Alzheimer’s Disease (AD) is an ever-pervasive neurodegenerative disorder affecting the elderly in the United States. With the advent of medical imaging technology, effort is being directed towards quantitatively detecting biomarkers which can be used to identify patients with AD. This paper attempts to reliably classify patients who exhibit mild cognitive impairment (MCI) into those who develop AD (MCIc) and those who do not (MCInc). MRI scans from subjects who exhibited MCI) were collected from the ADNI online database and labeled either MCIc or MCInc through a prior study (Salvatore et al.). A convolutional neural network in Tensorflow was attempted to classify between MCIc scans and MCInc scans with 0.004% success; however, the program crashed without training on the entire set of images. Therefore, the neural network attempted is presented as a proposal to be computed by a research initiative with available computing resources. Images were then analyzed using Tableau in order to detect sizeable differences in tissue volumes by age, sex, and patient classification. This brief analysis yielded complete overlaps between all segregated categories, implying that there are no significant volumetric differences between Further steps are proposed in order to successfully classify between MCIc and MCInc patients.

# Introduction

Alzheimer’s Disease (AD) is one of the most pervasive neurodegenerative disorders and the leading cause of dementia among the rising elderly population in the United States; approximately five million patients are currently suffering from the disease with varying degrees of severity. AD poses a significant societal loss in terms of human life and opportunity cost, with an estimated 90,000-100,000 victims passing away every year and aggregate $230 billion and 18 billion hours spent in care, treatment, and diagnosis, respectively. For these reasons, immense research initiative is being directed towards improved detection and treatment of AD.

The proliferation of medical imaging technology in the last few decades has given researchers and clinicians insights into physiological, metabolic and functional biomarkers that identify AD’s internal mechanisms. Technologies such as magnetic resonance imaging (MRI), functional magnetic resonance imaging (fMRI), electroencephalography (EEG), and positron emission tomography (PET) provide fast, noninvasive monitoring of the activity and structures in a patient’s brain. Through these techniques, several physical symptoms have been directly identified as distinguishing symptoms of AD, including the buildup of amyloid plaques, atrophy in medial temporal regions,

The resulting ability to quantify the physical structures and activity of the brain has spawned has led researchers to explore machine learning techniques in order to detect distinguishing patterns between different classes of patients, those being CN (healthy control), MCI (Mild Cognitive Impairment), and AD (patients with a fuller, more severe form of Alzheimer’s Disease). There have been previous studies successfully classifying structural MRI images belonging to each category to above 90% accuracy; however, literature indicates that differentiating between MCIc subjects and MCInc subjects has not been achieved above 66% accuracy. Convolutional neural networks have routinely outperformed other learning algorithms when classifying patients. In this paper, a convolutional neural network (CNN) is proposed to differentiate between MCIc and MCInc patients and the feasibility of this CNN is discussed by analyzing tissue volume data in Tableau.

# Data

MRI images from patients in the MCIc and MCInc categories were obtained from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) online database (https://ida.loni.usc.edu/login.jsp?project=&page=HOME#) and labeled according to a compiled list of subject ID numbers provided by Salvatore et al. Scans from 74 male and female patients classified as MCIc ranging in age from 55 years to 91 were downloaded, as were scans from 118 male and female MCInc patients from ages 58 to 96 years, for a total of 2776 images. All scans were T1-weighted, procured using MPRAGE methods, and downloaded in the NIFTI file format (.nii extension).

The image sizes were highly variable; the width ranged anywhere from 128 to 176 voxels, and the height and depth ranged anywhere from 196 to 266 voxels. Additionally, the size of the brain relative to the rest of the image was nor uniform; some images were highly zoomed in whereas others contained a larger proportion. Furthermore, color intensity was highly variable; some images displayed a much high color saturation and contrast in comparison to others.

# Preprocessing

All images were preprocessed using the FSL free software library (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>). Skull, cartilage, and other extra-cranial matter were first removed by using the BET (Brain Extraction Tool), after which the extracted images of the brains were segmented into grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF) using the FAST (FMRIB’s Automated Segmentation Tool) tissue segmentation software. These steps served to isolate the relevant parts of the brain while also normalizing the color scheme of each image, accounting for the differences in color intensity. The full code may be viewed at (<https://www.github.com/arnavlohe15>).

# Proposed Neural Network

The convolutional neural network used contains a convolution layer, pooling layer, feature map extraction, a second convolution layer, a densely connected layer, and a dropout and readout layer. The first convolution layer utilizes a 5x5x5 (x32 features) convolutional filter with normally distributed values and operating on a 1x1x1 stride. The subsequent pooling layer downsamples features in 4x4x4 blocks. The second convolution layer still utilizes 5x5x5 filters, but replaces (x32 features) with (x64) features. Subsequently, the CNN utilizes a fully-connected layer with 1024 neurons, a dropout layer to reduce overfitting, and a readout layer with two dimensions to display probabilities. The full code may be viewed at (<https://www.github.com/arnavlohe15>).

# Image analysis in tableau

Due to the failure of the convolutional neural network to discover meaningful differences between MCIc scans and MCInc scans, tissue data was then analyzed using Tableau to look for meaningful differences by age, sex, and classification. Firstly, because structural symptoms of AD onset have been shown to include GM and WM atrophy, a tool was built using Python in order to quantify tissue volume for GM, WM, and CSF by obtaining the count of the different voxel values within fully preprocessed scans. The total CSF volume was taken as the total count of voxels valued at 1.0, and GM and WM volumes corresponded similarly with voxels valued at 2.0 and 3.0 respectively. Tuples containing the subject ID number and the tissue counts were then created as a csv file, concatenated with patient age, sex, and image number information, and visualized in Tableau.

Tissue volume counts were heavily varied by order of magnitude. The smallest GM count was 67505 voxels, while the largest was 6932881. The corresponding ranges of WM and CSF volumes are 18606-3715695 and 14276-6752268 respectively. This may be due to the variable sizes of the original MRI scans and other non-homogeneity in the images, such as zoom. However, it is equally likely that the tissue quantification tool utilized a rudimentary algorithm and did not account for background voxels and other such image variations.

**FIGURE: Ratio of WM to Total Volume vs GM to Total Volume**



While the downward slope of the apparent linear trend cannot be explained with the given information, this visualization demonstrates that structural MRI scans from both categories of subjects fall within the same general regions and cannot be reliably segregated using K-Means or any such classification algorithm on the basis of tissue volume alone.

**FIGURE: Ratio of GM and WM to Total Volume by Age Interval**

****

MRI scans of patients were segregated by their age intervals (calculated by rounding to the nearest 10 years). This figure indicates that the ratios of volumes of GM and WM with respect to total cranial volume are approximately equivalent to each other regardless of age or subject classification. It can therefore be inferred that there are likely still no meaningful differences that can be detected by the convolutional neural network described previously. While current literature indicates that age results in significant global atrophy, this does not seem to affect relative GM and WM changes that may result from AD onset.

**FIGURE: Ratio of GM and WM to Total Volume by Sex**



As can be seen above, the GM and WM ratios to total volume are largely consistent between both females and males. It may therefore be concluded that sex plays a minor role in determining relative GM and WM volumes, and that on the basis of volumetric differences alone, patient classification and sex display no meaningful differences that may be detected by a convolutional network.

Relative tissue values to the total image volume were therefore calculated in order to normalize tissue volume counts; however, significant variation was present even here that has no biological justification. Relative GM values ranged from 6.08%-67.2%, while the corresponding interval for WM is 10.5%-60.5%. This may once again indicate the simplistic nature of the tissue volume quantification tool in addition to incomplete preprocessing.

Because of the unexpectedly large ranges for tissue volume data, no meaningful differences were found between patient classifications even after segregating tissue data by age range, sex, or both.

# Conclusion and suggestions for future research

Due to the inhomogeneity of image sizes and volumes, and the simultaneous indistinguishable overlaps in relative tissue volumes between patients of both categories after taking age and sex into consideration, it may be concluded that a convolutional neural network may not be able to detect significant differences if trained on structural MRI images alone. In order to improve the performance of the convolutional neural network, it is suggested that further preprocessing steps be taken in order to align images and perhaps normalize for the amount of zoom that may be present. Algorithms to scale images to uniform sizes or normalize tissue volumes are also worth investigating.

Additionally, fMRI and EEG data may provide insight into potential differences in neural activity between MCIc and MCInc patients.

Lastly, it is recommended to rigorously demonstrate the lack of significant differences in tissue volumes across patient classifications and other segregations by employing formal statistical tests.

# Acknowledgment

I would like to acknowledge the MMEBS Program at Bethune Cookman University for providing me with the opportunity to pursue this investigation. I would like to especially acknowledge Dr. Juan Calderon for introducing me to the theory and implementation of convolutional networks in tensorflow. As this paper is a small write-up for internal purposes, references are not included, but are available upon request.