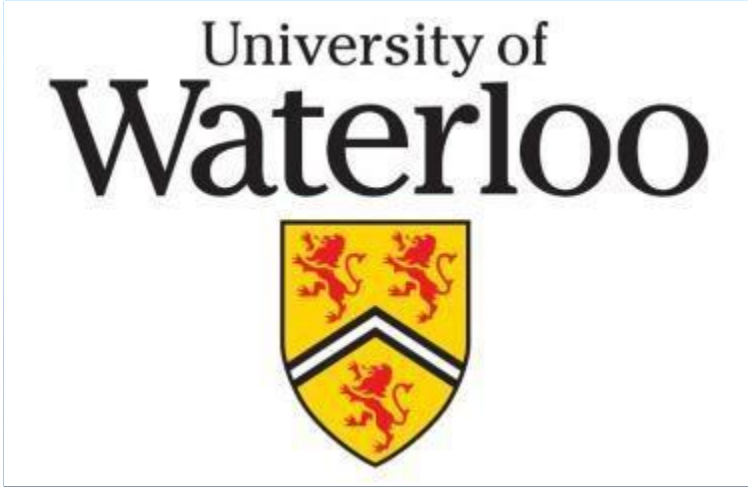

SYDE 675
PROJECT REPORT

CLASSIFICATION OF BRAIN MRI FOR DETECTION OF ALZHEIMER'S

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ABSTRACT

In this study, we propose a method for the classification of T1-weighted Magnetic Resonance Images (MRI) of the Brain in case of Alzheimer's disease based on extraction of different features. The dataset used comprises of right handed females of age group 18-96 years and is helpful to determine the onset and early detection of the disease. The processed MR images are used to obtain different features for training of classifiers. The whole Grey matter is considered as the Region of Interest (ROI) because it contains the Amygdala and Hippocampus, the regions most affected due to Alzheimer's. The features used for this study are some of the crucial second order features derived from Grey Level Co-occurrence Matrix (GLCM) such as Entropy, Energy, Homogeneity and Correlation and also the ratio of the Grey Matter Volume and the White Matter Volume to the Volume of the Cerebrospinal Fluid. An accuracy of 84% has been achieved with a sensitivity of 100%. This proves to be a better method than Voxel Based Morphometry extraction method which is cumbersome but has been proved to be more accurate but not as sensitive.

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CHAPTER 1: INTRODUCTION

1.1 The Brain

The brain is one of the most complex and integral parts of the human body. It is the command center for the human nervous system.[20] It receives input from the sensory organs and sends output to the muscles. It is made up of more than 100 billion nerves involved in trillions of connections.

Some important functions that the brain performs are:

- Creative Visualization
- Memory & Learning
- Executive Planning
- Language & Math
- Emotional Response
- Social Interaction

The brain structure is made of three main parts: the forebrain, midbrain, and hindbrain. The forebrain consists of the cerebrum, thalamus, and hypothalamus. The midbrain consists of the tectum and tegmentum. The hindbrain is made of the cerebellum, pons and medulla. Often the midbrain, pons, and medulla are referred to together as the brainstem.

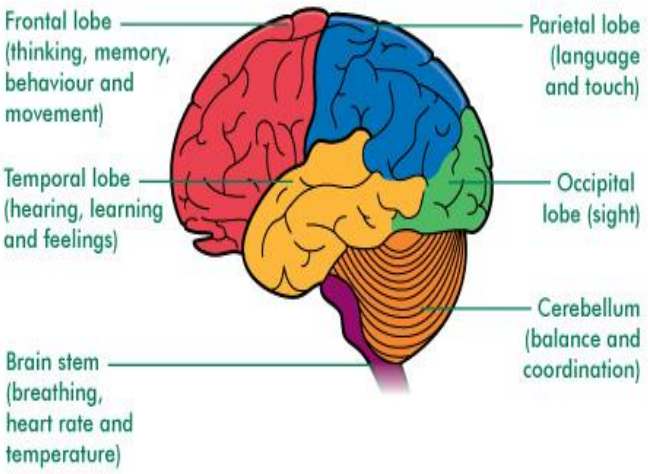

Figure 1: Parts of the brain and their functions

1.2 Alzheimer's Disease

Neurological disorders are diseases of the brain, spine and the nerves that connect them. There are more than 600 diseases of the nervous system out of which some common ones are:

Infections: Meningitis, Encephalitis, Brain abscess:

Seizures: Epilepsy

Degenerative: Alzheimer's disease, Cerebral Palsy, Dementia, Parkinson's disease

Abnormalities: Brain Tumor

Alzheimer's disease accounts for 60-80% of the cases with dementia. It is a slow progressive brain disease that begins well before clinical symptoms emerge.[3] The subsequent decline in cognitive functions worsens with time and eventually can lead to death. 1 out of 3 seniors in United States [4] die with dementia and every 67 seconds, someone in United States develops Alzheimer's. The prevalence of the disease is expected to grow fourfold by 2050 which makes it one of the important concerns of the hour. AD has no definitive cure.[5] The only current treatment available is to temporarily slow the worsening of dementia symptoms in the patient to delay death and hence the earlier the detection, the better.

Different diagnoses methods exist for the detection of Alzheimer's. The clinical treatment involves detecting whether the patient deficits in two or more cognitive functions and has a Mini-Mental State Examination Score of less than 23 and a Clinical Dementia Rating of more than 0.5. It has a 90% sensitivity and 70% specificity rate but has certain limitations. The Clinical Treatment is not possible with patients suffering from severe depression, aphasia and apraxia.[1] Moreover, the AD symptoms can be mimicked by other kinds of dementia too.

Figure 2: Tangles and Plaques formed during Alzheimer's

There are many structural and functional changes too that take place in the brain due to AD. The formation of tangles and plaques result in the shrinking of the brain due to which it loses functional capabilities as the neurons die.[6] Computer aided image analyses make use of these changes and help detect the disease at an early stage. The prominent structural changes include atrophies in the hippocampal and temporal parietal regions.

The best brain image acquisition required for this study is obtained by Magnetic Resonance Imaging because of high contrast, specificity, sensitivity and clarity it provides, which is optimal for the analyses unlike its counterparts like CT which is not useful at an early

stage of the disease.[1] MRI is also a safe method as it does not use X-rays or any foreign substance in the process which can otherwise, worsen the state of an AD patient.

1.3 Terms Related to Alzheimer's Disease

AD: Alzheimer's disease

CDR: Clinical Dementia Rating 5-point scale used to characterize six domains of cognitive and functional performance applicable to Alzheimer disease and related dementias.

0 = Normal

0.5 = Very Mild Dementia

1 = Mild Dementia

2 = Moderate Dementia

3 = Severe Dementia

MCI: Mild Cognitive Impairment

MMSE: Mini Mental State Examination

CN: Cognitive Normal

GM: Grey Matter – Where real processing takes place.

WM: White Matter – Which helps in communication to and from the grey matter and the rest of the body

CSF: Cerebrospinal Fluid – Which provides mechanical and immunological protection to the brain inside the skull and auto regulation of cerebral blood flow.

CHAPTER 2: LITERATURE REVIEW

2.1 Review

Research has been carried out for detection of Alzheimer's disease from structural as well as functional MRI. In case of structural MRIs there has been a prime focus on the extraction of structures where maximum atrophy is seen in case of AD. These atrophies can be compared with perfectly normal brain structures and the disease can be detected.

A lot of work has been carried out by Voxel Based Morphometry (VBM) using Brain MRI. VBM preprocesses the images by standardizing images to same stereotactic space using linear affine transformation and further warps, smoothens and performs a statistical analyses. This has been carried out using different software on different kind of MR images of different age groups and interesting results have come up. The optimized VBM (SPM2) on cross sectional data (Good CD et al.)[7] showed a reduction in parietal and medial temporal gray matter structures as well as in white matter volume. The SPM99 on longitudinal (Resnick UM et al) and cross sectional (Matsuda H et al) proved a reduction in gray matter but in different regions. Savio et al. [8] obtained SPM using VBM extraction of two kinds of features: Mean and Standard Deviation of voxel values of Gray Matter (GM) and a high dimensional vector for GM segmentation values for different voxel locations.

Research not involving VBM has not been that popular but the few existing works have given concrete results. Saima et al proposed extraction by defining a rectangular ROI mask derived from manual segmentation of the hippocampal region on one half of the images which served as a training set for hippocampus area calculation. [9] These left as well as right hippocampal regions along with the GM, WM and CSF areas were fed as features to different classifiers and their performance was compared. SVM and J48 showed best results with an ensemble of features.

Another fascinating approach to the problem is by using second order features of Gray Level Co-occurrence Matrix. Daniela et al [10] calculated features like Entropy, Energy, Homogeneity and Correlation from the Hippocampus as an ROI to use as a basis for classification.

2.2 Pipeline

In this approach, we simplify things and reduce computational time and instead of the cumbersome VBM approach, we try to improve the results by feeding a promising ensemble of features to the classifier – a combination of textures extracted using GLCM, the ratio of the Gray Matter volume and the White Matter Volume to the Cerebrospinal Fluid Volume. Literature says atrophies are also seen in the CSF and other areas of GM apart from the Hippocampus. [4] Since concentrating just on the hippocampal region for volume calculation is narrow in approach and tedious because it cuts down the chances of other atrophies and also involves accurate extraction and subsequent calculation and cannot be done without help from a Neuro-radiologist, we can make use of the a ratio with the gray matter and the CSF and a similar ratio of the white matter and CSF and hence assure a more intensive learning, therefore, better results due to a reduced dataset.

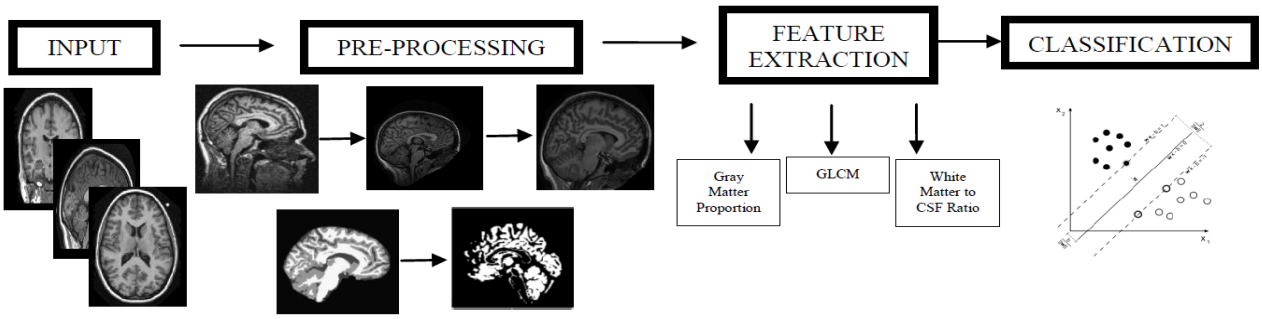

Figure 3: Pipeline showing different stages in the method. The Input consists of a 3D NIFTI data which is Skull stripped, Atlas registered, Motion Corrected and Thresholded in the Pre-processing step. This is followed by Feature Extraction which is then classified using SVM Classifier

CHAPTER 3: METHODOLOGY

3.1 Data

The Magnetic Resonance Imaging data for the proposed model has been obtained from Open Access Series of Imaging Studies (OASIS) database that originally consists of cross sectional and longitudinal MR images of 416 subjects aged 18-90 years. OASIS is a project aimed at making MRI data sets of the brain freely available to the scientific community. By compiling and freely distributing MRI data sets, they hope to facilitate future discoveries in basic and clinical neuroscience. [11] OASIS is made available by the Washington University Alzheimer's Disease Research Center, Dr. Randy Buckner at the Howard Hughes Medical Institute (HHMI) at Harvard University, the Neuro-informatics Research Group (NRG) at Washington University School of Medicine, and the Biomedical Informatics Research Network (BIRN).

Dementia in older people is common. The reduction in gray matter due to aging can also be categorized as a kind of dementia. But AD is also seen in young adults who have just crossed their teens. And since females, generally, pose a higher risk of developing the disease, and the brain structure is different in males and females, we only analyze female patients' MRIs in our study. [12]

It has also been seen that the brain structures of right and left handed people are different. Since majority of people are right handed, we will consider only those groups.

Thus our dataset consists of MR images of the brains of young right handed females of the age group 18-96 years. The images are T1 weighted and include both classes of data-people with AD and Cognitive Normal (CN) people i.e. people without the disease or any kind of dementia (who were tested negative only in the second MRI session which was held 90 days after the first). Crucial data regarding the subjects apart from the age, sex and handedness have also been provided along with the dataset for reference, like the Total Intra-cranial volume (TIV), the Clinical Dementia Ratio (CDR) and nWBV. CDR ratings vary from 0 to 2 with 0 being for non-demented, 0.5-very mild dementia, 1-mild dementia and 2-moderate dementia.[11]

The dataset mainly had Nifti files which include both hdr and img files. Each Nifti file in nii format gives a 3-Dimensional image showing all three views of the brain at different pixel positions (Axial, Coronal and Sagittal). Figure 4 shows a 3D view of the brain at the pixel position [88 104 88].

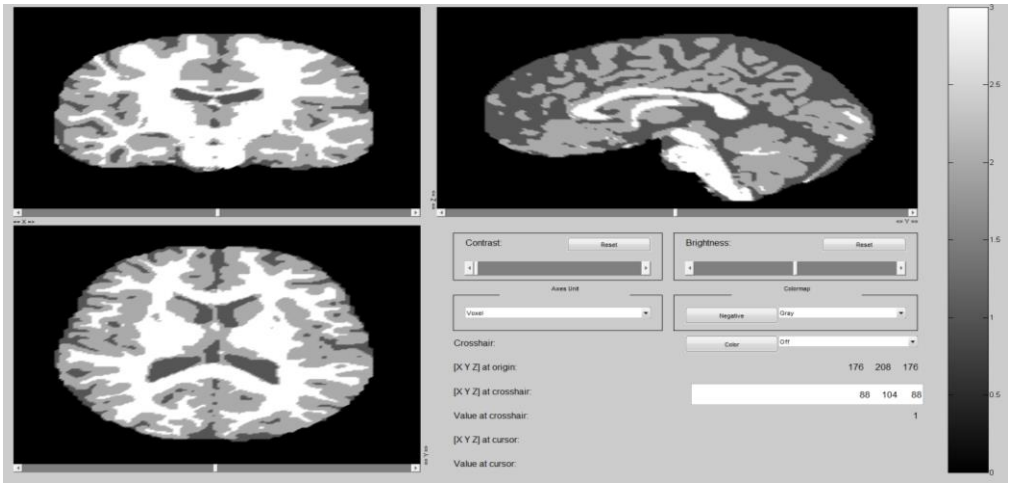

Figure 4: The Coronal, Sagittal and Axial views of the Brain MRI (segmented) at pixel position [88 104 88].

3.2 Preprocessing

The dataset was processed so that it could properly cater to the method requirements. Each dataset consists of 3D MR images from the sagittal, coronal and transversal views. After acquisition, the images were first defaced and then ATLAS registered gain field corrected and motion corrected. Because brain scans may differ in size and shape for individual subjects, wrapping these to same template will help in identification of the anatomical structures. In our approach we used most widely used brain template, that is, Talairach and Tournoux coordinate system.[11]

The brain image primarily consists of the White Matter (WM), the Grey Matter (GM) and the Cerebrospinal Fluid (CSF). These important tissue intensities may overlap with the other regions of the head after thresholding like the bone and skin. Therefore, there is a strong chance that the presence of these non-brain pixels in MR image may reduce the reliability of identifying interested brain regions. For this purpose we require that non-brain pixels be trimmed off the MR image. Brain surface extraction [13] is a preprocessing step in which non-brain tissue is removed from the MRI. The extraction parameter is set to 0.5 for optimal results.

A subsequent step included increasing the contrast in the images such that there is a clear distinction between the WM, GM and CSF. The Finite Fixture Method has simple mathematics but is ineffective with high noise. Thus the Hidden Markov Random Field

Model and Expectation Maximization (HMRF-EM) [21] algorithm after Otsu's Thresholding [22] was used.

- The maximum interclass variance is the desired threshold. This gives us initial parameter set $\Theta(0)$ and initial labels x(0).
- In an HMRF-EM segmentation implementation, if
    - $y=[y_1, y_2,\ldots y_n]$ represents an image where y_i is the intensity of pixels,
    - $x=[x_1, x_2,\ldots x_n]$ are all possible labels for classes
- With the EM algorithm using Θ, a parameter set is obtained iteratively till $Q(\Theta|\Theta(t))$ maximizes.
- For each parameter set, label sets are obtained. This repeats till total posterior energy is minimized i.e $x^* = \text{argmin}_{x\in\chi} \{U(y|x, \Theta) + U(x)\}$ (Hammersley–Clifford theorem).

The three intensities were labelled 1, 2 and 3 for White Matter, Gray Matter and CSF respectively.

3.3 Feature Extraction

After threshold, the Grey Matter, WM and CSF were extracted for further feature extraction. The GM, WM and CSF were of different intensities and labelled differently. This helped to distinguish and obtain the required regions. The features that were extracted for this proposed study were as follows:

1) Grey Level Co-occurrence Matrix features: The GLCM is a measure of how often different combinations of grey levels occur in an image at a fixed orientation and distance. A co-occurrence matrix $P_{d,\theta}$, is a two-dimensional array of size n × n, where n is the number of grey levels in an image. The (i,j)th element of $P_{d,\theta}$ is the probability of transition from a pixel with intensity i to a pixel with intensity j lying at distance d with a given orientation θ in the

$$Contrast = \sum_{i,j} \mid i-j \mid^2 \log P_{d,\theta}(i,j)$$

$$Correlation = \sum_{i,j} \frac{(i-\mu_1)(j-\mu_2)P_{d,\theta}(i,j))}{\sigma_1\sigma_2}$$

$$Homogeneity = \sum_{i,j} \frac{P_{d,\theta}(i,j)}{1+\mid i-j \mid^2}$$

$$Entropy = -\sum_{i,j} P_{d,\theta}P_{d,\theta}(i,j)$$

image. [14]

Using co-occurrence matrix, texture related features can be defined that have high discriminatory power. Contrast, correlation, homogeneity and entropy are few such commonly used measures.

Contrast is a measure of local level variations. High values are for image of high contrast. Correlation is a measure of association between pixels in two different directions. Homogeneity is a measure that takes high values for low-contrast images. It shows the level of uniformity in the intensities in an image. Entropy is the measure of randomness and takes low values for smooth images. Together all these features provide high distinction power to distinguish between two different kinds of images. [14]

Each 3 D nii image was divided into 11 slices at an interval of 16 pixels (The thickness was of 176 pixels). Second order statistics based features were built from co-occurrence matrix with d=1 and Θ = {0^o, 45^o, 90^o, 135^o} for each slice and were averaged to give the GLCM second order properties for the whole 3D image. An offset of [1 0] was defined with a gray limit of [0 1].

2) Gray Matter Proportion: Due to the atrophies seen in specific regions in the Grey Matter like the Hippocampus and Amygdala, we calculate a feature that would take both these structures into account and at the same time and not involve the cumbersome process of extraction of these structures individually. This feature is the ratio of the Grey Matter Volume and the Volume of the Cerebrospinal Fluid. Gray Matter can be obtained by extracting the pixels in the image labelled as 2. The segmented GM is used to calculate the GMV using the following equation:

$$Volume_{GM} = - \sum_{slice=1}^{n} \sum_{i=1}^{x} \sum_{j=1}^{y} f(i,j) == 2$$

The normalization of brain volume helps to remove the anomaly that may arise due to different brain sizes in different human beings. [15] This GMV is further used to calculate the ratio by dividing with CSF Volume calculated by the following equations:

$$Volume_{CSF} = - \sum_{slice=1}^{n} \sum_{i=1}^{x} \sum_{j=1}^{y} f(i,j) == 3$$

3) White Matter Volume to Cerebrospinal Volume Ratio: Literature states that there is a slight reduction in the White Matter volume too additionally along with a simultaneous expansion in the volume of the Cerebrospinal Fluid in AD patients. [4] This gives us another feature for our classification that is the ratio of the White Matter Volume to the Cerebrospinal Volume with the help of the following equations:

$$Volume_{WM} = - \sum_{slice=1}^{n} \sum_{i=1}^{x} \sum_{j=1}^{y} f(i,j) == 1$$

White Matter, Gray Matter and CSF are segmented from the Whole Brain by extracting pixels labelled as 1, 2 and 3 respectively. Then their volumes' ratio is taken which is a feature for our classifier.

3.4 Classification

The method involves classification of the available datasets into AD and CN classes as its final step. Since the number of classes required is two i.e. AD or CN, we use binary classification for the purpose.

Earlier works have used multiple available classifiers and have compared results to show that Support Vector Machines (SVM) give the best results in binary classification. [9] SVMs are supervised learning models that can be trained and tested in multiple folds to give the best results. The most fascinating thing about SVMs is that its performance does not get affected by the size of the dataset. Its dimensionality only varies with the number of feature inputs fed to the machine for classification.

Our feature vector was 6 dimensional because our classification was based on 6 features of the datasets vis-à-vis Gray Matter Proportion, Ratio of White Matter to CSF Volume, Contrast, Correlation, Homogeneity and Entropy. The accuracy, sensitivity and specificity were

calculated using the Confusion Matrix. [23] A confusion matrix (Kohavi and Provost, 1998) contains information about actual and predicted classifications done by a classification system. Performance of such systems is commonly evaluated using the data in the matrix. The following table shows the confusion matrix for a two class classifier.

The entries in the confusion matrix have the following meaning:

- *a* is the number of correct predictions that an instance is negative,
- *b* is the number of incorrect predictions that an instance is positive,
- *c* is the number of incorrect of predictions that an instance negative, and
- *d* is the number of correct predictions that an instance is positive.

•		Predicted	
		Negative	Positive
Actual	Negative	**a**	**b**
	Positive	**c**	**d**

CHAPTER 4: RESULTS

4.1 Case 1:

The MRI images are of 176 X 208 X 176 pixels. In the first case, we take 11 slices of the MR images, i.e. every 16 pixels, we take one slice and extract GLCM features. Then we average the features over all 11 slices. The Grey Matter and White Matter volume ratios are taken over the entire MR of the brain.

A 2-fold, 5-fold and 10 –fold cross validation process is carried out. The samples are divided into 5 (or 2 or 10) subsamples. One of the subsamples is retained as the testing data and the remaining 4 (or 1 or 9) subsamples are used as the training data. This is repeated for 5 (or 2 or 10) iterations, using one of the subsamples as testing data each time.

Average accuracy calculated was recorded as follows:

Folds	Accuracy
2	82%
5	73%
10	76%

4.2 Case 2:

In the second case, we only take the slices of the MR Images that contribute to the hippocampal and amygdala regions. The GLCM from these slices are averaged and fed to the classifier along with the Grey and White Matter volume ratios.

2-fold, 5-fold and 10-fold cross validations are carried out again and average accuracy was recorded as follows:

Folds	Accuracy
2	83%
5	73.3%
10	75%

4.3 Case 3:

In the third case, we only take 1 slice of the MR image, i.e. the centre slice. The hippocampal and amygdala regions are clearly visible in this slice. GLCM was calculated and fed to the classifier along with Grey and White Matter volume ratios.

2-fold, 5-fold and 10-fold cross validations are carried out again and average accuracy was recorded as follows:

Folds	Accuracy
2	84%
5	73.3%
10	78%

CHAPTER 5: CONCLUSION

The results had a perfect **sensitivity** of **100%** in each case. The accuracy is the highest in the 2-fold cross validation for Case 3 where only one slice of the MR image was considered.

The high sensitivity shows that even though all cases were detected with dementia during the first MRI session, some were declared as non-cognitive after the subsequent session. The method proved to be 100% effective for diagnosing the patients based on their MRI.

The method has a higher efficiency as compared to the VBM method which has shown a sensitivity of 85% [16], although VBM helps show the comparison of MRI of patients with early and late onset of AD. The method although performs worse than methods which have used features localized to the Hippocampal area also, which have shown an accuracy of 87.5% with SVM. They have shown an accuracy of 93.75% when they have used an ensemble of classifiers like SVM, MLP and J48. [4]

The same experiment was carried out with a limited dataset of female right handed patients between the ages 18-30 years. It showed an accuracy of 86.36% when 90% of the data was used for training and 10% for testing. The brain size and dementia levels do get affected with age. This shows that accuracy of classification increases when dataset within similar age group in taken.

The limitations were in getting only the regions from the MR images that were atrophied in case of Alzheimer's. This is only possible if we have annotations by doctors. The closest we could get in this study was only considering the slice with the maximum hippocampal and amygdala regions (case 3) and it does show a higher accuracy in that case.

CHAPTER 6: REFERENCES

[1] Joseph F. Norfray and James M. Provenzale, “Alzheimer’s Disease: Neuropathologic Findings and Recent Advances in Imaging”, AJR 2004;182:3–13 0361–803X/04/1821–3

[2] Life Extension, Health Concerns “http://www.lef.org/protocols/neurological/alzheimers-disease/page-01”

[3] 2014 Alzheimer’s Disease, Facts and Figures, Alzheimer’s Association, United States, “http://www.alz.org/downloads/Facts_Figures_2014.pdf”

[4] Chester V. Dolph, Manar D. Samad, Khan M. Iftekharuddin, “Classication of Alzheimer's disease using structural MRI,” Vision Lab, Old Dominion University, Norfolk, VA 23529.

[5] Escudero, J., J. P. Zajicek, and E. Ifeachor. "Machine Learning classification of MRI features of Alzheimer's disease and mild cognitive impairment subjects to reduce the sample size in clinical trials." Engineering in Medicine and Biology Society, EMBC, 2011 Annual International Conference of the IEEE. IEEE, 2011.

[6] Fox, Nick C., Peter A. Freeborough, and Martin N. Rossor. "Visualisation and quantification of rates of atrophy in Alzheimer's disease." The Lancet 348.9020 (1996): 94-97.

[7] Good, Catriona D., et al. "A voxel-based morphometric study of ageing in 465 normal adult human brains." Biomedical Imaging, 2002. 5th IEEE EMBS International Summer School on. IEEE, 2002.

[8] Savio, Alexandre, Manuel Grańa, and Jorge Villanúa. "Deformation based features for Alzheimer’s disease detection with linear SVM." Hybrid Artificial Intelligent Systems. Springer Berlin Heidelberg, 2011. 336-343.

[9] Farhan, Saima, Muhammad Abuzar Fahiem, and Huma Tauseef. "An Ensemble-of-Classifiers Based Approach for Early Diagnosis of Alzheimer’s Disease: Classification Using Structural Features of Brain Images." Computational and mathematical methods in medicine 2014 (2014).

[10] Daniela M. Ushizima, Andrea G. C. Bianchi, Weihong Guo, “Characterization Of MRI Brain Scans associated to Alzheimer’s Disease through texture analysis”, Computational Research Division, Lawrence Berkley National Laboratory.

[11] Marcus, Daniel S., et al. "Open Access Series of Imaging Studies (OASIS): cross-sectional MRI data in young, middle aged, nondemented, and demented older adults." Journal of cognitive neuroscience 19.9 (2007): 1498-1507.

[12] Chyzhyk, Darya, and Alexandre Savio. Feature extraction from structural MRI images based on VBM: data from OASIS database. Technical Report GIC-UPV-EHU-RR-2010-10-14, Grupo de Inteligencia Computacional UPV/EHU, 2010.

[13] Somasundaram, K., and T. Kalaiselvi. "Automatic brain extraction methods for< i> T</i> 1 magnetic resonance images using region labeling and morphological operations." Computers in biology and medicine 41.8 (2011): 716-725.

[14] Aggarwal, Namita, Bharti Rana, and R. K. Agrawal. "Detection of Alzheimer's Disease via Statistical Features from Brain Slices." The Twenty-Sixth International FLAIRS Conference. 2013.

[15] Whitwell, Jennifer L., et al. "Normalization of cerebral volumes by use of intracranial volume: implications for longitudinal quantitative MR imaging." American Journal of Neuroradiology 22.8 (2001): 1483-1489.

[16] Ishii, Kazunari, et al. "Voxel-based morphometric comparison between early-and late-onset mild Alzheimer's disease and assessment of diagnostic performance of z score images." American Journal of Neuroradiology 26.2 (2005): 333-340.

[17] Gadkari, Dhanashree. Image quality analysis using GLCM. Diss. University of Central Florida Orlando, Florida, 2004.

[18] Belmokhtar, Nabil, and Nacéra Benamrane. "Classification of Alzheimer's Disease from 3D Structural MRI Data." Age 78.8 (2012): 69-96.

[19] Ehsanirad, Abdolvahab, and Y. H. Sharath Kumar. "Leaf recognition for plant classification using GLCM and PCA methods." Oriental Journal of Computer Science and Technology 3.1 (2010): 31-36.

[20] "Brain Structure and Functions", Serendip Studio, http://serendip.brynmawr.edu/bb/kinser/Structure1.html

[21] Zhang, Yongyue, Michael Brady, and Stephen Smith. "Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm." Medical Imaging, IEEE Transactions on 20.1 (2001): 45-57.

[22] Wikipedia contributors. "Otsu's method." Wikipedia, The Free Encyclopedia. Wikipedia, The Free Encyclopedia, 29 Feb. 2016. Web. 30 Mar. 2016.

[23] "Confusion Matrix", http://www2.cs.uregina.ca/~dbd/cs831/notes/confusion_matrix/confusion_matrix.html