dimensional deep learning algorithm (Conv3d-lstm) to diagnose Alzheimer's disease (AD). Because it works directly with 4D fMRI data, this model employs information that is both structurally and temporally variable at the same time. The results of the experiment demonstrated that the algorithm is effective and produces promising results for the analysis of Alzheimer's dementia that are significantly better than those obtained under the same conditions using functional relationship data, 2-dimensional neuroimaging data, or 3-dimensional neuroimaging data. Not only is it conceivable, but it also allows for the full utilization of all the information that various types of 4D data have to offer in the detection of AD. This is a major improvement over earlier methods.

Experiments including parameter adjustments of the Conv3d-lstm were also carried out to demonstrate how we arrived at a model suitable for processing 4D fMRI data. We were able to successfully identify the fMRI data for Alzheimer's patients from normal control patients in this study with an accuracy of 91.06% and the AUC(area under the curve) is 96% using the combination of CNN and LSTM deep-learning algorithms (Conv3d-lstm) that were trained and evaluated with multiple datasets. This was accomplished by training and evaluating a model with a huge number of images. This deep learning technology not only opens new possibilities in the realm of medical image analysis but also allows researchers and physicians to make educated estimates about any new data that may surface. This is a significant advancement in the profession. This technique may also be used to forecast the various phases of Alzheimer's disease in people of various ages. This approach, which is based on deep learning, also allows researchers to do feature extraction and classification using a single architecture. Even though the network design for this study was very simple, it was still very accurate. This shows that the right network design was chosen.

5.2. Future Work

In the future, our goal is to broaden the scope of our work to improve Alzheimer's disease classification and diagnosis. If the disease continues to advance at its current rate, researchers predict that by the year 2050, more than 13.2 million old persons in the United States will have Alzheimer's dementia. This is our belief that the disease is progressing at an alarmingly rapid rate. There are numerous approaches to diagnosing Alzheimer's disease; however, the utilization of deep learning algorithms has shown some encouraging results after the availability of high-powered GPUs and a larger volume of data. There are many ways to make this job more efficient or to improve the accuracy of the detection algorithm, but the three options that we propose are the ones that we believe will result in a performance improvement. The three approaches are as follows: first, we can use regenerative deep learning algorithms to generate more data that is comparable to FMRI Alzheimer's data and train the algorithm on the larger dataset; second, we want to use the online learning deep algorithm to deploy our algorithm in the real environment and make the algorithm predict, and if the prediction is wrong, we want to take input from domain experts and learn from them; and the third one is to use the clustering algorithm to cluster brain regions and gives those extracted regions to Alzheimer classifier to learn important features from them. The regenerative deep learning algorithms can be used to generate more data that is comparable to the FMRI Alzheimer's data. All of the suggested methods that we want to use to make our algorithm perform more accurately have been explained below.

5.2.1. Regenerative neural network

Generative adversarial networks (GANs) are also known as the regenerative neural network and are relatively recent technology that provides a useful foundation for the use of medical pictures. More specifically, a GAN may produce high-quality data with little or no labeled input by pitting its generator network against a discriminator network in a competition. As a result, GANs are quickly establishing themselves as a cutting-edge basis, resulting in improved performances in a range of medical applications. Hence GANs are achieving promising results after the innovation in the deep learning algorithm so they can generate images that are similar to original data. We want to increase the data for Alzheimer's patients by using GANs to train our model on a larger dataset to improve its performance. **Figure 5.1** Represent a workflow of the GANs network [81].

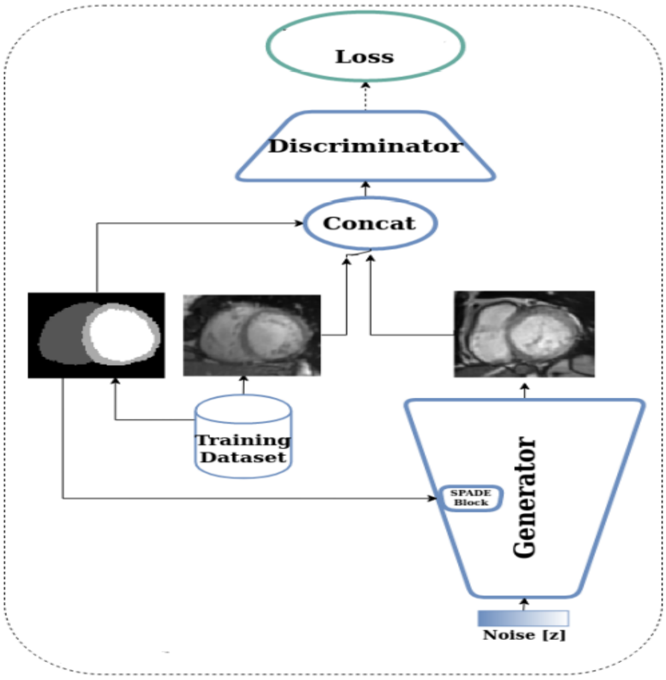

Figure 5.1: Represent a workflow of the GANs(Generative Adversarial) networks [81].

5.2.2. Online learning

Unlike batch learning systems, which provide the best prediction by learning on the whole training set at once, online learning employs data that becomes available sequentially to enhance the greatest association for each new dataset at each step. When employing out-of-core techniques and training over the whole dataset is computationally unfeasible, online learning is a common machine learning paradigm. It is also employed when the algorithm must actively adapt to changing data patterns or when the data is generated as a temporal function. We want to deploy our model in a real environment where the model can learn at run time to learn from a field expert and real-time data by the online learning technique.

5.2.3. Clustering

Clustering is one of the famous unsupervised machine learning techniques to categorize data into different classes without the knowledge of the original labels of the data. We are planning to categorize the different regions of the brain for the categorization of Alzheimer's dementia. We will categorize regions of the brain and feed those categorized brain regions to the classification algorithm for the diagnosis. The categorized regions will help the classifier extract features from each region and hence it helps the classifier algorithm to detect different architectural changes in the brain of the normal patient and Alzheimer's patients.

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