In Vivo Diagnosis of Alzheimer's Disease Using MRI Spectral Images and Machine Learning

I. Abstract

DEMENTIA a is the collective name of symptoms and medical conditions which causes a decline in cognitive abilities, deterioration in memory, thinking, and incrementally causes mental disability in patients.[1] The leading cause of Dementia is Alzheimer's disease(AD). Alzheimer's is caused by abnormal build up of protein inside the brain, two of which have most occurrence - Amyloid and Tau. Amyloid causes plaques inside the brain, while Tau causes deterioration of the brain and forms tangles inside the brain cells[2]. The hope is to use MRI scans of healthy and non healthy brains (affected by Alzheimer's Disease) and use the information in the high spectrum imaging to find features, trends and develop a framework to classify the patients in to categories and possibly automate the process using machine learning techniques and tools.

II. Keywords

Alzheimer's disease, Amyloid Proteins, Amyloid Precursor Protein (APP), Neurofibrillary Tangles (NFT),The Alzheimer's Disease Neuroimaging Initiative (ADNI), Dataset, K-Means Clustering.

III. Abbreviations

APP = Amyloid precursor protein
A = Amyloid beta proteins
NFT = Neurofibrillary tangles
AD = Alzheimer's disease
ADNI=The Alzheimer's Disease Neuroimaging Initiative
CN= Cognitive Normal

IV. Introduction

Alzheimer is an insidious, progressive and degenerative disease. This infers that it is hard to detect and does not show prominent early symptoms, it is progressive meaning that to date it is incurable and it is known to degeneration of brain as in the destruction of neurons in the brain. One of the most prominent effect of the Alzheimer's disease is dementia commonly known as memory loss. Alzheimer start from hippocampus which is the area of brain responsible for making new memories. From there the disease moves centrifugally outwards affecting the speech area and then in turn moving to the frontal lobe. This results in mood imbalances and impairs a person's ability to make decisions.
The main objective of studies up until now has been using basic imaging and hyper spectral data including positron emission tomography (PET) imaging, MRI and Infra Red imaging is to identify biological markers which make it easy to diagnose and detect the progression of the disease. Jung Shi [3] and Donghuan Lu [4] using the combination of PET and MRI images and attempt to distinguish white and grey matter from the imaging and later extract areas of interest from the images such as defibrillation and plaques. Jung Shi [3] then uses deep polynomial networks and combines the input from PET and MRI to build a classifer.Donghuan Lu [4] uses patch wise and ROI wise segmentation from the PET and MRI scans and uses multinodal deep neural network to build a classifier. Saman [5] uses fMRIs and Deep convolutional neural networks to build a classifier and shows features extracted by the different layers of the network to discuss and study the important parts of the scans which might be important biological markers for the detection. Most of these studies use data form ADNI (Alzheimer's disease neuroimaging initiative)[6].

V. Literature Review

In the year 1906 a clinical psychiatrist by the name of, Alois Alzheimer, described the case of a 50-year-old woman who had died after being admitted for behavioral abnormalities like paranoia, memory loss, confusion and aggression. He reported the existence of distinctive plaques and neurofibrillary tangles in the brain. Later, on this specific disease would become to be known as the Alzheimer's disease and become the one of the most expensive and common neurodegenerative disease to date. Alzheimer's disease is the main reason of dementia and memory related problems across the world. AD mostly occurs in people having more age. Estimate age of occurrence of AD is 65 years or more. This deteriorating disease is responsible for 60-80 percent of dementia related cases. Over the world more than 35

million people die due to Alzheimer's disease which is expected to increase till 2050. Researchers suggest that patients with AD show symptoms even before memory loss and so drastic changes in brain cells start occurring i.e. Plaques and tangles starts forming in the brain which disturb the normal functioning of brain cells due to which at late stages severe issues like memory loss or brain death occurs. Initially, Hippocampus (a part of brain which is involved in memory and behavioral activities) is damaged and consequently as the disease progresses it starts affecting the brain causing it to shrink.

A. Causes

Main cause of AD is unknown but mostly it is related to age but other than age another very important factor is causative agent of AD which is genetics. Genetics and our life style play an important role in causing AD, People who have APOE4 allele are at higher risk of having AD while the one's having E3 and E2 are at lower risk of developing AD. APOE gene is involved in transportation of brain lipids, inflammation of neurons and other brain related functions.

B. Symptoms

- Memory loss: The most prominent sign of the Alzheimer's disease is perhaps memory loss. The patient would continuously forget everyday tasks and dates and would repeatedly ask to be reminded the same things. The patient would also start to rely more and more on memory aides like notes, post its or family members.
- Problems with problem solving: The patient will find it increasingly difficult to keep us with numerical problems like calculating the bill, counting change and even keep track of every tasks.
- Confusion: People with Alzheimer's Disease have difficulty in keeping track of dates, season or general passage of time. They can suddenly lose track of where they are and how they got there.
- They may also have problem speaking, reading, remembering color and judging distance. They may even lose track of their words while listening or speaking.
- As their frontal lobe starts getting affected by the disease, they may lose their ability to make conscious and apt decisions and will also experience behavioral changes and sudden outbursts.
- They will eventually remove themselves away from social activities and hobbies as they will no longer be able to keep up with them.

C. Risk Factors for Alzheimer's disease

- **Age:**
  One of the most prominent and prevalent risk factors for Alzheimer's is the age. It has been noted that the patients of the disease increase drastically with age, with 32 percent of people above the age of 85 contracting the disease. However, it is important to note that old age is not the only factor that causes the disease and many factor contribute just as much as age.
- **Genetics:**
  A very small percentage of patients can develop Alzheimer's disease due to genetic mutations. The basic genes at work here are the presenilin gene 1 and 14, APP in the gene 21 and APO4 in the gene 19. APP mutation in the chromosome 21 can cause an abundance of APP production and thus can increase the risk of patient developing Alzheimer's disease.
- **Family History:**
  It has been noted by a lot of researchers that having a first-degree relative with Alzheimer's can increase the risk of a patient contracting the disease. It is much more surprising to know that this study was took into account the known genetic risk factors independent to family history. Since when diseases run in family both the hereditary and non-hereditary factors, like habits, access to food and healthcare etc., play a role.
- **Cardiovascular Disease factors:**
  It has been seen that the brain is largely affected by the health of the heart and the blood vessels. This happens because the heart is responsible to pump blood to the brain and the blood vessels make sure that the blood that reaches the brain is rich in nutrients and oxygen. It is perhaps due to this that all the risks associated with cardiovascular diseases are also indirect risk factors for Alzheimer's disease. These risk factors also include obesity, smoking and diabetes.
- **Education:**
  It has been seen in surveys that people with more years of formal education have lower risk of manifesting Alzheimer's Disease than people with little to no formal education. Although man theories have been presented so far, the researchers are not sure as to how formal education is affecting the brain and why it results in a reduced risk of the Alzheimer's disease. However, the most promising hypotheses says that formal education trains the brain to more efficiently use the cognitive networks even with

continuing changes in brain. Due to this even when the brain experiences the accumulation of beta-amyloids plaques and the hyperphosphorylation of TAU proteins inside the neurons the brain continues to function efficiently even with these changes.

- **Traumatic Brain Injury:**
  Another high-risk factor identified with Alzheimer's disease is TBI or traumatic brain injury. TBI is defined as a disruption in the normal function of the brain due to a severe blow or jolt to head or due to something penetrating the skull bone. Even thou even mild cases of TBI increase the risk of Alzheimer's Disease the greatest risk due to TBI is perhaps to those that get TBI continuously like players of contact sports. This continuous disruption to brain function causes changes to the brain such that the chances of contracting Alzheimer's disease increase exponentially.

D. Diagnosis of Alzheimer's disease:

Diagnosis of Alzheimer's disease Using Biomarkers:
A biomarker is biological factor that can be used to identify the presence or spread of a disease. Biomarkers are very useful tools in identifying and quantifying the spread of different disease. The most prominent biomarkers for the Alzheimer's disease are the levels of the beta-amyloids and abnormal TAU proteins. This discovery has helped doctors and experts diagnose the Alzheimer's disease at a much earlier stage. In order to detect the levels of beta-amyloids and abnormal TAU proteins in a subject we use the help of positron emission tomography (PET) imaging.

Diagnosis of Dementia Due to Alzheimer's disease: The diagnosis of dementia due to Alzheimer's disease is perhaps much more difficult as no formal tools or machine can accurately provide the complete information needed for the diagnosis. Thus, a mix of techniques are used by doctors and physicians in order to properly ascertain their diagnosis. Aside from using PET scans to determine the levels of beta-amyloids and abnormal TAU protein doctors employ lot of other techniques that include brain imaging and other test in order rule out any other problems that might be causing the dementia, inquiring family members about the psychiatric history of the patients and the cognitive and behavioral changes they might have observed and also cognitive, physical and neurological examination.

Diagnosis of Alzheimer's disease using In Vivo Methods:
The main objective of the studies, in our focus, were using basic imaging and hyper spectral data including positron emission tomography (PET) imaging, MRI, Raman spectroscopy, and Infra-Red imaging is to identify biological markers which make it easy to diagnose and detect the progression of the disease. The easiest and fastest among which was the diagnosis through MRI images. However, it was difficult to observe the changes in the brain caused by AD as in early stages these changes were minimal and could only be observed by experts in the field. Thus, using the knowledge gained by the approaches used we used images from the MRI to perform clustering on the images, the clusters divided the data into groups which could be labeled as developed stage of the disease, in progression of the disease, and healthy brains due to the features and markers obtained by the nature of the process and the imaging. The findings from the cluster analysis were then used in enhancing the detection itself when using the machine learning approaches to build a classifier and extract features inside images for manual use and assistance of medical personnel dealing and studying these diseases. Machine learning models such as Support Vector Machines, Decision Trees and Deep Neural Networks can now be trained using our data to automate the process of in vivo detection AD in patients.

VI. Pathophysiology

The pathophysiology of the Alzheimer's disease is really complex and thus even though much work has been done we do not of have a complete understanding of the disease. Several theories have been suggested in order to explain how the disease manifest in an individual the two most widely accepted hypotheses are the amyloid-cascade hypothesis and the hyperphosphorylation of protein tau hypothesis. APP known as amyloid precursor protein is present in all neuronal cell membranes. There are three enzymes, the alpha, beta and gamma secretase, which are responsible for cleaving of different part of APP from the neuronal cell membrane. In a healthy subject, the alpha secretase and the gamma secretase work together to cleave off parts of APP which into fragments that are digested in the Proteosomes. However, when a patient develops Alzheimer's one of the first changes that we see in the cleaving off of APP protein. The protein is now cleaved off by beta and the gamma secretes which result in a fragment that is insoluble. This fragment is called the beta amyloid or A Lipoprotein, these fragments then clump together to form the senile plaques or the amyloid plaques outside the neuronal cell. In a patient with Alzheimer's disease these plaques are found in the entorhinal cortex, the hippocampus and neocortical areas. [4] The presence of the beta amyloid

plaques activates the immune system cells known as the microglia. The microglia cells try to clean up the plaques but as it fails to do so inflammation starts to occur inside the brain which causes tissue damage and brain degeneration. Moreover, the beta amyloids can attach themselves to the synapses of the neurons disrupting the neuron-neuron communication and causing the neurons to die. [5] The second hypothesis used to explain the Alzheimer's disease is the hyperphosphorylation of the protein TAU. The protein TAU is responsible to stabilize the microtubules. Microtubules are the pathway that runs throughout the exons in the neuron. These microtubules are responsible to transport proteins which in turn bring the nutrients and the neurotransmitters that are made in the cell body, from the soma to the exons and to the synapses. The beta amyloid proteins also play a major role here as they hyperphosphorylated the TAU protein inside the microtubules leading to the formation of paired helical filaments (PHF) and eventually NFTs. This causes the TAU protein to get together and make clumps inside the neuron because of which the microtubules fall apart and thus no nutrient and the neurotransmitter cannot travel within the cell. Due to the absence of neurotransmitters at the synapses the synaptic function falls apart. Soon the dendrites and exons cannot get enough nutrients to survive and they start to die which results in the cell getting shriveled up and losing most of its function. A bunch of these shriveled up neurons are called the neurofibrillary tangles.

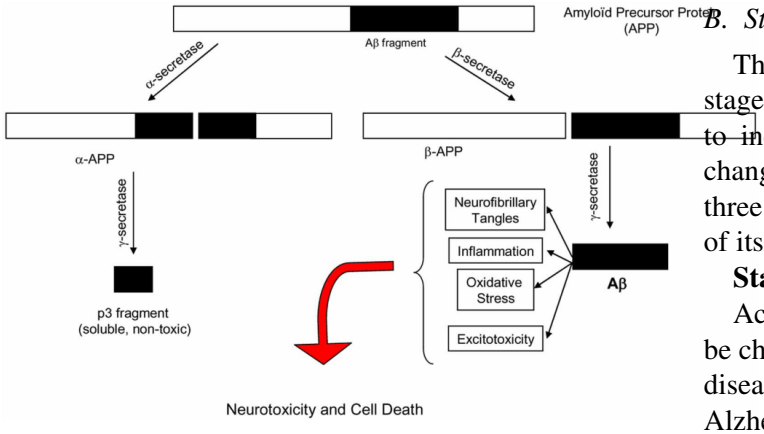


Fig. 1: Alzheimer Pathophysiology

VII. Aims And Motivation

Alzheimer's disease is one the most common neurodegenerative disease. With more than 24 million cases worldwide there is a dire need to stop the spread of this disease which causes billions of dollars each year to the world economy.[1] [2] The pathophysiology of Alzheimer's disease is complex and difficult to understand. Thus, the aims of the project are to:

- Discuss the current known bio markers of AD which include 'plaques', neurofibrillary tangles and degenerative vasculature.[3]
- Categorize how the changes in Brain can lead to the detection of these bio markers through MRI Brain Scan.
- Use a clustering technique to train a model to detect the differences between the MRI scan of a cognitive normal (CN) and AD subject.
- Create an in vivo diagnostic tool that can enable doctors to reduce the diagnostic time of AD.

VIII. Methodology

A. Data Acquisition

The dataset has been acquired through the The Alzheimer's Disease Neuroimaging Initiative (ADNI) database. The ADNI database is a multicenter study designed to accumulate that data of the clinical, imaging, genetic, and biochemical biomarkers of Alzhiermer Disease (AD). The dataset included dicom images MRI scans from 462 subjects with congnitive normal (CN) and 218 subjects with Alzhimer's Disease (AD) at variable stages. The subjects include both male and female ranging from 52 to 85.

B. Stages Of AD

The dataset included subjects effected with different stages of AD and thus it was important for the dataset to include subjects from all stages, as the anatomical changes in the brain tend to vary greatly and thus the three stages of AD tends to differentiate both in terms of its effects as well in biochemical makeup of the brain.

Stages of Alzheimer's disease:

According to current research Alzheimer's disease can be characterized into three stages preclinical Alzheimer's disease, mild cognitive impairment (MCI) due to Alzheimer's disease, and Dementia due to Alzheimer's disease.

Preclinical Alzheimer's disease:

This stage of Alzheimer's disease is still under analysis and thus, more research is needed in order to be able to have a concrete diagnosis in this stage. In this stage none

of the symptoms of the disease has yet manifested and thus diagnosis is difficult. It is interesting to note that even in this early stage there are measurable changes to the brain anatomy and detectable biomarkers are present which can be detected through tools and experts. However, much work is needed in order to fine tune these tools in order for them to be used in hospitals and clinics.

Mild Cognitive Impairment (MCI) Due to Alzheimer's Disease:
In this stage of Alzheimer's disease, the patient now has easily detectable levels of beta-amyloids and starts to experience a decline in their cognitive functions. These declines are usually much greater than expected according to the age of the patient and thou, not noticeable to the patient can be seem easily by family members or caretakers. In recent studies conducted on patients with MCI it was found out than within years 32 percent of the subjects had developed Dementia due to Alzheimer's disease. It is become extremely crucial right now to ascertain which individuals with MCI will develop dementia.

Dementia Due to Alzheimer's Disease:
This is the last stage of the disease in which a patient may exhibit noticeable thinking, memory and behavioral changes as well as high levels of biomarkers associated with the Alzheimer's disease. It becomes extremely difficult for the patient to function and constant care is needed in order to survive. Subjects diagnosed with Alzheimer's Dementia experiences many symptoms over a course of years which shows the amount of damage suffered by the brain and how far through the brain the disease has spread. During, the initial stages the individual may be able to function independently with minimal assistance. In the second stage with lasts the longest the patient will start to exhibit drastic behavioral changes paired with drastic decrease in many cognitive functions. The patient will experience trouble communicating as well as performing many activities and will require a lot more care. In the last and most severe stage of Alzheimer's Dementia the patient will lose most if not all of his memories and even basic cognitive functions such as those of movement and would eventually be bedridden. In this stage the patient will need around the clock care and would be especially prune to infections and blood cloths which could lead to organ failure.

C. Data Prepossessing and Visualisation

We observed data from numerous MRI scans in multiple planes and slices. Out of the 3 planes observed i.e sagittal, colonial and axial, the axial plane was most capable in acquiring optimal results and clearly showed changes as the AD progressed. Moreover from hundreds of slices observed only a few prominently showed the changes occurring in the brain during AD and thus we localised our result into only 3-planes a technique known as 3-plane localization.

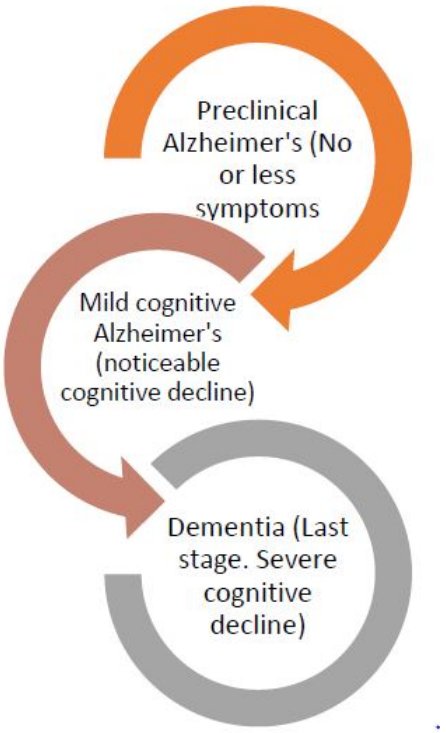


Fig. 2: Stages Of AD

D. Data Modelling

Machine Learning: Machine learning are applied methods from artificial intelligence, an applied field originating from computer science. The machine - a computer is given a subset of the data - called training data, which the algorithms developed by mathematical and statistical methods use to calculate and find patterns in the data so as to identify, classify and divide the data into subsets which are of use to the application they are used in. These are automated methods and come later in the data science pipeline. The first task when data comes in is to apply visualizations to extract useful information and patters from hundreds and thousands of lines of data - whether it be written text or images. Cleaning the data, ie removing missing or invalid values, statistical information and probability distributions of the data are visualized, calculated and understood in this step to make sure the data is in good form, and an appropriate model is used to model the data. These tasks are classified into EDA - Exploratory Data Analysis which is a part of the data science pipeline.

Supervised learning: Supervised learning is a kind of machine learning in which the computer is guided and given prior information about the data - usually labels, which might be singular or plural to use them to correct its mistakes. A very simple example of this is an image with the label of a cat, identifying the image which the computer later uses to correct its mistake if it for example identifies it as a dog. Deep learning which is a model inspired by biological model of the brain is an example of the supervised machine learning methods.

Unsupervised learning: As opposed to supervised learning, unsupervised learning does not use labels or any other prior information about the data, and uses automated methods, usually methods developed by applied linear algebra, statistics and probability to find patterns and insights about the data. Clustering, specifically K-means clustering is and example of the unsupervised machine learning methods.

Clustering: Clustering is mainly used to tackle unsupervised learning problems in which we aim to find and observe specific structures in a data without them being tied down to any outcomes.[11] Thu, clustering helps us identify similar data groups in a dataset by dividing the data points into separate group called clusters. Data points that are similar to each other are grouped together such that data points in a single cluster share traits more similar to each other than those in other clusters.

K-means Clustering: The objective of K-means Clustering is to group data points with simple traits into defined clusters and identify the underlining traits or properties that make up a data cluster. In K-means Clustering we define a 'k' number of clusters that in turn results in the same number of centroids (a central point in a cluster).[12] After identifying the centroids, the algorithm then allocates each data point to a specific centroid while keeping the centroid and data points as close together as possible. In the start the algorithm assigns a randomly selects the centroids and then repeatedly perform mathematical iterations in order to achieve the best possible positions of the centroids. The algorithm achieves completion when the centroids achieve a stable position.

E. Enviroment, Tools And Libraries

Python3 was used as a core programming language for the implementation of the models and scripting necessary for processing the data. The zip files downloaded from the ADNI site were uploaded to the drive, extracted and using glob the images in the sub folders were processed into singular folders for alzheimer's and the cognitive normal group.

A google Colab notebook was used to easily observe the results of the execution in parts and for ease of access of the data and code through the cloud.

Pydicom and dicom libraries were used to read and visualize the MRI dicom images. For image preprocessing and scaling the openCV library was used, while numpy and matplotlib were used for mathematical manipulation of data and plotting the images respectively. The dicom images were then converted into jpg images for ease of access in the modeling process.

The Scikit learn library was used for the modeling process.The dicom and jpg images were visualized respectively to observe changes in the images after conversion.K means clustering algorithm was used to cluster images in different sub sections to extract insight about the working of the algorithm on the data as it is an unsupervised learning technique.

IX. Result and Conclusion

A. Findings And Insights

The clustering algorithm was run on the groups separately keeping K = 2 constant on the groups separately, the first iteration consisted of running K means on the CN group. We observed that the clusters were different with respect to size and structure i.e the brains in the first cluster were smaller, and had different brain structure than the brain scans in the second cluster. The second iteration consisted of running K means on the AD group. This time we observed the changes in the images from the clusters were with respect to disintegration amount of the brain, and locality of the disintegration - ie in the middle or the frontal cortex. The images from the first cluster had lower disintegration comparatively than the images in the second cluster. The final iteration of the clustering was implemented on the the two images mixed together, and ideally this time the image clusters would cluster the images of AD and CN into different clusters.

Fig. 3: Changes in Brain Anatomy due to AD

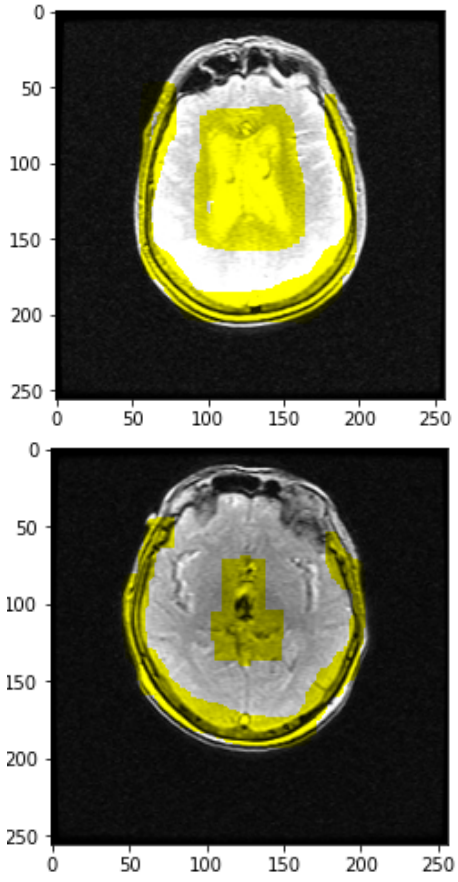
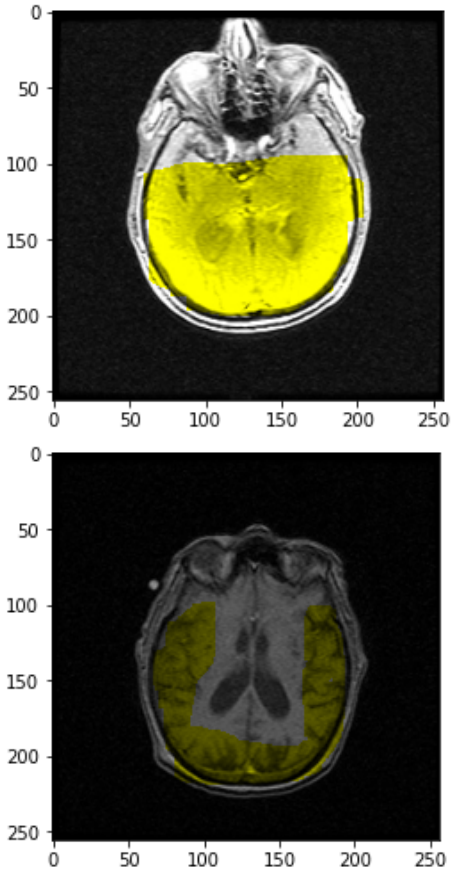


Fig. 4: Grey Matter Disintegration due to AD



Much of the results were positive, some very clear results are shown in the figures, and the disintegration in the grey matter of the brain and decrease in size is highlighted in the images as yellow. The features extracted from the clustering are useful in differentiating between full blown AD ie Alzheimer's in its last stages and the healthy brains. The clustering algorithm can be iterated many times by domain experts with varying numbers of K (in the K means algorithm) with a varying mix of the data to separate data into divisions where valuable information might be extracted which might prove useful in diagnosing the disease in its early stages and possibly reverse the affects. The findings might also be useful in studying the structural changes in the brain and extracting patterns about the changes which might be useful in investigating the causes of the disintegration.

X. Conclusion

The findings and learning outcomes from the work suggest that an automated tool with the multiple clustering approach has not been worked on and is a novel approach to find useful features from images in the field. The unsupervised manner or learning is also helpful in correcting data annotation errors as it does not look at the labels while functioning.A similar approach on PET scans combined with the current approach worked on would be useful in finding anatomical changes in the brain throughout the course of the disease, and in observing changes while working on cures and/or treatments on the disease. Furthermore combined with image segmentation and deep learning supervised models this approach could be developed as a useful tool for doctors and scientists in the field to hopefully help diagnose the disease in its early stages, in research for the disease propagating via genetic code and building and improving the current datasets. The visualizations aid layman and people with applied knowledge in other various fields to understand the disease and changes in the brain structure which opens even more horizons for development in the field.

XI. Future Work

The current work illustrates that artificial intelligence methods are very useful in finding differences between healthy and brains with AD. The work uses just one axial view from the three views namely, Axial, Sagittal and Coronal views. The work could be extended by using all slices available for a brain combining machine learning and deep learning methods with the applied methods of deep learning such as image segmentation and other information about the subject such as data about blood, cerebrospinal fluid and other information to develop an automated diagnosis and hopefully early diagnosis method for Alzheimer's disease and a very powerful tool for doctors and scientist in the biomedical and medical field.

XII. References :

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XIII. Appendices

A. *Iteration 1: Clustering Of AD Images*

AD Cluster 1

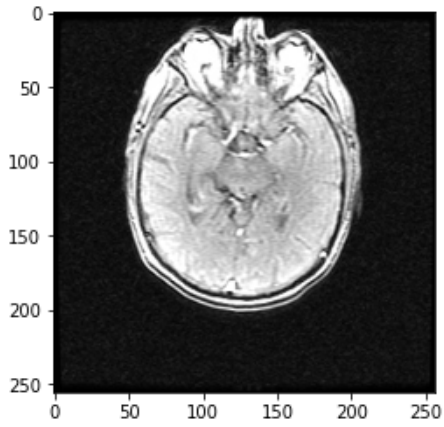

Fig. 5: Image 1

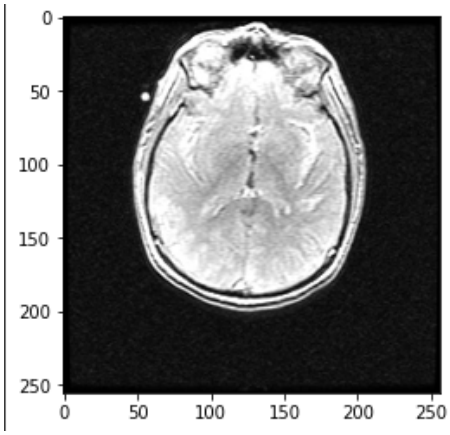

Fig. 6: Image 2

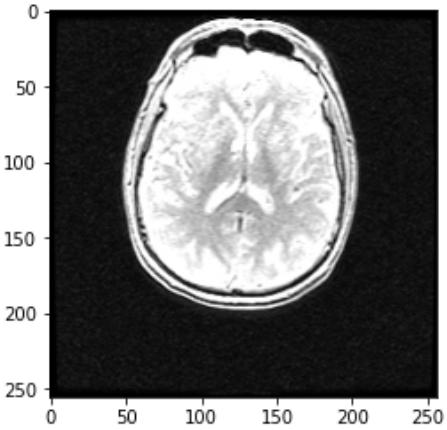

Fig. 7: Image 3

AD CLUSTER 2

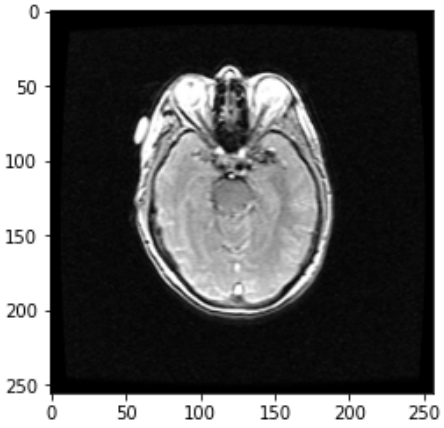

Fig. 8: Image 1

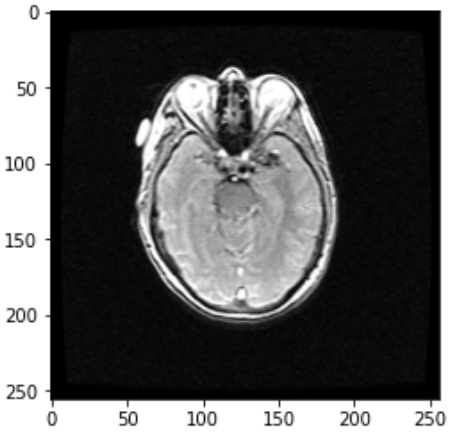

Fig. 9: Image 2

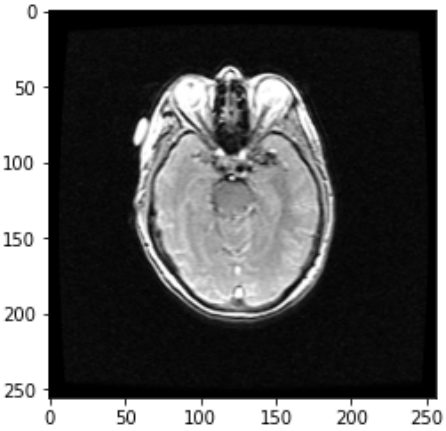

Fig. 10: Image 3

B. Iteration 2: Clustering Of CN Images

CN CLUSTER 1

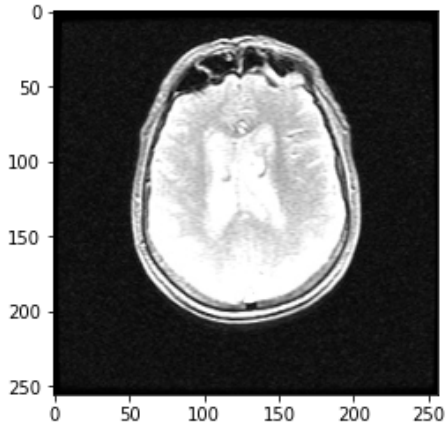

Fig. 11: Image 1

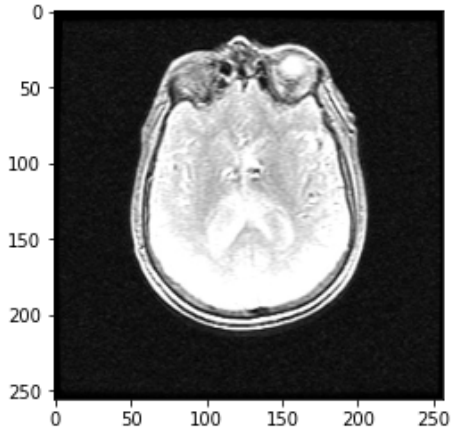

Fig. 12: Image 2

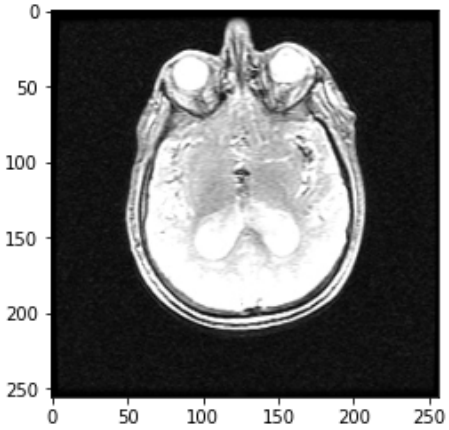

Fig. 13: Image 3

CN CLUSTER 2

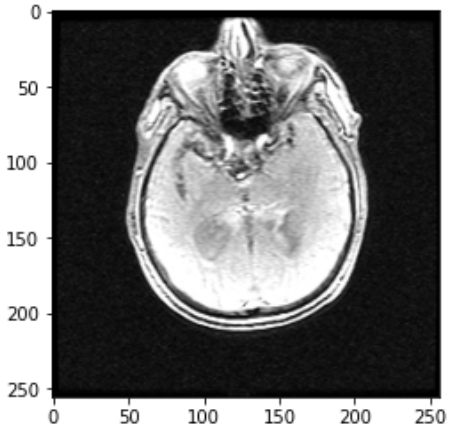

Fig. 14: Image 1

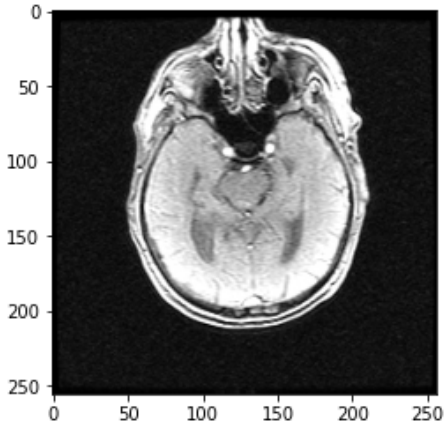

Fig. 15: Image 2

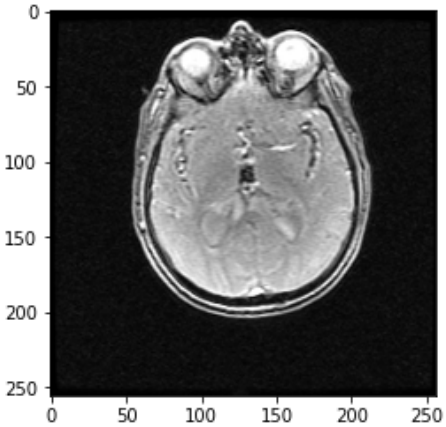

Fig. 16: Image 3