COMPUTER-AIDED DIAGNOSES (CAD) SYSTEM: AN ARTIFICIAL
NEURAL NETWORK APPROACH TO MRI ANALYSIS AND
DIAGNOSIS OF ALZHEIMER'S DISEASE (AD)

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ABSTRACT

Computer-Aided Diagnoses (CAD) System: An Artificial Neural Network Approach to MRI Analysis and Diagnosis of Alzheimer's Disease (AD)

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Alzheimer's disease (AD) is a chronic and progressive, irreversible syndrome that deteriorates the cognitive functions. Official death certificates of 2013 reported 84,767 deaths from Alzheimer's disease, making it the 6th leading cause of death in the United States. The rate of AD is estimated to double by 2050. The neurodegeneration of AD occurs decades before symptoms of dementia are evident. Therefore, having an efficient methodology for the early and proper diagnosis can lead to more effective treatments.

Neuroimaging techniques such as magnetic resonance imaging (MRI) can detect changes in the brain of living subjects. Moreover, medical imaging techniques are the best diagnostic tools to determine brain atrophies; however, a significant limitation is the level of training, methodology, and experience of the diagnostician. Thus, Computer aided diagnosis (CAD) systems are part of a promising tool to help improve the diagnostic outcomes. No publications addressing the use of Feedforward Artificial Neural Networks (ANN), and MRI image attributes for the classification of AD were found.

Consequently, the focus of this study is to investigate if the use of MRI images, specifically texture and frequency attributes along with a feedforward ANN model, can lead to the classification of individuals with AD. Moreover, this study compared the use of a single view versus a multi-view of MRI images and their performance. The frequency, texture, and MRI views in combination with the feedforward artificial neural network were tested to determine if they were comparable to the clinician's performance. The clinician's performances used were 78 percent accuracy, 87 percent sensitivity, 71 percent specificity, and 78 percent precision from a study with 1,073 individuals.

The study found that the use of the Discrete Wavelet Transform (DWT) and Fourier Transform (FT) low frequency give comparable results to the clinicians; however, the FT outperformed the clinicians with an accuracy of 85 percent, precision of 87 percent, sensitivity of 90 percent and specificity of 75 percent. In the case of texture, a single texture feature, and the combination of two or more features gave results comparable to the clinicians. However, the Gray level co-occurrence matrix (GLCOM), which is the combination of texture features, was the highest performing texture method with 82 percent accuracy, 86 percent sensitivity, 76 percent specificity, and 86 percent precision. Combination CII (energy and entropy) outperformed all other combinations with 78 percent accuracy, 88 percent sensitivity, 72 percent specificity, and 78 percent precision. Additionally, a combination of views can increase performance for certain texture attributes; however, the axial view outperformed the sagittal and coronal views in the case of frequency attributes. In conclusion, this study found that both texture and frequency characteristics in combinations with a feedforward backpropagation neural network can perform at the level of the clinician and even higher depending on the attribute and the view or combination of views used.

Keywords: Alzheimer's disease, artificial neural networks, feedforward, MRI, image attributes, texture, frequency, Fourier Transform, Discrete Wavelet Transform, GLCOM, energy, entropy, correlation, contrast, axial, sagittal, coronal, ADNI

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“Let the future tell the truth, and evaluate each one according to his work and accomplishments. The present is theirs; the future, for which I have really worked, is mine.”

-Nikola Tesla

TABLE OF CONTENTS

	Page
LIST OF TABLES.....	xi
LIST OF FIGURES	xiii
LIST OF EQUATIONS	xiv
CHAPTER	
CHAPTER 1: INTRODUCTION	1
1.1 Alzheimer’s Disease	1
1.1.1 Overview of Alzheimer’s disease	1
1.1.2 Symptoms	2
1.1.3 Alzheimer’s Diagnosis.....	4
1.1.4 Computer Aided Diagnostic (CAD) system	4
1.2 Project Justification.....	4
1.2.1 Overview	4
1.2.2 Specific Aims.....	6
1.2.3 Project Goal	7
CHAPTER 2: LITERATURE REVIEW	8
2.1 Overview of AD.....	8
2.1.1 Etiology.....	8
2.1.2 Prevalence and Risk Factors	8
2.1.2.1 Genetic Factors	9
2.1.2.2 Aging.....	10
2.1.2.3 Additional factors.....	11
2.1.3 Diagnosis Methods.....	11
2.1.3.1 Background	11
2.1.3.2 Recent Diagnosis Modifications	12
2.1.4 Imaging as Diagnostic Tools	13
2.1.5 MRI Imaging and Its Limitations	13
2.1.6 Current Treatments	14
2.2 Computer Aided Diagnosis (CAD) Systems	15
2.2.1 Overview	15

2.2.2 Background	15
2.2.3 Automated Computer Diagnosis and CAD.....	16
2.2.4 CAD system	17
2.2.5 CAD systems performance	17
2.2.6 Artificial Neural Network	18
2.2.7 Feature identification	19
CHAPTER 3: PROJECT APPROACH	20
3.1 Background	20
3.1.1 ADNI database.....	20
3.1.2 MATLAB neural network toolbox	20
3.1.3 Brain regions	20
3.2 Approach Overview	21
CHAPTER 4: MATERIALS	23
4.1 MRI Images	23
4.2 Subjects data	23
4.2.1 Normal control (NC) subjects and Alzheimer's disease (AD) subjects	23
4.3 The Software and hardware	23
4.4 MRI acquisition	24
CHAPTER 5: STAGE ONE: PILOT STUDY	25
5.1 Materials for pilot study.....	25
5.2 Sample size and demographics	25
5.3 Methods.....	25
5.3.1 Image pre-processing.....	25
5.3.1.1 Sagittal images	25
5.3.2 Axial images	27
5.4 Image processing	29
5.4.1 Frequency Domain Processing	30
5.4.1.1 Fourier Transform.....	30
5.4.2 Statistical approach	31
5.4.2.1 Properties of gray-level co-occurrence matrix.....	31

5.4.3 Contrast	33
5.4.4 Correlation	33
5.4.5 Energy	34
5.4.6 Homogeneity	34
5.4.7 Entropy	35
5.5 Artificial Neural Network	35
5.5.1 Neural Network structure	35
5.5.2 Training Function and Cut off value	36
5.6 Stage One Results	37
5.6.1 Features relevance	37
5.6.2 Fourier Transform	37
5.6.2.1 Magnitude results	37
5.6.2.2 Phase results	38
5.6.3 Contrast results	39
5.6.4 Correlation results	40
5.6.5 Energy results	41
5.6.6 Homogeneity	42
5.6.7 Entropy	43
5.7 Artificial Neural Network	43
5.7.1 Classifier and performance evaluation	43
5.8 Summary of Results	51
CHAPTER 6: STAGE TWO TEXTURE AND FREQUENCY RESULTS	52
6.1 Materials	52
6.2 Methods	52
6.3 Transforms comparison at low frequencies	53
6.3.1 Fourier Transform (FT)	53
6.3.2 Discrete Wavelet Transform (DWT)	53
6.3.3 Feature extraction	55
6.4 Artificial Neural Networks (ANN)	55
6.4.1 Network structure	55
6.4.2 Classifier and performance evaluation	55

6.4.3 Cutoff values	56
6.5 Stage two results	57
6.5.1 Transform results and comparison.....	57
6.5.1.1 Discrete Wavelet Transform (DWT) Results	57
6.5.1.2 Fourier Transform (FT) Results.....	59
6.5.2 Texture features (TF)	61
6.5.2.1 Texture features and entropy results	61
6.5.2.2 Individual texture features performance	62
6.5.2.3 Combination of features.....	64
6.6 Statistical results	69
6.7 Summary of Results	70
CHAPTER 7: STAGE THREE VIEW COMPARISON RESULTS	73
7.1 Materials	73
7.2 Methods.....	73
7.2.1 Fourier transforms.....	73
7.3 Statistical results	78
7.4 Summary of results	79
CHAPTER 8: DISCUSSION.....	81
8.1 MRI texture and frequency attributes	81
8.2 Single view performance vs. combination of views	86
8.3 Network performance	88
CHAPTER 9: CONCLUSION AND FUTURE WORK.....	91
9.1 Conclusion	91
9.2 Future work.....	92
REFERENCES	94
APPENDICES	
Appendix A	101
Appendix B.....	103
Appendix C.....	104
Appendix D	106
Appendix E.....	107

Appendix F	108
Appendix G	109

LIST OF TABLES

Table	Page
Table 2.1: Alzheimer's Disease Brain Observations After Autopsy.....	8
Table 2.2: Established Alzheimer's genes and their functional relevance.	9
Table 2.3: FDA Approved AD Therapies.....	14
Table 5.1: Summary of P-Value for Maximum and Minimum Magnitudes	38
Table 5.2: Summary of P-Values for Minimum and Maximum Phase	39
Table 5.3: Summary of P-Values and Confidence Interval for Contrast.....	40
Table 5.4: Summary of Correlation P-Values Among AD and NC groups.....	41
Table 5.5: Summary of Energy P-Values for Both AD and NC groups.....	41
Table 5.6: Summary of Homogeneity P-Values for AD and NC Groups	42
Table 5.7: Summary of Entropy P-Values for All AD and NC Groups	43
Table 5.8: ANN-Backpropagation Structure Results.....	45
Table 6.1: Discrete Wavelet Transform training results for both window size	58
Table 6.2: Discrete Wavelet Transform testing results for both window sizes	59
Table 6.3: Fourier transform training results for both window sizes.....	60
Table 6.4: Fourier Transform testing results for both widow sizes.	60
Table 6.5: Training results for Gray level co-occurrence matrix (GLCOM), and Gray level co-occurrence matrix (GLCOM) + entropy.....	61
Table 6.6: Testing results for Gray level co-occurrence matrix (GLCOM), and Gray level co-occurrence matrix (GLCOM) + entropy.....	62
Table 6.7: Training performance for individual texture features.....	63
Table 6.8: Testing performance for individual texture features	64
Table 6.9: Training results for combination A.....	65
Table 6.10: Testing results for combination A	66
Table 6.11: Training results for combination B.....	67
Table 6.12: Testing results for combination B.....	67
Table 6.13: Training results for combination C and D	69
Table 6.14: Testing results for combination C and D.....	69
Table 7.1: Training performance of each view's Fourier Transform	74

Table 7.2: Testing performance of each view's Fourier Transform	74
Table 7.3: Training results for all three views using the GLCOM	75
Table 7.4: Testing results for all three views using the GLCOM	75
Table 7.5: Training results for all three views using the combination of correlation values	76
Table 7.6: Training results for all three views using the combination of correlation values.....	76
Table 7.7: Training results for combination CII (energy and entropy).....	77
Table 7.8: Testing results for combination CII (energy and entropy)	77
Table C.1: Group A definition of combinations	104
Table C.2: Group B definition of combinations	104
Table C.3: Group C definition of combinations	104
Table C.4: Group D definition of combinations	105

LIST OF FIGURES

Figure	Page
Figure 1.1: Neuron Comparison in AD.....	1
Figure 1.2: 10 Early Signs and Symptoms of Alzheimer's.	3
Figure 1.3: Time base diagram the effect of early diagnosis.	5
Figure 2.1: Pathophysiology of Alzheimer's disease.	10
Figure 2.2: Decision tree for an individual tested for Alzheimer's disease (AD).	13
Figure 2.3: Historical timeline of CAD systems.....	16
Figure 3.1: Regions of interest and brain comparison among AD and HC.	21
Figure 5.1: Sagittal ROI Process Extraction.	26
Figure 5.2: Axial ROI Process Extraction.	28
Figure 5.3: Thickness ROI Process Extraction.	29
Figure 5.4: Multilayer Feedforward Backpropagation Artificial Neural Network Structure.....	36
Figure 5.5: MATLAB Neural Network Interface.	47
Figure 5.6: Performance Plot for Selected Network.	48
Figure 5.7: Histogram of Networks Performance.	49
Figure 5.8: Regression Plot at Minimum Gradient of 15 epochs	50
Figure 7.1: Box Plot of NC and AD subject for each view.	78
Figure 8.1: Principal Components plot for Texture features.	85
Figure A.1: Structure 1:35 with 9 inputs and 1 output	101
Figure A.2: Structure 2:35 with 16 inputs and 1 output	101
Figure A.3: Structure 1:15 with 9 inputs and 1 output.	102
Figure B.1: Structure 1:35 with 8 inputs and 1 output (combination of any two features except entropy).....	103
Figure G.1: Comparison plot of single view and combination view of CII	109
Figure G.2: Correlation Comparison Plot single view vs. combination view	110

LIST OF EQUATIONS

Equation	Page
(5.1).....	26
(5.2).....	30
(5.3).....	30
(5.4).....	31
(5.5).....	31
(5.6).....	32
(5.7)	32
(5.8).....	33
(5.9)	33
(5.10).....	34
(5.11).....	34
(5.12).....	35
(5.13).....	36
(5.14).....	37
(5.15).....	37
(5.16).....	44
(5.17).....	44
(5.18).....	44
(5.19).....	45
(6.1)	54
(6.2)	54
(6.3)	54

CHAPTER 1: INTRODUCTION

1.1 Alzheimer's disease

1.1.1 Overview of Alzheimer's disease

Alzheimer's disease (AD) is known to be the most common form of dementia, comprising 70 percent of all dementia cases [1]. Dementia is a chronic and progressive, irreversible syndrome that deteriorates the cognitive functions. In AD, there is a gradual damage to the neurons which causes them to stop functioning, lose connections, and ultimately die [2], (**Figure 1.1**).

Figure 1.1: Neuron Comparison in AD.

AD aggressively destroys neurons and their connections in several regions of the brain related to memory, entorhinal cortex, and hippocampus [2]. Alzheimer's disease damage to the brain is irreversible and extremely severe. The impact of the condition is such that eventually, the individual affected stops performing basic tasks.

1.1.2 Symptoms

Alzheimer's disease studies indicate that symptoms might be part of an already progressing disease and not initial onset. For example, an individual might already have Alzheimer's disease, but it does not show any indicators. Furthermore, the symptoms of AD can become present one at a time or few at a time; additionally, not all individuals experience the same signs [3].

Even though AD onset varies from individual to individual, there are common symptoms that can help classify the early and late stages of the disease [3].

Early symptoms: Difficulty remembering names, places, recent conversations, apathy, and depression

Late symptoms: Impaired communication, disorientation, confusion, poor judgment, and behavioral changes.

Acute late symptoms: Difficulty speaking, swallowing, and walking

The difficulty with AD characterization is the overlap of normal aging characteristics and AD symptoms. The difference becomes evident in the progression, re-incidence, and acuteness of the symptom. Ten typical characteristics of aging can become a sign for AD as they become more acute and severe, (**Figure 1.2** [4]).

MEMORY LOSS THAT DISRUPTS DAILY LIFE	<ul style="list-style-type: none"> •Age-related change: forgetting names or appointment, but remembering later •AD symptom: Forgetting a recently learned information, asking for the same information over and over, an increasing need for memory aids.
CHALLENGES IN PLANNING OR SOLVING PROBLEMS	<ul style="list-style-type: none"> •Age-related change: Occasional errors when balancing a checkbook or dealing with numbers •AD symptom: Change in the ability to develop and follow a plan, work with numbers, follow a familiar recipe and difficulty concentrating.
DIFFICULTY COMPLETING FAMILIAR TASKS AT HOME, AT WORK OR AT LEISURE	<ul style="list-style-type: none"> •Age-related change: Occasionally needing help with technology record a television show. •AD symptom: Difficulty completing a daily task. Trouble driving to a familiar location or remembering the rules of a favorite game.
CONFUSION WITH TIME OR PLACE	<ul style="list-style-type: none"> •Age-related change: Getting confused about the day of the week, but figuring it out later •AD symptom: Lose track of dates, seasons and the passing of time.
TROUBLE UNDERSTANDING VISUAL IMAGES AND SPATIAL RELATIONSHIPS	<ul style="list-style-type: none"> •Age-related change: Vision changes due to cataracts or other eye problems •AD symptom: Difficulty reading, judging distances, and determining color or contrast
NEW PROBLEMS WITH WORDS IN SPEAKING OR WRITING	<ul style="list-style-type: none"> •Age-related symptom: Having trouble finding the right word •AD symptoms: Trouble following or joining a conversation. Stop in the middle of a conversation or repeat themselves over and over.
MISPLACING THINGS AND LOSING THE ABILITY TO RETRACE STEPS	<ul style="list-style-type: none"> •Age-related change: Misplacing things from time to time and retracing steps to find them •AD symptom: Put things in unusual places. Unable to retrace their steps to track misplaced items.
DECREASED OR POOR JUDGMENT	<ul style="list-style-type: none"> •Age-related change: Making a bad decision once in a while •AD symptom: Changes in judgment or decision-making. Lack of self-grooming.
WITHDRAWAL FROM WORK OR SOCIAL ACTIVITIES	<ul style="list-style-type: none"> •Age-related change: Sometimes feeling weary of work, family or apathetic to social obligations •AD symptom: Forgetting how to complete a hobby, or play a favorite sport, and ultimately removing themselves from social activities, work projects or sports.
CHANGES IN MOOD AND PERSONALITY	<ul style="list-style-type: none"> •Age-related change: Developing a specific way of doing things and become irritable when a routine is disrupted. •AD symptom: Mood and personality changes, becoming confused, suspicious, depress, fearful or anxious.

Figure 1.2: 10 Early Signs and Symptoms of Alzheimer's.

AD symptoms have an overlap with age-related changes. However, AD symptoms are severe, permanent, frequent, and ultimately alter the overall behavior and mood of the individual [4].

1.1.3 Alzheimer's Diagnosis

The characteristics of Alzheimer's disease, aging changes, and other forms of dementia are highly similar that making a proper diagnosis becomes complex. Thus, as with any other medical condition, a proper diagnosis can lead to a more successful treatment. However, currently, there are not reliable tests that can definitively diagnose AD in living individuals [5].

1.1.4 Computer Aided Diagnostic (CAD) systems

In a medical setting, human error becomes a limiting factor for proper diagnosis due to the complexity of the human eye-brain system, the training, and the experience of the diagnostician. Additionally, some situations can further influence a diagnosis such as physical fatigue, distractions, and biases. Consequently, the introduction of image enhancement or medical imaging has emerged, and even though extremely useful, it cannot aid with fatigue or distractions [6]. For many conditions, a proper and early diagnosis can be the difference between life and death; therefore, a tool that can minimize human error and aid diagnosis, is nothing less than essential [7]. Computer Aided Diagnosis (CAD) systems aim to enhance current diagnostic methods.

1.2 Project Justification

1.2.1 Overview

Official death certificates of 2013 reported 84,767 deaths from Alzheimer's disease, making it the sixth-leading cause of death in the United States. The rate of AD is estimated to double by 2050 due to the large number of aging individuals especially in United States, China, and India [8] [9]. Moreover, the current cost associated with AD

will also increase from \$100 billion to a \$116 billion per year [10]. The neurodegeneration of AD occurs decades before symptoms of dementia are evident. PET and MRI images of individuals between 20-39 years of age with AD biomarkers presented abnormally low rates of glucose metabolism in the areas known to be affected by AD (parietal, temporal, and prefrontal cortex) [11]. Therefore, having an efficient methodology for the early and proper diagnosis can lead to better treatments, (**Figure 1.3**). However, the issue is in the method for a non-invasive, proper, and early diagnosis. Due to the pathological overlapping of the clinical symptoms of dementia, many individuals can be misdiagnosed, leading to the use of wrong medications with unknown health consequences. A report suggested that the number of people giving inappropriate medication can be as high as 67.10 percent [12].

Figure 1.3: Time base diagram the effect of early diagnosis.

Early diagnosis combined with effective treatment can improve individual's overall quality of life [13]. An early and accurate diagnosis of AD, even before clinical

symptoms appeared can aid individuals to take preventive measures before they lose the ability to do so [14] [15].

1.2.2 Specific Aims

The principle questions to be investigated through this thesis are as follows:

- Aim 1: Investigate if texture image attributes and frequencies domains attributes from MRI images contain valid information which can serve as classification attributes, and therefore aid for the classification of Alzheimer's disease.
- Aim 2: Investigate if one view of an MRI image gives comparable results vs. using a combination of three views (axial, coronal, and sagittal).
- Aim 3: Investigate if the combination of a feedforward artificial neural network, texture and frequency attributes from MRI images achieve the same level of performance as the clinicians

1.2.3 Project Goal

Computer aided diagnosis (CAD) systems are part of a larger number of efforts being made to identify the proper approach for machine learning programming. An Artificial Neural Network (ANN) system which utilizes image processing techniques can offer an alternative approach to the current CAD systems. Additionally, there is no consensus on the best image attributes for the identification of AD. The goal of this thesis is to investigate if the use of MRI images, specifically texture and frequency attributes in combination with a feedforward artificial neural network, can lead to the classification of individuals with Alzheimer's in comparison with the clinician's performance.

CHAPTER 2: LITERATURE REVIEW

2.1 Overview of AD

2.1.1 Etiology

A 51-year-old female patient that presented hallucination, language deficit, cognitive deficient, and memory loss was the first diagnosis of the neurodegenerative disease. After the patient's death in 1901, Dr. Alois Alzheimer performed microscopic analyses of her brain observing that there were structures identified as plaques and tangles. He also identified atherosclerotic changes (built up of plaque) in the large cerebral arteries matching several observations of other neurologists which performed similar observations in other patients [16]. These similar observations are among the most obvious abnormalities found in deceased individuals whose brains were microscopically analyzed, (Table 2.1).

Table 2.1: Alzheimer's Disease Brain Observations After Autopsy

Abnormality	Location	Description
Amyloid Plaques	Spaces between neurons	Plaques are in its majority formed by abnormal deposits of beta-amyloid.
Neurofibrillary tangles	Inside the neurons	Abnormal tau protein clumps
Loss of neural connections/cell death	Axon	Synaptic connections failure leads to degeneration of the brain, and ultimately dead

2.1.2 Prevalence and Risk Factors

Age influences AD prevalence. Individuals between ages 60-64 have about 1 percent occurrence of the disease while individuals 85 years and older have a higher

prevalence of 33 percent [17]. Even though aging plays a role in the onset and progression of AD, the syndrome is a complex multifactorial disease influenced by many other elements including environmental and genetic factors.

2.1.2.1 Genetic Factors

Some genetic factors increase the risk for AD. The genetics of AD show that the syndrome can be familial and sporadic. The autosomal inheritance of the disease occurs in less than 2 percent of AD individuals. The autosomal AD is present in an early onset and associated with specific genes. (**Table 2.2**). The clear majority have a sporadic and late-onset of AD accounting for 90-95 percent of the cases [18].

Table 2.2: Established Alzheimer's genes and their functional relevance

Gene (protein)	Chromosome	Inheritance	Role in AD pathogenesis
APP (amyloid precursor protein)	21	Autosomal dominant	Mutations in the APP gene promote cleavage at b or g sites leading to overproduction of A β
PSEN1 (presenilin 1)	14	Autosomal dominant	Mutations in the PS1 gene promote cleavage at the g site leading to overproduction of A β
PSEN2 (presenilin 2)	1	Autosomal dominant	Mutations in the PS2 gene promote cleavage at the g site leading to overproduction of A β
APOE (apolipoprotein E)	19	Modifies age of onset	Promotes the deposition of A β ?

PS1 is the most frequent form of the mutation while APP and PS2 are less common on their impact in the beta-amyloid protein. The A β is one of the principal components of senile plaques. The apolipoprotein E gene (APOE) is identified as a major risk-factor for late-onset AD [19].

Although the causes of sporadic forms of AD are not entirely understood, it is evident that with aging there are interactions between genetics and the environment that contribute to the onset. The primary genetic risk factor in the overall population is the

ApoE ϵ 4 allele which increases the accumulation of the amyloid-beta (A β) [18]. A significant decrease of β -amyloid₁₋₄₂ levels and an increase of tau proteins (p-Tau) lead to the formation of fibril tangles and the A β plaque that in turn resulted in neuron necrosis [20],(**Figure 2.1**).

Figure 2.1: Pathophysiology of Alzheimer's disease.

Low levels of β -amyloid₁₋₄₂ lead to amyloid accumulation into extracellular plaques.

Increase of p-Tau leads to intra-neurofibrillary tangles (NFT) [21]

2.1.2.2 Aging

The highest factor associated with Alzheimer's disease is aging. Most individuals with AD are people 65 years or older. About 44 percent of AD individuals are 75-84 years old, and about 15 percent are 65-74 years of age [3]. However, not all aging individuals are known to develop AD or other dementias.

2.1.2.3 Additional factors

Other factors are indirectly related to AD, which related to increasing other health conditions due to lifestyle. Mild cognitive impairment (MCI) individuals have a higher risk of developing Alzheimer's disease. Moreover, vascular health issues such as diabetes mellitus, raised blood pressure, obesity, hyperlipidemia among others cardio vascular diseases make vascular health a key factor underlying age-related cognitive decline [22]. Thus, is concluded that vascular health can influence the onset of AD. Consequently, Regular exercise, an active way of life, and a balanced diet can reduce the risk of vascular disorders and consequently the risk for AD [23].

2.1.3 Diagnosis Methods

2.1.3.1 Background

The characteristics of Alzheimer's disease, aging changes, and other forms of dementia are highly similar that making a proper diagnosis becomes complex. Thus, as with any other medical condition, a proper diagnosis can lead to a more successful treatment. However, currently, there are not reliable tests that can definitively diagnose AD in living individuals [5]. The current diagnosis of AD follows a specific clinical diagnosis criteria established in 1984. The National Institute of Neurological and Communicative Disorder and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) known as the NINCDS-ADRDA Alzheimer's criteria in combination with the Statistical Manual for Mental Disorders (DSM-IV-TR) were the original bodies that introduce the guide for AD diagnosis [24].

The NINCDS-ADRDA provides a table for the PROBABLE, POSSIBLE, and DEFINITE Alzheimer's disease diagnosis. The diagnosis is a multi-step process where

the first step is in identifying whether the patient has dementia or not. If dementia is present, then an assessment of what type of dementia the individual has is performed. An AD diagnosis focuses on identifying a memory disorder and a deficiency of at least one other cognitive area or a combination of physical deterioration [24]. Additionally, family history and laboratory results from a lumbar puncture, and Electroencephalogram (EEG) or a computerized tomography (CT) are also part of the assessment [25]. However, a major limitation of the current diagnostic methods is that A DEFINITIVE diagnosis can only occur after a brain biopsy or an autopsy.

2.1.3.2 Recent Diagnosis Modifications

Within the last few years, the clinical diagnosis of Alzheimer's disease has extended to include magnetic resonance imaging (MRI), and positron-emission tomography (PET) [2].(**Figure 2.2**). AD is a complex problem because of its diverse range of symptoms and because of its overlap with other conditions. Two agencies, The National Institute on Aging and the Alzheimer's Associations, are working together to revise the Diagnosis criteria after 27 years [26]. The newly proposed clinical criterion for AD diagnosis has two major groups: clinical settings core criteria and research purpose. The clinical settings are an extension of the 1984 guidelines, but more comprehensive and sensitive to other conditions. The research purpose follows the clinical criteria but includes biomarkers for definitive diagnosis.

Figure 2.2: Decision tree for an individual tested for Alzheimer’s disease (AD).

Mild Cognitive Impairment (MCI) is linked to 50 to 70 percent of AD cases [13]. Even though MCI is a cognitive decline, its symptoms are not severe enough to interfere with daily life; however, 15 percent of MCI individuals develop dementia within a year and 80 percent within 6 years. Additionally, MCI is not isolated to a risk of AD only, but to other dementias like Parkinson’s disease (PD) [13]. California has developed a classification guide that consolidates the general symptoms of AD [27]

2.1.4 Imaging as Diagnostic Tools

2.1.5 MRI Imaging and Its Limitations

The early changes in the brain in living subjects which can improve diagnostic tools with higher sensitivity and specificity are observed by neuroimaging techniques like magnetic resonance imaging (MRI) [28]. Currently, it is recommended for European nations to perform a neuroimaging study to rule out reversible dementia or other causes for the symptoms. MRI’s high resolution and tissue contrast are used for the assessment of cerebral atrophies, and other conditions such as the case of small vessel ischemic

disease, white matter sensitivity, medial temporal atrophy, and global cortical atrophy [26, 27]

2.1.6 Current Treatments

Since the beginning of last century, Alzheimer's disease still is an incurable condition. Currently there are therapies that aid with symptomatic improvements of some AD; however, there is no evidence that such therapies slow or stop the progression of the disease [26]. There are a total of five FDA-approved drugs to treat Alzheimer's disease, (Table 2.3)

Table 2.3: FDA Approved AD Therapies

Drug name	Brand name	Approved For	FDA Approved
1. donepezil	Aricept	All stages	1996
2. galantamine	Razadyne	Mild to moderate	2001
3. memantine	Namenda	Moderate to severe	2003
4. rivastigmine	Exelon	All stages	2000
5. donepezil and memantine	Namzaric	Moderate to severe	2014

The U.S Food and Drug Administration (FDA) approve the donepezil in 2014, but the studies for approval took place at the beginning of 2000 [3]. The donepezil and memantine were originally intended for the treatment of mild-to-moderate AD; however, in 2012 studies show that this treatment can benefit moderate to severe AD individuals.

2.2 Computer Aided Diagnosis (CAD) Systems

2.2.1 Overview

Medical images are by far one of the best diagnostic tools in the market today; however, one significant limitation is human error. Even though physicians and radiologist have formal training, the level of training, the experience, the methodology, and other factors such as distractions, fatigue, and environment, can affect the outcome of the diagnosis [6]. Thus, CAD systems can minimize diagnostic errors, and provide a confirmation of the diagnosis to the radiologist. However, CAD systems performance depends on the type of machine learning technique applied to it.

2.2.2 Background

In the mid-1950s the idea of using an automated diagnosis computer in radiographs sparked. In 1967, Fred Winsberg described the first CAD system for mammograms [29]. However, CAD systems extensive and severe research begun in the 1980s. Today in the United States, they form part of most routine clinical work to detect breast cancer with the use of mammograms [29], (**Figure 2.3**). Before the 1980s the concept of automated diagnosis or automated computer diagnosis originated, but in the 1980's the current concept of CAD systems changed the scope, expectations, and role of the computer in diagnosis.

Figure 2.3: Historical timeline of CAD systems.

The early studies of the computer-aided diagnostic systems began in late 1950. In 1988, the CAD systems' research gained force, and the philosophy of CAD systems changed [29].

2.2.3 Automated Computer Diagnosis and CAD

The main similarities between both systems are the quantitative analysis of digital medical images, and that both require a high sensitivity and high specificity [6]. The difference between the systems depends on the role of the diagnostician. Automated computer diagnosis's core idea is the use of a computer to replace the physician or radiologist. Consequently, automated computer diagnosis is the primary source of diagnosis, and its performance is equal to the performance achieved by the computer.

On the other hand, CAD systems use the computer's output to aid the diagnostician rather than to replace the physician. CAD systems are a diagnosis confirmation, and their performance level is equal to the performance achieved by the expert [6]. In conclusion, automated computer diagnosis systems seek to replace the

physician in its role of diagnostician, while CAD systems aim to improve diagnosticians' ability to detect abnormalities as discussed later on the text.

2.2.4 CAD system

The two categories of CAD systems depends on the function of the computer. Computer-aided detection (**CADe**) systems are used to mark abnormal regions in an image that the clinician can use for diagnosis. Computer-aided diagnosis (**CADx**) systems provide the clinician an assessment of a condition such as giving disease type, stage, the probability of progression or the severity of illness [30].

2.2.5 CAD systems performance

Computer-aided diagnosis (CAD) systems can aid physicians, provide a second “expert” opinion, and ultimately decrease the health cost and misdiagnosis rate [31]. In the case of MRI images for breast cancer diagnosis, the CAD system resulted in a higher sensitivity (97.9 percent) and specificity (86.4 percent) while compared to two expert breast cancer radiologists. The mean values for the radiologist were 84.6 percent for sensitivity and 68.8 percent for specificity [32]. Similar results were obtained for other conditions such as coronary artery which the CAD system gives an accuracy of 98.5 percent (higher than the gold standard of 97.32 percent). In the diagnosis of gliomas with MRI images the CAD system achieved an accuracy of 87 percent, a sensitivity of 79 percent and a specificity of 90 percent. The radiologist results were lower with an 81 percent for accuracy, 87 percent for sensitivity, and 84 percent for specificity [33]. These studies demonstrated that CAD systems accurate predictions can improve the diagnostician's levels of performance.

2.2.6 Artificial Neural Network

CAD systems use data and machine learning techniques to assist with the diagnosis of several conditions. Commonly the systems include segmentation, feature extraction, and classification [34]. In the case of AD, there have been a significant number of classifiers used such as Random Forest which has good accuracy and robustness, but it presents bias towards multi-categorical features [35]. The most common classifier in literature applied to Alzheimer's disease diagnosis is the Support Vector Machine (SVM) or a deviation of it. This algorithm is a supervised classifier that uses pattern recognition to predict the category of the sample provided. The major shortcomings of SVM are the large number of features required for classification because those can lead to over computer power, and computational complexity [36]. Moreover, a high number of input features relative to the number of subjects can inquire issues such as dimensionality and large hypothesis space [37].

Artificial Neural Networks (ANN) had been useful for image classification where the complexity of the data is high, and where the input and output have a nonlinear relationship. In the comparison of brain aging, the implemented ANN model achieved superior prediction accuracy than the manifold learning combined with SVM. Additionally, in the comparison of wavelet classifications (using Discrete Wavelet Transform from MRI images), ANNs have outperformed SVM achieving 100 percent accuracy [38]. The limitations of the ANN models are the identification of the neural network structure.

2.2.7 Feature identification

There are several approaches to identification of abnormalities in the diagnosis of AD. Most are related to specific Regions of Interest (RIO'S) the issue with those are the process of extraction, and the features used for analysis [39]. Another approach has been the comparison of white matter volume and white matter lesions which are also localize regions; however, the limitation is that usually matter lesions are present on later stages and not on all the patients. There is evidence that supports that brain morphology changes with AD, and that there is low-frequency fluctuations also associated with the disease [40].

CHAPTER 3: PROJECT APPROACH

3.1 Background

3.1.1 ADNI database

Due to the limitations of acquiring MRI images, this study used the MRI images from the ADNI database. The Alzheimer's Disease Neuroimaging Initiative (ADNI) is a global cooperative research grant whose main objective is to use clinical, imaging, and genetic biomarkers for the identification AD. The database provides data for Alzheimer's disease (AD) subjects, Mild Cognitive Impairment (MCI) subjects, and Normal Control subjects (NC) [41].

3.1.2 MATLAB neural network toolbox

MATLAB is a high-performance language used for diverse fields, and it integrates computation, visualization, and programming to express the solution in a mathematical form. The Neural Network Toolbox is used to model complex nonlinear systems that are not able to be modeled with a closed-form equation. The Neural Network Toolbox supports ANN and other dynamic networks [42].

3.1.3 Brain regions

MRI technology depends on the changes in energy states of protons, which result in radio-frequency signals. A combination of a different number of pulses can become sensitive to different tissue characteristics. Thus, MRI images can aid to assess atrophy and changes in tissue [43]. The hippocampus is one of the tissue areas known to be affected in the earliest stages of AD. The hippocampus or hippocampal formation is in general applied to the dentate gyrus (DG) [44]. Also, AD is associated with the decrease

in brain mass, which leads to larger ventricles and a shrinkage of the cerebral cortex [3], (Figure 3.1).

Figure 3.1: Regions of interest and brain comparison among AD and HC.

The left images are color coded to show different regions: blue is used to indicate the rostral anterior cingulate, green indicates the caudal anterior cingulate. Red is associated with the posterior cingulate. The image of interest is image b which shows the hippocampus with a blue collar and the entorhinal cortex with orange. [44]. The right image compares a healthy control brain (left side) against an advanced AD brain. The images show a difference in the brain size, ventricles volume and cortex thickness [3].

3.2 Approach Overview

The MRI of the same number of healthy controls and AD subjects will be obtained from the ADNI database. The MRI images will be processed, and regions of interest (ROIs) will be identified for feature extraction through image processing techniques. The

results of the feature extraction will be classified utilizing a feedforwards backpropagation neural network, which is a specific structure of feedforward artificial neural network. Additionally, the neural network toolbox from Matlab, which is an integrated program to run neural networks would be used for the programing portion of the project. The neural networks ideal structure will be identified in terms of hidden layers and neurons in each layer. The results of classification and the features will be examined.

CHAPTER 4: MATERIALS

4.1 MRI Images

All ADNI subjects underwent a pre-screening process which included several neuropsychological examinations. The results are associated with specific clinical characteristics that aid diagnosis. Some of the examinations include the Clinical Dementia Ratio (CDR) and Mini-Mental State Examination (MMSE score). The MRI images for both Alzheimer's disease (AD) subjects and Normal control (NC) subjects were acquired using the ADNI only database with a 3 Tesla and a T1-weighted using the SAGITAL Siemens scanner. Additionally, the acquisition was a 3D type with a Pa Coil, and a 9-degree flip angle, [240, 256, 176] pixel matrix and a 1.2 mm slice thickness.

4.2 Subjects data

4.2.1 Normal control (NC) subjects and Alzheimer's disease (AD) subjects

An advance search was conducted to select specific subject characteristics to allow for a balance data acquisition. The pilot study had fewer subjects than stage two and stage three. The demographics are discussed within each stage. The NC group MMSE scores range from 27 to 33, and all NC subjects had a CDR score of zero for all stages. For the AD group, the MMSE scores for these subjects range from 8 to 29, and their CDR scores ranged from .3 to 2, which was the same for all three stages.

4.3 The Software and hardware

The Mathworks student edition package with the neural network and image processing toolbox was utilized for all programming and image processing. Adobe Photoshop was used to save the MRIs to a *.png and to ensure all images had the same

dimensions and pixel ratio. A Lenovo laptop idea pad with an i7 core processor was used for all the data and image processing.

4.4 MRI acquisition

The MRI images obtained were 3D MPRAGE T1-weighted. These types of images are achieved by using a short Time to Echo (TE) and short Repetition Time (TR). Additionally, all the images were corrected by using Gradwarp, B1 non-uniformity, and N3 correction. The Gradwarp allows for the correction of geometry distortion due to gradient non-linearity. B1 non-uniformity is performed during acquisition to correct any non-uniform intensity results. N3 employs a sharpening of the image utilizing histogram equalization.

CHAPTER 5: STAGE ONE: PILOT STUDY

5.1 Materials for pilot study

5.2 Sample size and demographics

There were a total of 212 images used, which were equally distributed: 106 for NC, and 106 for the AD group. For the NC group the females' age ranges from 58 to 89 years with a mean of 73.5 years, while the male subjects had a range of 61 to 90 years and a mean of 75 years. The AD group age range for the females was 58 to 93 years and the males' age range was 56 to 88 years with a mean of 72 years.

5.3 Methods

5.3.1 Image pre-processing

There were 212 sagittal view images and 212 axials view images used for the analysis. The selected brain regions for both sagittal and axial views linked with specific changes consequence of AD presence were selected. Furthermore, there were two main regions selected from the axial images which are referred as thickness view images.

5.3.1.1 Sagittal images

Several structural imaging studies have identified the hippocampus as a diagnostic marker for AD because both the hippocampus and thalamus are associated with the decrease of volume matter evident of AD [45]. Furthermore, the structural studies showed that the hippocampus is reduced by about 15-25 percent volume in individuals mildly affected by AD [45]. Thus, these two areas were identified as regions of interest (ROIs). The ROIs were extracted from the sagittal images through the process of convolution, (**Equation 5.1**).

$$g(x, y) = h(x, y) * f(x, y) \quad (5.1)$$

Where $g(x, y)$ is the enhance image (region of interest), $h(x, y)$ is the mask (binary image), and $f(x, y)$ is the original image [39]. An NC MRI was used as a baseline image. The baseline was converted from a three-color array to a two-color array, and then the ROI was selected as a single region, (**Figure 5.1**). Then the original image was changed from a gray color image to a binary image. The original image was converted to a binary image as the mask finds isolated points corresponding to the region. Both images were multiplied together (convoluted) resulting in the ROIs. When a satisfactory resulted image was achieved, then the mask was used to process the rest of the images, (**Figure 5.1**). A function was created for extraction and used on all images simultaneously. Utilizing one mask for all images allows for a standardized size of the ROIs, so all values extracted from the feature have the same parameters.

Figure 5.1: Sagittal ROI Process Extraction.

The baseline image (top left) was marked with a polygon to select the ROI (hippocampus area). Then a binary mask was created to process the unmarked image (top center, and top left). The area and the centroid were applied to the baseline image, and then the masked was used to extract the region (center bottom image). The resulting image was the ROI with the centroid displayed at its center (bottom left)

5.3.2 Axial images

In addition to hippocampal atrophy, ventricular enlargement and cerebral cortex shrinkage have been associated with Alzheimer's disease [46] . Therefore, two different sections of the axial images were extracted: the ventricles, and the cerebral cortex portion. Consequently, two masks were created following the same process of convolution used for sagittal images. The axial image was the view from the NC baseline which was used to extract the sagittal view for analysis. Once a desire ventricle area was identified, the mask was created and utilized for all following images, (**Figure 5.2**). The cerebral cortex ROI was selected from the top right area of the axial images, and it was label thickness, (**Figure 5.3**). Two functions were created: one for ventricle extraction and one for cerebral cortex extraction.

Figure 5.2: Axial ROI Process Extraction.

The baseline image (top left) was marked with a polygon to select the ROI (ventricle section). Then a binary mask was created to process the baseline image (top center, and top left). The area and centroid were applied to the baseline image, and the masked was used (center bottom image). The resulting image was the ROI with the centroid displayed at its center (bottom left)

Figure 5.3: Thickness ROI Process Extraction.

The baseline image (top left) was marked with a polygon to select the ROI (Cortex thickness section). Then a binary mask was created to process the baseline image (top center, and top left). The area and centroid were applied to the baseline image, and the masked was used (center bottom image). The resulting image was the ROI with the centroid displayed at its center (bottom left)

5.4 Image processing

Mathematical morphology is a tool for extracting descriptive components of a picture which contains significant information. The binary mask used to remove the ROIs is an example of a mathematical morphology [39]. However, because of some of the morphological changes in brain deterioration, due to AD, causes changes in volume, another image analysis comes into play. Texture analysis does not have a formal definition but refers to the descriptors which are statistical, structural, and spectral. The

focus of this study is to use images as inputs, but retrieve attributes as outputs to use for classification.

5.4.1 Frequency Domain Processing

5.4.1.1 Fourier Transform

The Fourier transform gives properties primarily to detect global periodicity of an image. For a given image the Fourier transform extracts the magnitude and the phase, (**Equation 5.2**).

$$F(u, v) = \sum_{x=0}^{M-1} \sum_{y=0}^{N-1} f(x, y) e^{-j2\pi ux/M} e^{-j2\pi vy/N} \quad (5.2)$$

Where $F(u, v)$ is the discrete Fourier transform. $u=0, 1, \dots, M-1$, and $v=0, 1, \dots, N-1$ and the result is a complex value. $f(x, y)$ is the given image, where $x=0, 1, \dots, M-1$, and $y=0, 1, \dots, N-1$ [39].

All the images were converted to their Discrete Fourier Transform (DFT) which means that each picture were changed from their spatial domain to its frequency domain. In the frequency domain, the image is a series of sine and cosines. From this step, the magnitude of each MRI section was obtained, (**Equation 5.3**).

$$f_{mag}[m, n] \leftrightarrow |F[i, k]| \quad (5.3)$$

Where the $f_{mag}[m, n]$ is the two-dimensional magnitude and $|F[i, k]|$ is the phase [39].

Both the magnitude and phase are complex values with real and imaginary parts.

All images were first converted to two-dimensional images by converting them from three color spectrums to two.

The magnitude of the Fourier was calculated per **equation 5.4**

$$f[m, n] = \sqrt{R(f(u, v))^2 + i(f(u, v))^2} \quad (5.4)$$

Where $f_{mag}[m, n]$ is the magnitude, $f(u, v)$ is the DTF, R is the real part and i , is the imaginary part of the transform [39]. The magnitude provides information regarding the amount of frequency components present; therefore, the maximum and minimum values of the magnitude were stored as attributes.

The phase provides information regarding the location of the frequency components from which the real part is the focus of analysis. All images phase were calculated per **equation 5.5**

$$|F[i, k]| = \tan^{-1} \left(\frac{i(f(u, v))}{R(f(u, v))} \right) \quad (5.5)$$

Where $F[i, k]$ is the magnitude, i is the imaginary part of DTF and R is the real part of the transform [39]. The maximum and minimum phase values of the real parts were part of the image analysis.

5.4.2 Statistical approach

The statistical approach can be used as a confirmation of the neural network performance since the data can be study to determine if there is a statistical significant difference among the parameters study. The statistical approach is not directly related to the aims of this work; however is a tool to study the data (inputs) being feat to the neural network.

5.4.2.1 Properties of gray-level co-occurrence matrix

The intensity of a picture can be obtained by a histogram which provides information about the intensity range of intensity levels in the image; however, the histogram

provides not useful information for texture analysis. On the other hand, the analysis of image intensity with the relative position of the pixels provides valuable information. This combination is known as the gray level co-occurrence matrix (GLMC). A calculation of how often a gray-level pixel occurs in the horizontal adjacent direction of a pixel with a specific value is needed to obtain the matrix.

Q is the position of two pixels relative to each other, and the total number of pixel pairs that satisfies Q is the sum of the elements of the matrix G . G contains the number of occurrences of pixels in image f . Then the probability that certain pair of points can satisfy Q is given by **equation 5.6**

$$p_{ij} = g_{ij}/n \quad (5.6)$$

Where p_{ij} is the probability, g_{ij} the pair of points, and n is the total number of pixel pairs that satisfy Q [39].

Thus, sum of probabilities equals one as they are in the range of [0,1]

$$\sum_{i=1}^k \sum_{j=1}^k p_{ij} = 1 \quad (5.7)$$

Where k is the dimension of the column or row of the square co-occurrence matrix (G) [39].

Thus, all the images were converted to grayscale images, and the co-occurrence matrix was calculated for each image where the maximum probability of each image was stored for analysis.

5.4.3 Contrast

The measure of the contrast is linked to the randomness of the content of an image. The value of contrast is the measure of intensity contrast between a pixel and its neighbor over the entire picture. (**Equation 5.8**)

$$Contrast = [0 \left(\sum_{i=1}^k \sum_{j=1}^k (i - j)^2 P_{ij} \right)] \quad (5.8)$$

When G (matrix) is constant, then the value of the range (contrast) is zero to k (k is the row or column of the squared matrix G [39]. Thus, contrast is the variance which measures the randomness with respect to the mean or how spread-out the pixels are from their GLMC values. The contrast of all three sets of images were obtained from the GLMC and stored as a texture attribute

5.4.4 Correlation

Correlation is a descriptor of the strength and direction of the relationship between the pixels and its neighbor over the entire images, which is a measure of redundancy. Correlation is calculated in the frequency domain and is a multiplication of complex conjugate values, (**Equation 5.9**).

$$\sum_{i=1}^k \sum_{j=1}^k \frac{(i-m_r)(j-m_c)p_{ij}}{\sigma_r \sigma_c} \quad (5.9)$$

$$\sigma_r \neq 0 ; \sigma_c \neq 0$$

Where m_r is, the mean computed along the rows and m_c is the mean computed along the columns, σ_r , and σ_c represent the standard deviations along the rows and columns respectively. The range is from 1 to -1 corresponding to the perfect positive and perfect

negative correlations [39]. The correlation values for all images were obtained and saved as a feature for analysis

5.4.5 Energy

Energy is a measurement of uniformity with a range from 0 to 1. A value of 1 represents a consistent image. Energy also is a second-moment equation, **(Equation 5.10)**

$$E = \sum_{i=1}^k \sum_{j=1}^k p_{ij}^2 \quad (5.10)$$

Energy (E) is proportional to the probability squared; thus, as the probability squared increases, the uniformity of the image increases [39]. All the images energy was used as a statistical texture measured.

5.4.6 Homogeneity

Homogeneity (H) measures the concentration of values or the spatial closeness of the distribution of the elements in G with respect to the main diagonal, **(Equation 5.11)**.

$$H = \sum_{i=1}^k \sum_{j=1}^k \frac{p_{ij}}{1+|i-j|} \quad (5.11)$$

The value of $1 + |i - j|$ are the same as the values of G, and they decrease as $i=j$ [39]. Therefore, the highest homogeneity is the matrix with the highest probability near the main diagonal. Thus, images with higher gray level content have a higher homogeneity value, 1. The range of homogeneity is from 0 to 1. The values for all images were used as an attribute

5.4.7 Entropy

Entropy (S) is the statistical analysis of randomness of the elements in G and can be calculated in three or two dimensions, (**Equation 5.12**).

$$S = - \sum_{i=1}^k \sum_{j=1}^k p_{ij} \log_2(p_{ij}) \quad (5.12)$$

The randomness in the co-occurrence matrices is zero when the probability in all elements in G are constant; therefore, its range is [0,1] [39]. All the entropies were calculated and saved for analysis

5.5 Artificial Neural Network

The algorithm used for the classification of the data was the backpropagation algorithm, which is known to handle significant amounts of data and has been widely used in artificial intelligence models. The neural network consists of a forward pass, which knows the desired outputs and compares the calculated outputs with those already known. A second element is the backward pass where the error from the desired and actual output is computed. The resultant error from the backward pass is used to alter the weights in the network to reduce the error (**Figure 5.4**). Forward and backward passes are repeated until the error is low enough and converges to state where the learning patterns are bounded [47].

5.5.1 Neural Network structure

The neural network receives the data (input), then trains and processes the data. The inputs and biases are the connections among the inputs and outputs. The weights and biases are then summed and added up by a transfer function into one or more outputs

depending on the process. There were four different structures compared which differed in the number of hidden layers and neurons in each layer, (**Figure 5.5**).

Figure 5.4: Multilayer Feedforward Backpropagation Artificial Neural Network Structure

The neural network mimics the brain interconnecting structures and each neuron represent the information being received by the system. The neural network changes according to the structure selected for example this network shows three input variables (x_1, x_2, x_3) being received, but only one response variable (y) being given. However, the number of inputs, hidden layers, and outputs can be increase or decrease as needed [48].

5.5.2 Training Function and Cut off value

The training function used was the `trainlm`, which uses the Levenberg-Marquardt optimization to update the weight and bias values. This methods was designed to approach the Hessian matrix rather than computing it (**Equation 5.13, 5.14, 5.15**)

$$H = J^T J \quad (5.13)$$

$$g = J^T e \quad (5.14)$$

Where H is the Hessian matrix, g is the gradient, and J is the Jacobian matrix with the first derivatives of the network errors in respect to the biases and weights, and e is a vector of networks. Therefore, the approximation of the Hessian matrix that the Levenberg-Marquardt employs following the Newton like update is shown by the following equation:

$$X_{k+1} = X_k - [J^T J + \mu I]^{-1} J^T e \quad (5.15)$$

μ is a scalar and when it equals zero the equation is Newton's method; however when μ is large then it becomes a gradient descent with a small reduction in performance function.

During this stage the cut-off value was arbitrarily chosen to be 0.5; thus, any output less than the cut-off value is consider negative. Similarly, any value equal or greater than 0.5 is assumed positive.

5.6 Stage One Results

5.6.1 Features relevance

One of the aims of this thesis was to determine the relevant features for comparison. A statistical t-test was performed among the 28 features to compare for the difference between the AD group and the NC group.

5.6.2 Fourier Transform

5.6.2.1 Magnitude results

The Fourier transform magnitude and phase for axial, thickness, and sagittal extractions were analyzed. The analysis of the magnitudes shows that there is no

difference in the magnitude among groups for any of the views of the images, (**Table 5.1**).

Table 5.1: Summary of P-Value for Maximum and Minimum Magnitudes

Image View	Maximum magnitude p-value	Minimum magnitude p-value
Axial	0.364	0.462
Sagittal	0.135	0.135
Thickness	0.130	0.576

There is not a significant statistical difference between minimum and maximum magnitudes for AD and NC groups in any of the views of the images analyzed.

5.6.2.2 Phase results

The phases arising from the Fourier transform were also analyzed, and the results show that there was a significant difference among the AD and NC images. The p-values for all image views show a significant statistical difference. The minimum thickness phase does not demonstrate a significant difference, (**Table 5.2**).

Table 5.2: Summary of P-Values for Minimum and Maximum Phase

Image Description	Maximum phase p-value	Minimum phase p-value
Axial	0.001	0.035
Sagittal	0.000	0.992
Thickness	0.028	0.876

The p-values indicate that there is a statistical difference among the AD and NC for the axial view of the images. The results suggest that there is a 95 percent confidence that the true value of the standard deviation is in the range of 17 and 63 for the maximum and 1.9 and 51 for the minimum. Additionally, the sagittal view p-values also indicate that there is a significant statistical difference in the maximum phase of AD and NC with a p-value of .000; however, the p-value for minimum phase values was greater than .05 indicating that there is not a significant difference among the groups. Similarly, the results for thickness show a p-value of 0.028 which is less than .05, showing that there is a significant statistical difference among the groups. However, like with the sagittal view, the minimum value indicates that there is not a significant difference among the groups.

5.6.3 Contrast results

A t-test statistical analysis with a 95 percent critical interval was performed in the contrast values. The comparison of all contrast values among the images led to statistical differences, (**Table 5.3**).

Table 5.3: Summary of P-Values and Confidence Interval for Contrast

Image View	Contrast p-value	95% Confidence Interval
Axial	0.005	-0.00883, -0.00162
Sagittal	0.248	-0.00951, 0.00248
Thickness	0.001	-0.01764, -0.00472

The contrast p-values for axial and thickness views show a statistical significance among the groups with p-values of 0.005 and 0.001, respectively. The sagittal view p-value is greater than .05, and the interval includes zero showing not a statistical difference among the AD and NC groups.

5.6.4 Correlation results

The correlation values among the AD and NC groups were analyzed using a t-test with a 95 percent confidence interval. The sagittal and thickness correlation values show that there is a statistical difference among the AD and NC groups with a p-value of .001 and 0 correspondently, (**Table 5.4**).

Table 5.4: Summary of Correlation P-Values Among AD and NC groups

Image View	Contrast p-value	95% Confidence Interval
Axial	0.79	-0.01125, 0.02619
Sagittal	0.001	0.0213, 0.0791
Thickness	0.000	0.0507, 0.1296

The axial image view resulted in a p-value of .079, which is greater than .05 and the interval contains zero; therefore, there it is concluded that there is not a statistical difference among the groups.

5.6.5 Energy results

The energy results for all images views among the AD and NC groups were analyzed using a t-test with a 95 percent confidence interval, (**Table 5.5**).

Table 5.5: Summary of Energy P-Values for Both AD and NC groups

Image View	Contrast p-value	95% Confidence Interval
Axial	0.005	0.000793, 0.004345
Sagittal	0.247	-0.00122, 0.00468
Thickness	0.001	0.00234, 0.00860

The energy analysis shows that there is a significant statistical difference among AD and NC groups for the axial and thickness views; however, the sagittal view resulted in a p-value of 0.247. The large sagittal p-value shows that there is not a significant statistical difference among the groups which is confirmed by the presence of zero in its interval.

5.6.6 Homogeneity

The t-test with a 95 percent confidence interval was also calculated for all homogeneity measures. The homogeneity values show that the only significant statistical difference among the AD and NC groups is in the homogeneity of the sagittal view, (**Table 5.6**).

Table 5.6: Summary of Homogeneity P-Values for AD and NC Groups

Image View	Contrast p-value	95% Confidence Interval
Axial	0.310	-0.000674, 0.002114
Sagittal	0.000	-0.005601, -0.001852
Thickness	0.803	-0.00247, 0.00191

The axial and thickness views p-values are higher than 0.05 which show no significant difference between the groups and it is confirmed the presence of zero among their intervals.

5.6.7 Entropy

The statistical analysis of entropy among the AD and NC resulted in p-values for all axial, sagittal, and thickness views are below 0.05. The low p-values show that there is a significant statistical difference among the groups, (Table 5.7).

Table 5.7: Summary of Entropy P-Values for All AD and NC Groups

Image View	Contrast p-value	95% Confidence Interval
Axial	0.001	-0.1483, -0.0368
Sagittal	0.001	-0.2087, -0.0533
Thickness	0.000	-0.3126, -0.1160

Entropy p-values were consistent with all the views of the images. None of the ranges contain zero; therefore, it confirms that there is a significant statistical difference among the subjects.

5.7 Artificial Neural Network

5.7.1 Classifier and performance evaluation

The experimental results were analyzed with respect to four different percentages: accuracy, precision, sensitivity, and specificity. These allow for deeper insight and analysis of the classification results obtained. Sensitivity is a measure of how many true positives are correctly identified as true positive. Specificity is a measure of the number of true negatives which are correctly identified as being true negative [49]. Also,

accuracy is a measure of how many of the predictions are correct, whereas precision is a measure of accuracy given that a certain class has been predicted [50].

For this study, a value of 1 is considered a negative since there is not AD associated with the image. A value of 2 is considered positive since the images are associated with the presence of AD. Then, a true positive is defined as a correctly classified AD presence, whereas a false positive is defined as an incorrectly classified AD presence. Furthermore, a true negative is defined as a correctly classified normal image with not AD present. A false negative is defined as an incorrect classification of a normal control. The degree at which the result of the algorithm conforms to the correct value provided by the dataset is referred to as accuracy (**Equation 5.13**):

$$Accuracy = \frac{TP+TN}{TP+TN+FP+FN} \quad (5.16)$$

Precision is defined as how exact and correct the values are when compared to the data (**Equation 5.14**)

$$Precision = \frac{TP}{TP + FP} \quad (5.17)$$

Additionally, sensitivity is the measurement of the true positive rate or the percentage of correctly identified true positives (**Equation 5.15**).

$$Sensitivity = \frac{TP}{TP + FN} \quad (5.18)$$

Finally, specificity refers to the true negative rate and correctly identifies the correct percentage of individuals not having the condition (**Equation 5.16**).

$$Specificity = \frac{TN}{TN + FP} \quad (5.19)$$

TP represents the number of classified true positives, TN represents the number of classified true negatives, FP represents the number of falsely classified positives, and FN represents the number of incorrectly classified negatives.

The backpropagation ANN was trained with 50 percent of the data resulting in 124 samples. The testing and validation were done with the remaining 50 percent of the data points. There were four neural network structures analyzed to determine the best structure, (Table 5.8)

Table 5.8: ANN-Backpropagation Structure Results

Algorithm structure	Accuracy	Precision	Sensitivity	Specificity
Network 1 2 layers 65 neurons	52.38	53.3	15.68	87.1
Network 2 6 layers 65 neurons	53.3	56.3	17.7	87.04
Network 3 4 layers 6 neurons	57.7	60	30	91.3
Network 4 4 layers 20 neurons	53.3	55.0	21.6	83.3

The network with 4 hidden layers and 35 neurons had the best performance with 91.3 percent specificity and 57.7 percent accuracy. The accuracy of all networks was within the 50 percent. The highest precision was 60, and the lowest was 53.3, achieved by network 3, and 1 respectively. The sensitivity value was very low for all four networks tested. The highest achieved value was from Network 4 with a high of 30 percent, while the worst was network 1 with a 15.7 percent. The networks with 65 neurons took a longer time and a higher computer power, while the networks with fewer neurons ran much faster and did not require a high-performance power. The number of epochs that resulted in the best performance ranged as low as 2 and as high as 8, (**Figure 5.5**).

Figure 5.5: MATLAB Neural Network Interface.

Interface displays the type of training use, the epochs, time it took to run the simulation, and performance. From this interface plots for performance, training, and error histogram were obtained. Furthermore, the interface shows the training function used, which was Levenberg-Marquardt [42].

An epoch refers the iteration where the validation performance reached a minimum, and training continued for .18 more runs. The same trend is seen for both the validation and test curve; therefore, there is no issue of overfitting, (**Figure 5.6**).

Figure 5.6: Performance Plot for Selected Network.

The network needed only an additional run to meet the goal and optimal point. The training curve (blue line) indicates that the information with the data might be limited; however, the validation (green line) and testing (red line) follow the same shape. The similarity among the curves shows that there is no problem of overfitting or overtraining; therefore, the performance of the network is generalizing.

The histogram of the data indicates that there are several out layers. The blue bars represent training data, the green bars represent validation data, and the red bars represent testing. The major out layers are found in validation and testing data

Figure 5.7: Histogram of Networks Performance.

The neural networks highest error rate happened during training in a 20-bit histogram.

The training error can be the result of low data points.

The regression plots show that the targets and outputs are very close to each other. For training the R-value is 1, so is for validation and testing. However, the data set is skewed and does not follow a normal distribution.

Figure 5.8: Regression Plot at Minimum Gradient of 15 epochs

5.8 Summary of Results

The feature extraction results were summarized according to the extraction order. The results show that the maximum phase shift feature was statistically significant among the groups for all three views with p-values below .05, (**Table 5.2**). The minimum phase was only statistically significant for the axial view with a p-value of 0.035. Contrast had a statistically significant difference in the axial and thickness views with p-values below .05, (**Table 5.3**). Similar results were observed for correlation where sagittal and thickness views were statistical significant with p-values below 0.05; while, the axial view showed no significant statistical difference, (**Table 5.4**). In the same way, energy was statistically significant for the thickness views, but in contrast the axial view was also statistical significant, (**Table 5.5**). Homogeneity was only statistically significant for the sagittal view, (**Table 5.6**), but energy p-values for all three views show that there is significant evidence to state a statistical difference among the groups.

The tabulated results from the algorithm performance correspond to the algorithms programmed with MATLAB using the 206 data points collected from all images giving a total number of 209 inputs, (**Table 5.8**). The best performance structure was the 4 layers 65 neural network with the highest specificity, but an underachieving accuracy, precision, and sensitivity to those compare with literature values. The literature values report all scores above the 90 percent, while the algorithm presented achieve values in the 50 percent for accuracy and precision [35]. The lowest performance value achieved was the sensitivity value with the highest score of 30.

CHAPTER 6: STAGE TWO TEXTURE AND FREQUENCY RESULTS

6.1 Materials

The number of subjects was increased to 300 images. There were 75 normal female controls, 75 normal male controls, 75 AD females, and 75 AD males. There was a significant effort to select similar age groups to keep a balance study; thus, the age range for all four groups was 55 to 85 years old. However, the average age for males and females in the normal control group was 73 years. The median age of AD patients, both male and females were 78 years of age.

6.2 Methods

The pilot study was used as a raw approach to refine the information being process from the MRI images. Thus, the purpose of stage two is to compare the frequency domain techniques, to compare the neural network structure, and to compare texture features against the frequency components. Moreover, to identify the method or methods with the highest performance that will give results comparable to those of the clinicians. During this phase, the only the axial view was used to compare the different techniques. The axial view was selected based on the statistical results from the pilot study. The results suggested that the axial view was the least useful to detect differences between the NC and AD groups. Thus, if the axial view performance is comparable to the clinician's, there is a higher probability that the other views have higher performance values than those of the clinicians.

6.3 Transforms comparison at low frequencies

There are two main frequency approaches for image processing the Fourier transform (FT) and the discrete wavelet transform (DWT). Both techniques give different information; however, they can be compared in the low frequency domain. comparable using the low frequencies only.

6.3.1 Fourier Transform (FT)

The mathematical fundamentals of the FT were described earlier (5.4.1.1). During stage one, the maximum and the minimum values for the real parts of magnitude and phase shift were used for comparison. In contrast, for stage two the FT was obtained and then moved to the center. Additionally, a Gaussian low-pass filter was applied to eliminate the high frequencies, and the resulting transform was used for analysis. Due to the large volume of the resulting values due to the picture size, only a region was selected after processing. However, to evaluate if the area size impacted the results two different sizes were compared. In summary, a 3x3 window, which gives a total of 9 inputs, and a 4x4 window, which gave a total of 16 inputs, were compared.

6.3.2 Discrete Wavelet Transform (DWT)

The wavelet transforms as the Fourier transforms, is also in the frequency domain. The FT decomposes the signals into sine and cosines, and if the transform is taken over the entire axis, one particular frequency cannot be identified in a precise instant [39]. On the other hand, wavelet transforms are localized in both the real and Fourier space. Additionally, DWT returns a data vector which will have the same length as the input. The transform decomposes the data into a set of orthogonal wavelets many of the vector

data are almost zero. Thus, there are some restrictions applied to the scaling function which is based on mathematical conditions per equation 6.1 [38,48].

$$f(x) = \sum_{k=-\infty}^{\infty} a_k \phi(Sx - k) \quad (6.1)$$

S is the scaling factor, a_k is the set of coefficients, and $\phi(Sx - k)$ is the expansion function.

If the scaling function and wavelet function are given by any of the family such as Haar, Daubechies, and so on, then the bases are known. Therefore, the discrete signal in $l^2(Z)^1$ is per equation 6.2

$$f[n] = \frac{1}{\sqrt{M}} \sum_k W_\phi[j_0, k] \phi_{j_0, k}[n] + \frac{1}{\sqrt{M}} \sum_{j=j_0}^{\infty} \sum_k W_\psi[j, k] \psi_{j, k}[n] \quad (6.2)$$

Where $f[n]$, ϕ_{j_0} , and $\psi_{j, k}$ are discrete functions from 0 to $m-1$. Thus, since the sets are orthogonal then their inner product gives the approximation coefficients according to equation 6.3 [51]

$$W_\phi[j_0, k] = \frac{1}{\sqrt{M}} \sum_n f[n] \phi_{j_0, k}[n] \quad (6.3)$$

A single-level two-dimensional wavelet decomposition was performed in all gray scale axial images. The DWT provides four different values a coefficient matrix value (cA), and three detail coefficients matrices for horizontal, vertical, and diagonal components (cH, cV, and cD, respectively) [39]. However, only the coefficient matrix was used as it contains the low-frequency elements of the image. Due to the high volume of values as with the Fourier transform only a region was also selected. The same approach of a 3x3 and 4x4 windows were obtained.

6.3.3 Feature extraction

Another approach to image processing is feature extraction, which was applied in stage one. The same features were utilized for phase two: contrast, correlation, homogeneity, energy, and entropy. Each texture gives four outputs; therefore, their entire combination is 16 inputs plus one more for entropy. Each of the features was analyzed independently, and as a combination (GLCOM); there was a total of four combination groups at different levels. A total of 12 combinations were used, which included a comparison of the four features together and in combination with entropy.

6.4 Artificial Neural Networks (ANN)

The artificial neural network approach and how it works was introduced on stage one. Step two compares four different parameters to identify the highest performance structures.

6.4.1 Network structure

Four different structures were analyzed with the axial images. Structure one and two were used to compare if increasing the number of neurons positively impacted performance. Therefore, one layer 15 neurons (structure 1:15), and one layer 35 neurons (structure 1:35) were used for comparison. Similarly, to compare the impact of increasing the number of layers the one layer 35 neurons (structure 1:35) was compared to the two layers 35 neurons structure (structure 2:35).

6.4.2 Classifier and performance evaluation

Stage two also used accuracy, precision, sensitivity, and specificity to compare the classifier performance; the definitions and mathematical description are layouts in section 5.7.1. In contrast to stage one, stage two uses 1 to identify individuals with AD,

and 0 for NC. Additionally, to compare the impact of increasing training percentage, which reduces testing, two different percentages were used. All the different structures were run with 60 percent training; therefore, a 20 percent testing, and a 70 percent training with a 15 percent for testing.

The texture feature used the highest performing algorithm, which results from the combination of all five features. There were a total of four combination groups with sublevels: Combinations A with four sublevels, Combination B with three sublevels, Combination C with two sublevels and combination D with one sublevel. Additionally, each feature was tested for performance.

6.4.3 Cutoff values

The output of the classifier is in the range of 0 to 1; therefore, to be able to study the performance of the classifier a cutoff value is to be assigned. The cutoff value will determine what values correspond to 1 (AD group) or 0 (Normal control). In the case of training, the performance was evaluated using the value 0.5333 after moving up and down of 0.5 the 0.5333 gave the highest performance. After training the performance of testing was evaluated using the receiver operating characteristic (ROC) curve. The ROC curve finds the threshold or evaluates the performance in the regions of high sensitivity and high specificity. The function `perfcurve` is used to produce the ROC; there are not requirements or assumptions about the nature of inputs or their relationship. The `perfcurve` can be used with any classifier that returns scores (0 and 1), which will return a point because the classification can be divided into positive or negative instances only. The test targets and the test output are used to find the threshold for the rate of positives and the rate of negatives after training [52]. The resulting value is used to evaluate the

matrix with the true positives, true negatives, false positives, and false negative, which are used for accuracy, precision, sensitivity, and specificity.

6.5 Stage two results

The frequency transforms and texture features were compared based on their performance, which was evaluated with the four parameters: accuracy, precision, sensitivity, and specificity. The highest performing transforms were those that give comparable values to clinician's performance (71-87 percent sensitivity, and 44-71 percent specificity) simultaneously. Additionally, the performances that had values for sensitivity and specificity in a close range, and their accuracy approached 78 percent were evaluated as the highest performing algorithms. The performances which simultaneously gave values below the clinicians were assigned to low performance. Each structure was run five times, and the values for all runs were evaluated; however, only the maximum and minimum performances were tabulated for the discussion.

6.5.1 Transform results and comparison

The Fourier Transform and the Discrete Wavelet Transform were compared to determine, which of them provided enough and sensitive information for classification. Both transforms used a 3x3 window and a 4x4 window and only the low frequencies of the transforms were used. Using only the low frequencies allows for an even comparison of the performance of the transforms.

6.5.1.1 Discrete Wavelet Transform (DWT) Results

The DWT 3x3-window resulted in a nine input to the network, which was tested with the four structures. In the case of training, the highest performance was achieved with the 1:35 structure and a 60 percent training, while the lowest performing training

was seen with structure 2:35 at 70 percent. In contrast, the lowest performance for testing was with the 60 percent training and structure 1:35, while the highest testing performance was achieved with 70 percent training and structure 1:15. For the 4x4 window and 16 inputs, the highest training performance was achieved with structure 1:15 and 60 percent training. Similarly, the lowest training, performance occurred also with the 60 percent training, but with structure 1:35. In the instance of testing the highest performing classification occurred with 70 percent training and structure 2:35, while the lowest performance was 60 percent training and structure 1:15,(Table 6.1, Table 6.2, Appendix A).

Table 6.1: Discrete Wavelet Transform training results for both window size

Window size	Structure	Highest performing training results				Percentage for training
		Accuracy	Precision	Sensitivity	Specificity	
[3x3]	1:35	81	79	85	76	60
[4x4]	2:35	91	92	92	91	70
		Lowest performing training results				
		Accuracy	Precision	Sensitivity	Specificity	
[3x3]	2:35	75	78.2	66.1	82.2	70
[4x4]	1:35	62	60	62	62	60

Table 6.2: Discrete Wavelet Transform testing results for both window sizes

Window size	Structure	Highest performing testing results				Percentage for training
		Accuracy	Precision	Sensitivity	Specificity	
[3x3]	1:15	74	78	78	67	70
[4x4]	2:35	78	80	50	93	70
		Lowest performing testing results				
		Accuracy	Precision	Sensitivity	Specificity	
[3x3]	1:35	63.3	60	64	63	60
[4x4]	1:15	57	65	41	75	60

6.5.1.2 Fourier Transform (FT) Results

The Fourier transform had significantly higher performances for all windows, percentages, and structures. In the case of the 3x3 window (9 inputs), the highest training performance occurred with structure 2:35 and 60 percent training, (**Table 6.3, Appendix A**). On the other hand, the lowest training performance was seen with 70 percent training and structure 2:35. Similarly, the highest testing performance occurred with 70 percent training and structure 1:15, while the lowest testing performance took place at structure 2:35 with 60 percent training, (**Table 6.4**). In the case of the 16 inputs (4x4), the highest performance training was 100 percent with structure 2:35 and 60 percent training, (**Table 6.3, Appendix A**). The lowest training performance occurred with 70 percent training and structure 1:15, (**Table 6.3**). The highest performance for testing occurred with 70 percent training and structure 2:35, while the lowest testing performance was structure 1:35 with 60 percent training, (**Table 6.4**).

Table 6.3: Fourier transforms training results for both window sizes.

Window size	Structure	Highest performing training results				Percentage for training
		Accuracy	Precision	Sensitivity	Specificity	
[3x3]	1:15	86	85	87	84	60
[4x4]	2:35	100	100	100	100	60
		Lowest performing training results				
		Accuracy	Precision	Sensitivity	Specificity	
[3x3]	2:35	69	67	84	53	70
[4x4]	1:15	68	85	74	91	60

Table 6.4: Fourier Transform testing results for both widow sizes.

Window size	Structure	Highest performing testing results				Percentage for training
		Accuracy	Precision	Sensitivity	Specificity	
[3x3]	1:15	85	87	90	75	70
[4x4]	1:35	82	83	90	71	70
		Lowest performing testing results				
		Accuracy	Precision	Sensitivity	Specificity	
[3x3]	1:35	73	67	68	50	60
[4x4]	1:15	77	74	79	74	60

The overall performance for training and testing suggest that the Fourier transform perform has higher sensitivity and specificity while compared to the DWT. The maximum performing transform was the FT with a 4x4 window.

6.5.2 Texture features (TF)

The texture features (TF) performance was also evaluated. The texture features from the gray-level co-occurrence matrix (GLCOM) were evaluated as a single entity (contrast, correlation, energy, and homogeneity). Additionally, the GLCOM plus entropy was also evaluated. Furthermore, each TF was individually evaluated, as well as in a series of combinations at different levels. Thus, the first comparison is the single entity vs. single entity plus entropy. The second comparison will be the independent performance of each, and the third comparison will be the combination performance.

6.5.2.1 Texture features and entropy results

The combinations of the four features making the GLCOM and the GLCOM in combination with entropy were measured for performance during training and testing.

(Table 6.5,Table 6.6).Table 6.5: Training results for Gray level co-occurrence matrix (GLCOM), and Gray level co-occurrence matrix (GLCOM) + entropy

	Highest training performance			
	Accuracy	Precision	Sensitivity	Specificity
GLCOM	70	72	67	72
GLCOM + entropy	84	84	83	84
	Lowest training performance			
	Accuracy	Precision	Sensitivity	Specificity
GLCOM	64	67	59	71
GLCOM + entropy	61	59	64	54

Table 6.6: Testing results for Gray level co-occurrence matrix (GLCOM), and Gray level co-occurrence matrix (GLCOM) + entropy

	Highest testing performance			
	Accuracy	Precision	Sensitivity	Specificity
GLCOM	82	86	86	76
GLCOM + entropy	80	90	71	91
	Lowest testing performance			
	Accuracy	Precision	Sensitivity	Specificity
GLCOM	76	76	86	67
GLCOM + entropy	56	54	60	52

The results suggest that entropy lowers the performance of the network during the testing stage; however, during training, the results suggest that entropy values are much higher. On the other hand, entropy significantly reduces the testing performance as its lowest values are about 20 points below the clinician's highest performance. Conversely, the testing without entropy gave values slightly below than the maximum performance of the clinicians. Moreover, the values were much higher than the minimum values recorded for sensitivity and specificity. Accuracy was still 2 points less than the reported for the clinicians.

6.5.2.2 Individual texture features performance

Each independent feature was its own output; therefore, a four input was used to test performance. Using the results from the transforms the individual features were only evaluated with structure 1:15 and 70 percent training. The highest and lowest performance for both training and testing were recorded.

In the case of the individual features the training performance was lower than the clinicians for accuracy, and sensitivity; however, the values for specificity were higher than the maximum performance given by the clinicians by up to 20 points, (**Table 6.7**). In contrast, the testing performance gave comparable and slightly higher performance values than those of the clinician, (**Table 6.8**). The two most top performing features were contrast and correlation. Contrast had the same accuracy as the clinician and greater specificity; however, its sensitivity was only higher than the minimum value recorded from clinicians. Similarly, the correlation was higher in accuracy and specificity, but slightly lower than the maximum sensitivity of the clinicians by one point, (**Table 6.7**, **Table 6.8**).

Table 6.7: Training performance for individual texture features

Features	Highest training performance				Lowest training performance			
	Acc.	Prec.	Sens.	Spec.	Acc.	Prec.	Sens.	Spec.
Contrast	70	75	59	81	54	61	34	61
Correlation	67	67	63	71	65	68	64	67
Energy	62	63	75	47	54	58	57	59
Homogeneity	66	70	71	60	57	58	57	59
Entropy	62	67	42	81	57	52	22	92

Table 6.8: Testing performance for individual texture features

Features	Highest testing performance				Lowest testing performance			
	Acc.	Prec.	Sens.	Spec.	Acc.	Prec.	Sens.	Spec.
Contrast	78	76	76	79	60	54	74	67
Correlation	79	75	86	74	78	71	91	67
Energy	76	78	85	61	65	61	67	62
Homogeneity	74	72	84	60	60	67	62	58
Entropy	76	70	74	77	54	57	68	44

6.5.2.3 Combination of features

A series of possible combinations were created to test if one combination of features is preferable than another. Also, the combo features were only tested with structure 1:35 and training of 70 percent, (**Table 6.9, Appendix B**). There were a total of four combinations umbrellas with sub-combination numbers: Combo A (AI, AII, AIII, AIV), Combo B (II, III, IV), Combo C (III, IV), and combo D. Combination A is all combinations related to contrast, combination B compares correlation in conjunction with the other features excluding contrast, combo C compares energy against homogeneity and entropy, and combo D evaluates the combination of homogeneity and entropy. (**Table 6.9, Table 6.10, Appendix C**).

Table 6.9: Training results for combination A

Combination	Highest training performance				Lowest training performance			
	Acc.	Prec.	Sens.	Spec.	Acc.	Prec.	Sens.	Spec.
AI	79	83	74	84	66	64	62	68
AII	64	66	61	64	69	74	57	81
AIII	78	73	80	76	71	71	74	69
AIV	73	76	66	54	54	56	66	52

AI and AIII had the highest training performance. Combination AI is contrast and correlation together, which gave an accuracy value greater than the clinician's as well as specificity. However, in the case of sensitivity, the values were slightly higher than the minimum reported for the clinicians. The training values were lower to those of the clinicians for all values. Combination AIII was contrast and homogeneity, and their training performance was higher for sensitivity while compared to combo AII, (**Table 6.9**). However, its performance was lower than the highest performance reported for the clinicians by 6 points. On the other hand, accuracy was comparable to the clinicians and specificity was greater than the maximum clinician's range. In the case of the lowest training performance combination, AIII had higher values to those for combination AI where both sensitivity and accuracy were greater than the minimum performance for the clinicians. (**Table 6.10**)

Table 6.10: Testing results for combination A

Combination	Highest testing performance				Lowest testing performance			
	Acc.	Prec.	Sens.	Spec.	Acc.	Prec.	Sens.	Spec.
AI	78	75	88	67	60	59	48	71
AII	76	76	85	64	55	57	55	56
AIII	71	74	67	76	56	54	66	46
AIV	73	77	77	68	67	69	77	53

In the case of testing the highest performance was AI and AII. AIII accuracy was lower than the values for the clinicians and AI and AII. In the case of Sensitivity, the values for AIII were significantly lower than for the other two combinations and then the lowest value reported for the clinicians. On the other hand, combination AII had higher values than AIII,

but lower than the clinician's highest performing values. Thus, combination AI outperforms the testing performance having equivalent values to clinician's accuracy, and outperforming in sensitivity. The specificity value was slightly lower than those for the clinicians.

The next set included three different combinations with correlation, (**Appendix C**). The highest training performing combinations for set B were BI and BII with specificity of 78, which is much greater than the one reported for the clinicians. On the other hand, the accuracy was three points below than the clinicians and the sensitivity was comparable to that of the clinicians. Combination BIII gave slightly lower values for accuracy compared to the other two combinations, higher precision, comparable

specificity, and much lower sensitivity than the one reported for the clinician's lower range, (**Table 6.11**)

Table 6.11: Training results for combination B

Combination	Highest training performance				Lowest training performance			
	Acc.	Prec.	Sens.	Spec.	Acc.	Prec.	Sens.	Spec.
BI	75	74	71	78	67	64	67	66
BII	75	77	71	78	68	70	67	70
BIII	74	80	63	71	57	68	24	84

Contradictorily to the training results, the values for testing were much different for combination BIII. BIII was the combination of correlation and entropy which outperformed the clinician's value for accuracy by up to 5 points, and specificity by up to 19 points. On the other hand, sensitivity was lower than the highest reported value for clinician's performance, but much greater than the lower range for the clinicians, (**Table 6.12**).

Table 6.12: Testing results for combination B

Combination	Highest testing performance				Lowest testing performance			
	Acc.	Prec.	Sens.	Spec.	Acc.	Prec.	Sens.	Spec.
BI	78	81	74	82	67	67	50	80
BII	73	74	90	47	56	54	64	48
BIII	82	91	76	90	62	57	60	64

Two combinations including energy composed set C and combination D was Homogeneity and entropy. In the case of training, the three combinations were underperforming on all four parameters. The highest combination CII (energy and

entropy) had an accuracy of 73, precision of 68, sensitivity of 60, and specificity of 61 which were much lower compared to the clinician's, (**Table 6.13**).

Table 6.13: Training results for combination C and D

Combination	Highest training performance				Lowest training performance			
	Acc.	Prec.	Sens.	Spec.	Acc.	Prec.	Sens.	Spec.
CI	70	75	62	78	61	67	53	70
CII	73	68	60	61	57	66	40	75
D	67	71	63	71	57	58	60	54

In the case of testing combination CII had more promising values as accuracy was comparable to the clinicians, and sensitivity and specificity slightly higher than those maximum values reported from clinician's performance, (**Table 6.14**).

Table 6.14: Testing results for combination C and D

Combination	Highest testing performance				Lowest testing performance			
	Acc.	Prec.	Sens.	Spec.	Acc.	Prec.	Sens.	Spec.
CI	76	72	96	44	64	58	70	60
CII	78	78	88	72	76	76	80	72
D	77	71	60	80	64	63	78	50

6.6 Statistical results

From the logistic regression model, the p-value for all texture features, Fourier transform, and Discrete wavelet transform was obtained. The statistical analysis shows that the TFs are statistically different between AD and NC's as all their p-values were below .05, (**Appendix D**).

The frequency transform had similar results were the statistical analysis shows that there was a significant statistical difference between AD and NC's for both FT

windows, and for the DWT 3x3 window only. However, the statistical p-value for the DWT with a window size of 4x4 was not statistically significant for AD and NC's, (Appendix E).

6.7 Summary of Results

The training for both FT and DWT was much higher for the 4x4 window than for the 3x3 region, which was also the same in the case of performance for the DWT, but not for the FT. The Fourier transform achieved training values up to 100 percent in all four parameters, and its higher training performance outperformed the DWT and the clinician's values. In contrast to DWT, the FT testing performance was similar for both windows size. The 3x3 window had slightly higher values than the 4x4 window, but the 4x4 window lowest performance was closer to the clinician's results. Overall, the highest performing algorithm on both training and testing was the FT with values outperforming the clinician's (accuracy of 85, a precision of 87, sensitivity of 90, and specify of 75). In conclusion using a 70 percent training resulted in higher performance for testing, but lower for training. The fewer neuron structures (1:15) were favorable to instances were fewer inputs were used, and the increase of neurons favor a higher number of inputs (1:35). The addition of layers did not seem to improve performance.

The combination of the sixteen values for contrast, correlation, energy, and homogeneity were compared to those same four plus entropy. In the case of training, the highest performance was in combination with entropy having much higher values than the clinician's in accuracy and specificity and closer values to the maximum range for sensitivity. In contrast, the testing shows that the single entity (four features only) had much higher values for accuracy and specificity. Sensitivity was one-point lower than the

clinician's performance and precision was 86 percent. The most inferior testing performance was also significantly better for a single entity than with the combination of entropy.

The individual features performance was evaluated, and the lowest training performance was seen by entropy alone. The highest training performing feature was that of contrast; however, none of the training gave comparable values to the clinicians. Moreover, the training performance was significantly lower than those of the clinicians. Nevertheless, the correlation's testing performance was higher than the clinicians in the case of accuracy and specificity; sensitivity was one-point lower than the most top performing range of the physician's 86 percent.

In the event of the combinations, the training and testing for combination A resulted in combination AI as the highest performing combination. AI training performance was greater than the clinician's performance in accuracy, outperformed in specificity, and was larger than the lower range in sensitivity. For testing AI outperformed the clinicians in both accuracy and sensitivity; however, it was slightly less than the upper range of the clinician's. None of the training performance of combination B was higher than combination A, and none of the combinations outperform the clinicians in two simultaneous values. In the case of testing performance, BI was comparable to the clinicians in accuracy, slightly higher than the minimum value in sensitivity, and outperformed in specificity. On the other hand, BIII significantly outperformed in accuracy and specificity, and its sensitivity was higher than the lower range. A similar trend was seen for combination C where the training performance was below the clinician's values; however, the testing shows that CII outperformed the

clinicians in sensitivity, and upper specificity ranges, and was comparable in accuracy. Thus, single entity slightly exceeded the clinicians and the combination with entropy. Moreover, the correlation was the highest performing texture feature outperforming the clinician's performances in two values simultaneously. Combination CII outperformed all other combinations in testing. Furthermore, it outperformed the clinicians in sensitivity and specificity and was comparable in accuracy.

CHAPTER 7: STAGE THREE VIEW COMPARISON RESULTS

7.1 Materials

The same database and demographics used in stage two were applied to stage three. The fundamental difference of this phase was the addition of two views coronal and sagittal. There was a total of 300 images from coronal and 300 from sagittal used for the comparison.

7.2 Methods

The purpose of this stage was to determine if adding additional MRI views will increase performance, or one single view suffices for a comparable classification. Thus, the coronal and sagittal view were processed according to the results of stage two where the highest frequency techniques are being used; thus, the FT of each view. The GLCOM was also used to compare each view's performance, but as with the FT not in the combination of all views due to the volume of inputs. To examine if a mix of views leads to higher performance the greatest texture feature (correlation) and the most top combination of features (CII) will be used for the analysis.

7.2.1 Fourier transforms

The three views were compared for performance during training and testing. The comparison of the views aims to determine if one view is more favorable than the other. In the case of the FT the axial view outperformed the other two views during training performance; however, the other two views also outperformed the clinicians at accuracy and specificity and were comparable in sensitivity, (**Table 7.1**).

Table 7.1: Training performance of each view's Fourier Transform

View	Highest training performance				Lowest training performance			
	Acc.	Prec.	Sens.	Spec.	Acc.	Prec.	Sens.	Spec.
Axial	86	81	94	77	71	67	77	65
Coronal	81	83	78	82	62	63	53	61
Sagittal	80	82	78	83	67	67	73	61

In the case of testing the axial view had a higher performance than the other views. The second-best view was the coronal also outperforming the maximum performance of the clinicians. In contrast, the sagittal view best testing performance only compared to the clinician's accuracy. It outperformed the clinician's sensitivity but was only higher to the lowest range for specificity, (**Table 7.2**).

Table 7.2: Testing performance of each view's Fourier Transform

View	Highest testing performance				Lowest testing performance			
	Acc.	Prec.	Sens.	Spec.	Acc.	Prec.	Sens.	Spec.
Axial	85	87	90	75	67	64	47	81
Coronal	80	82	85	74	60	57	57	63
Sagittal	78	74	96	55	64	62	83	46

Similar results were seen in the case of GLCOM (combination of contrast, correlation, energy, and homogeneity), where the sagittal view had the lowest performing training. However, the coronal view had much higher training performance than the axial view. Furthermore, the axial view was superior in accuracy, precision, and sensitivity to both views and higher than the lower clinician's values for all parameters, (**Table 7.3**)

Table 7.3: Training results for all three views using the GLCOM

View	Highest training performance				Lowest training performance			
	Acc.	Prec.	Sens.	Spec.	Acc.	Prec.	Sens.	Spec.
Axial	70	72	67	72	64	67	59	71
Coronal	75	76	79	71	69	67	83	52
Sagittal	63	62	65	63	58	54	72	46

In contrast, the axial view had a much higher testing performance outperforming the clinicians and the other two views. The coronal view had comparable accuracy and much greater sensitivity, but its specificity was only higher than the lower limit of the clinicians. On the other hand, the sagittal view was much lower in accuracy, precision, specificity, (**Table 7.4**).

Table 7.4: Testing results for all three views using the GLCOM

View	Highest testing performance				Lowest testing performance			
	Acc.	Prec.	Sens.	Spec.	Acc.	Prec.	Sens.	Spec.
Axial	82	86	86	76	76	76	86	67
Coronal	78	78	93	50	69	67	83	52
Sagittal	69	70	89	35	64	61	67	63

Additional to the comparison of views was the comparison of the axial vs the combination of axial plus the other two views. The first combination tested was the correlation, which showed a higher training performance than the single axial view, (**Table 7.5**). Nevertheless, its performance was lower than the clinicians. Similar results were seen in testing if the combination of views outperformed the single axial view and

the clinician's performance, (**Table 7.6**). The values were significantly higher for accuracy, precision, and specificity, and only slightly higher for sensitivity.

Table 7.5: Training results for all three views using the combination of correlation values

View	Highest training performance				Lowest training performance			
	Acc.	Prec.	Sens.	Spec.	Acc.	Prec.	Sens.	Spec.
Axial correlation	70	75	59	81	54	61	34	61
Combination (axial+ coronal+ sagittal)	72	73	68	76	64	66	76	50

Table 7.6: Training results for all three views using the combination of correlation values

View	Highest testing performance				Lowest testing performance			
	Acc.	Prec.	Sens.	Spec.	Acc.	Prec.	Sens.	Spec.
Axial correlation	78	76	76	79	60	54	74	67
Combination (axial+ coronal+ sagittal)	84	85	88	80	79	81	74	83

Another combination tested was the CII combination which included entropy and energy. The entropy and energy for all views gave a total of 15 values, which were used as inputs. In the case of training, the combination of views outperformed the axial view significantly. It also gave comparable accuracy values and higher specificity values than those of the clinician; the sensitivity value was only greater than the lower range of the clinicians, (**Table 7.7**).

Table 7.7: Training results for combination CII (energy and entropy)

View	Highest training performance				Lowest training performance			
	Acc.	Prec.	Sens.	Spec.	Acc.	Prec.	Sens.	Spec.
Axial CII	73	68	60	61	57	66	40	75
Combination (axial+ coronal+ sagittal)	78	84	73	84	64	64	64	65

The testing performance was as the correlation combination where the testing performance of the combination was higher than the single axial view. The sensitivity value was only comparable to the lowest clinician's performance. Nevertheless, the accuracy, precision, and specificity values were much higher in comparison to the other views and the clinician's performance, (**Table 7.8**).

Table 7.8: Testing results for combination CII (energy and entropy)

View	Highest testing performance				Lowest testing performance			
	Acc.	Prec.	Sens.	Spec.	Acc.	Prec.	Sens.	Spec.
Axial CII	78	78	88	72	76	76	80	72
Combination (axial+ coronal+ sagittal)	80	90	71	91	67	79	48	86

7.3 Statistical results

The statistical results from the logistical regression model are in concordance with the performance observed during training and testing. In the case of the individual view comparison, all three views resulted in p-values below .05 showing the statistical difference between AD and NC. (**Figure 7.1**).

Figure 7.1: Box Plot of NC and AD subject for each view.

The image shows that the means for the groups differ within each of the views. FT33 corresponds to the 3x3 window from the axial view. Ft Coronal corresponds to the 3x3 window for the coronal view. Ft Sagittal corresponds to the 3x3 window for the sagittal view. The 0 is represents normal control groups, the 1 AD groups and the asterisk represents the outliers; there are four outliers total.

The statistical analysis shows that even though each view has a statistical difference among the groups, the views also differ from each other. The axial and coronal

views are closer to each other, and the sagittal view shows a larger difference in comparison. In the assessment of a single view vs. the combination of views for both correlation and combination CII, a difference was noted among the views. The single view had a larger standard deviation than those in the combination view for both cases of correlation and combination CII, (**Appendix G**).

7.4 Summary of results

The Axial view had a higher performance than the coronal and sagittal views for both training and testing of the Fourier transform and the combination of all texture features (single entity). Furthermore, the lowest performing image view for both cases and both training and testing was the sagittal view. Additionally, the Fourier transform had higher performance values for all views and while compared to the single entity approach. The coronal view performance was greater than the clinicians for all values obtained with the FT, except slightly lower for sensitivity.

In the case that multiple views can increase performance, it was determined that in the event of correlation the training performance was higher for the combination of views. The axial view had much lower values; however, the combination values even though higher, were still below the performance of the clinicians in the case of correlation. During testing, the axial view had only comparable accuracy, higher upper-level specificity, but lower sensitivity. In contrast, the combination of all views correlation values resulted in much greater testing performance. The testing performance was much higher than the single view, and then the execution of the clinician for all values. Similar results were obtained in the case of combination CII where all the values for energy and entropy were combined for all views resulting in 15 inputs. The

combination of the views outperformed the single view during both training and testing. In the case of training the axial view's performance was lower than the clinicians; however, the combination view was higher in precision, and specificity, comparable in accuracy, and greater than the lower bound in sensitivity. Moreover, the testing performance outperformed the axial view except for sensitivity which was lower, and only comparable to the clinician's lower bound. On the other hand, the accuracy, precision, and specificity were much higher. Overall, the Fourier transform axial view had a higher performance in both training and testing while compared to all the other techniques, and the clinician's highest performing values. However, the combination of all correlation values for all views was also significantly greater than the single axial view and the performance of the clinicians.

CHAPTER 8: DISCUSSION

The primary objective of this study was to investigate if the texture and frequency attributes of MRI images in combination with a feedforward artificial neural network could lead to the classification of AD in a way that is comparable to the clinician's performance. The studies that reported clinician's performance were limited to, accuracy, sensitivity, and specificity. Thus, the accuracy of the clinicians was determined to be 78 percent based on the number of successes confirmed by autopsy [53]. The sensitivity value for the clinicians had a range of 71 to 87 percent of studies between 2005 and 2010 [54]. Additionally, an average performance of 81 percent was reported from 13 studies published much recently. The same approach gave a specificity range of 44 to 71 percent and an average of 70 percent [54] [55]. There were no studies that report the precision values for the clinicians; however, the precision percent estimated from one of the studies were the exact values for true positive and false positives were given. Thus, the cutoff for precision is at 78 percent similar to accuracy [53]. Moreover, precision was used to distinguish between the highest performing networks. For this work, the best performing ANN structures were those with simultaneous values comparable or greater than those of the clinicians. Thus, the use of artificial neural networks (ANN models) in the combination of a particular frequency and texture attributes can lead to a comparable performance of those of the clinicians.

8.1 MRI texture and frequency attributes

One of the main questions being addressed through this study was whether image attributes and frequency domains attributes from MRI images contain valid information for classification of Alzheimer's this work. The comparison of the discrete wavelet

transform and the Fourier transform at low frequencies showed that the Fourier transform gave higher performance than the DWT. Furthermore, its performance results were comparable and even higher the clinician's performance. The FT low-frequency characteristics to distinguish between AD and NC groups were in concordance with other studies. In the case of the Fourier transform and electroencephalogram (EEG), the research showed that there was a higher magnitude in the low-frequency range for AD individuals than those compared to NC [56]. It is important to note that several studies suggested the use of DWT detail coefficient as attributes rather than the approximation coefficients [57]. Nevertheless, the comparison between the Fourier transform and the DWT in a one to one ratio is only achievable with the low frequencies because the DWT contains both time and frequency components [51]. Another, visible difference between the transforms is the window size and the performance of each transform. For the DWT, the larger window size had higher performing values for training (**Table 6.1**), and testing which suggests that limiting the window might reduce the information, and therefore reduce performance. On the other hand, the Fourier transform showed almost no difference in the testing performance due to the window size. However, there was a difference during training where the FT achieved 100 percent accuracy, precision, sensitivity, and specificity. Overall, the use of low-frequency domain was much more favorable for the Fourier transform surpassing the clinician's values.

The texture attributes from the images had a larger range of success. The individual texture features when used as inputs resulted in lower performance for both training and testing while compared to the clinicians; however, when used in combination (GLCOM) the contrast, correlation, energy, and homogeneity provided training and

testing performances comparable and even higher than the clinicians, (**Appendix C**). The result obtained by the GLCOM gives similar approaches than the case where the GLCOM has been used to increase the sensitivity and specificity of brain tumors; however, one major difference is that these brain studies use a 3D co-occurrence matrix [58]. A similar study using MRI images and GLCOM used a much higher number of attributes a total of 16 but concluded that a larger number of texture features did not improve accuracy [59]. Another comparison was the performance of the GLCOM and the performance of the GLCOM in combination with entropy. The result showed that entropy lowers the performance of the network, which might be a result that entropy cannot be normalized. The value acquired for entropy is a single value; therefore, its normalization will lead to one, which will be insignificant if all entropies are normalized. In the case of the GLCOM, the texture features obtained by the matrix give testing performances higher than the clinicians. A major difference between this study and previous studies is the analysis of the independent features forming the GLCOM. All previous studies had focused on study all features in combination; however, in this approach correlation was identified as a high texture feature that can give comparable performance results to the clinicians. Furthermore, the study of the combination of different features allowed for the understanding of which features can lead to higher performance. Another study determined that the reduction of elements can improve performance; the research suggested that reducing texture features alleviates the effects of high dimensionality, and speeds up retrieval rates [60]. Therefore, a lower number of texture features can have better performances than a combination of multiple features.

The elements of the GLCOM (contrast, correlation, energy, and homogeneity) had different levels of performance; however, correlation had higher accuracy, sensitivity, and specificity performance in comparison with the clinicians. Additionally, the combination of energy and entropy also had higher sensitivity and specificity performance, and comparable accuracy. Entropy alone performed lower than the clinicians in accuracy, and sensitivity, but higher in specificity. On the other hand, the performance of energy had a higher sensitivity, but lower accuracy and specificity. Thus, the combination of energy and entropy improved performance. Another, study that observed texture attributes in images individually used CT scans, and pulmonary nodules; however, it showed that entropy was higher in affected lungs, and energy was greater in healthy lungs [61]. Such observation might suggest that entropy and energy are opposing measurements. Perhaps, similar results are true in the case of AD, and therefore, their combination is complimenting and leads to higher performance, (**Figure 8.1**). The graph shows the energy and entropy are different as they contrast with each other; thus, there is a high probability that features opposed to each other, give better performances because they complete each other given a larger range of information. However, a deeper study should be run to confirm these inferences.

Figure 8.1: Principal Components plot for Texture features.

Lines running parallel to each other are closely related; therefore, there are highly collinear. On the other hand, if the lines are orthogonal, then there is no correlation among the variables. Entropy was the only variable that gave a single value; therefore, there is no mean available. For all other variables, the mean was utilized.

The results obtained from the neural network performance were like those achieved by the logistic regression. The P-values for all means of all texture features showed that there was a statistical difference among the groups; thus, individual texture elements can be used for the differentiation of AD from NC, (**Appendix D**).

8.2 Single view performance vs. combination of views

The analysis of using one view only for classification or using all three views was another point of investigation in this study. The three views were compared among each other based on the highest performance obtained by the axial view. The highest performing view in the case of FT was the axial view having values greater than those of the clinicians. In comparison with the GLCOM, the axial view showed higher performance than the other two views and was comparable to the clinician's performance. However, this is contrasted to other studies where the favorable image is the coronal view because it provides a much clearer picture than the other two directions [59]. The coronal view did perform higher than the sagittal, and the clinician's performance, but no greater than the axial. One possible reason this study differs from others might be the region selected for analysis. The area size did not affect significantly the performance the FT; however, it influenced the performance of the DWT. The DWT with the larger window had better performance values than the one with the smaller area. Thus, processing the full image, and then selecting a window could change the results. The rationale for choosing a ROI was that there are specific sections of the brain known to be affected by AD, and using those regions only reduces noise. Therefore, the probability of overfeeding the network is reduced, and the likelihood of having useful information increases. The use of any of the views as for classifier was statistically variable, as the p-value for the axial, sagittal, and coronal showed a statistical difference among the groups, (**Appendix F**).

From the texture features, correlation had the highest performance. The correlation reflects the consistency in the texture of the image, and it has been used to identify

changes in digital images over time [62]. However, even though the correlation in the axial view outperforms the other views, is only comparable to the performance of the clinicians. On the other hand, the combination of the correlations from all three views significantly increases the performance of the network having superior percentages than the clinicians. Moreover, the statistical analysis showed that there was a difference in the means of the correlation in the axial view, and the combination of correlations, **(Appendix G)**.

In the case of combination CII, which is composed of entropy and energy, the results showed that the combination of the features from all three views improved the accuracy, precision, and specificity. However, the specificity was barely comparable to the clinician's lowest performance. The statistical analysis provided similar results where there was a significant difference among the AD and NC. Moreover, there was also a difference between the mean of the single view and the combination of views, **(Appendix G)**. Overall, the combination of the three views provides a higher performance. The use of three views can give the full information of the region being analyzed, and therefore, a more detail information of the area. Similar studies support that use images for analysis had showed that the three views are favorable to reconstruct the full image of the region being observed [63] . The three views provide a three-dimensional information of all the sides of the areas being study; therefore, their combination is desired to increase accuracy.

8.3 Network performance

The use of computer-aided diagnosis systems has been used for the classification of Alzheimer's; however, the combination of texture attributes, frequency attributes of MRI images in conjunction with an ANN model has not yet been studied. Moreover, this study seeks to investigate if the feedforward artificial neural networks (ANN) in combination with the texture and frequency attributes of MRI images can provide a diagnosis comparable to the performance of the clinician. The same values described earlier were used for the comparison: accuracy (78 percent), sensitivity (71-87 percent), and specificity (44-71 percent). The study shows that texture features can be useful for differentiating among groups. The use of correlation measures the linear dependency or the probability of occurrence of particular pixel pairs; thus, previous studies used correlation to observe and identify changes that occurred over time with the use of digital images [3]. Therefore, the greater performance observed in this study using the correlation of the MRI might be detecting the changes that occurred over time due to the progression of AD. The shrinkage or enlargement of voids is a key identifier of AD [62]. Therefore, texture features sensitive to changes in area or mass volume will give higher performances if there are detectable differences between NC and AD subjects.

A peculiar finding of this study was the performance of energy and entropy. Both features had low performances when used individually; however, in combination, their performance increased significantly. Energy measures the local uniformity, and entropy the randomness present in the image. They are opposite of each other as shown earlier; however, their combination suggests that they might be complements of each other.

However, such inference needs to be further evaluated since homogeneity and contrast were also opposite of each other, but their combination did not increase performance. Thus, it might be that is not only enough that the features are different from each other, but the degree of difference and the level of difference in their measurements.

The frequency features obtained from the images show that low frequencies are useful for classification; however, they hinder the performance of the DWT. One limitation to the DWT is the normalization as it is an orthogonal matrix its normalization is much complex than that of the FT. In this study, the normalization of the DWT was performed in the selected window after processing; however, a better method might include an orthogonal normalization or no normalization at all. Thus, in the case of frequency and texture attributes both were used and gave values comparable and higher than those of the clinicians. However, not all texture features and frequencies techniques provide these results.

Additionally, the networks structure and training size influence performance. This study showed that in the case where nine inputs were used the single layer, and fewer neurons performed much higher than with the additional layers and neurons. Regarding larger inputs such as 16, the single layer with a higher number of neurons performed better (structure 1:35). It is suggested to increase the number of neurons to improve performance [52]. However, there are no studies investigating the relationship between the number of neurons and the volume of inputs. Similarly, there are no studies that looked at the relationship between the training size and its effects on performance. Moreover, forums for professional programmers and artificial neural networks experts have numerous suggestions. There is no clear consensus on how to determine the training

size other than trial and error. However, this study found that in the cases where training performance was lower the testing performance was much higher. Similarly, in the cases where training was lower testing had much higher performing values; especially, when either training or testing performance values were in the 60 percent. However, the difference in performance was much closer for cases of where the training performance was above 70 percent. A proposed solution to increase both training and testing performance can be increasing the number of samples. A larger number of data samples can give testing and training enough values to perform adequately. There are not studies supporting that such approach would be adequate; however, increasing the sample size will increase performance [52].

In summary, some texture attributes provided comparable performance results to those of the clinicians. The low-frequency transform specifically the FT provided higher performance values than the clinicians. Therefore, both texture and frequency attributes in combinations with a feedforward neural network can perform at the level of the clinician and even higher.

CHAPTER 9: CONCLUSION AND FUTURE WORK

9.1 Conclusion

Alzheimer's disease is a growing concern due to the population it targets, the rate it affects it and the number of individuals living with the condition. Furthermore, the increasing growing projection rate will cause a substantial economic burden on the individuals, their families, and their countries. Efforts on achieving proper and effective therapies are being studied; however, a significant limitation is the adequate and early diagnosis of the condition. Thus, the use of CAD systems is employed for the analysis of MRI images, and diagnostic classification of AD. However, there are not studies investigating the combination of MRI image attributes, and backpropagation artificial neural networks (ANN). Therefore, this study proposed the use of frequency and texture features from MRI images in combination with the ANN model to classify AD subjects at a comparable rate to the clinicians. This study found that the texture and frequency attributes extracted from the MRI images provided useful information about the picture. Additionally, measures of correlation, energy, and entropy can have higher performance for classification. Moreover, the use of low frequencies from the FT performed far greater than texture attributes and can have better performances regarding specificity, accuracy, sensitivity, and precision, than the clinicians. It was also found that the combination of texture attributes from axial, sagittal, and coronal views improved the performance of the network; however, the axial view outperformed all other views. It was also found that fewer neurons performed better for fewer inputs, and that increasing the number of neurons improve performance for inputs above nine. However, increasing the layers did not improve performance. Furthermore, the training size influenced both

training and testing performance. The training performance was lower when the testing performance was higher, and vice-versa.

In conclusion, this study showed that texture and frequency attributes in combination with a feedforward artificial neural network could lead to the classification of Alzheimer's disease with a similar and even higher performance of the clinicians. Therefore, the ANN models can help as a second-hand diagnosis to aid the clinicians to increase their level of confidence. However, the limitations of computer aided diagnostic should be noted, and even though high performances are acquired, they are not enough to be a primary diagnostic tool. The clinicians have other skills set that in combination with CAD systems can improve the early diagnosis of AD.

9.2 Future work

Time and resources limited this study; therefore, there are still investigative inquiries that can be further addressed. Additional texture features and combinations can be used to determine the relationship of combinations of elements and their relationship regarding their different measurements, such in the case of entropy and energy. Another inquiry would be the normalization of the DWT by a means that not lead to only zeroes. Furthermore, the combination of DWT and FT can be study to determine if performance is increased by combing both frequencies. Likewise, to study if the combination of the transforms from all three views also increase performance as in the case of texture features. A further study is necessary to compare the use of different programming languages to determine if the performance is limited by the capabilities of the software and not the data. Another study can include to increase the sample size, and to add a group such as Parkinson patients to study if the classification performance is still

comparable to the clinicians and if it is sensitive to overlapping regions. A significant improvement of this study will be the use of MRI images of individuals who are known to have AD or have a higher probability of AD, but whose symptoms are non-present. A superior performing ANN model with such population could suggest that the ANN models could improve the early diagnosis of the disease, and therefore increase the probability of successful treatments.

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APPENDICES

APPENDIX A

Figure A. 1: Structure 1:35 with 9 inputs and 1 output

Figure A. 2: Structure 2:35 with 16 inputs and 1 output.

This structure has two hidden layers and each layer contains 35 neurons. There is one output only.

APPENDIX A (CONT.)

Figure A. 3: Structure 1:15 with 9 inputs and 1 output.

This structure has one hidden layer and 15 neurons within the hidden layers. Here are 9 inputs and 1 output; however, the number of inputs can be increased or decreased. Though, the expected output will always be one.

APPENDIX B

Figure B. 1: Structure 1:35 with 8 inputs and 1 output (combination of any two features except entropy). Entropy only adds one input; therefore, the number of inputs will change to 5.

APPENDIX C

Table C. 1: Group A definition of combinations

Combination Group and Number	Features combined
AI	Contrast and Correlation
AII	Contrast and Energy
AIII	Contrast and Homogeneity
AIV	Contrast and Entropy

Table C. 2: Group B definition of combinations

Combination Group and Number	Features combined
BI	Correlation and Energy
BII	Correlation and Homogeneity
BIII	Contrast and Entropy

Table C. 3: Group C definition of combinations

Combination Group and Number	Features combined
CI	Energy and Homogeneity
CII	Energy and Entropy

Table C. 4: Group D definition of combinations

Combination Group and Number	Features combined
DI	Homogeneity and Entropy

APPENDIX D

Targets	1	150	(Event)
	0	150	
Total		300	

Deviance Table

Source	DF	Seq Dev	Contribution	Adj Dev	Adj Mean	Chi-Square	P-Value
Regression	5	29.649	7.13%	29.649	5.9298	29.65	0.000
Mean Contrast	1	7.669	1.84%	5.042	5.0421	5.04	0.025
Mean correlation	1	7.429	1.79%	7.085	7.0850	7.09	0.008
Mean energy	1	0.481	0.12%	5.071	5.0709	5.07	0.024
Entro	1	14.051	3.38%	13.989	13.9887	13.99	0.000
Gender	1	0.019	0.00%	0.019	0.0186	0.02	0.892
Error	294	386.239	92.87%	386.239	1.3137		
Total	299	415.888	100.00%				

APPENDIX E

Response Information

Variable	Value	Count
Targets	1	150 (Event)
	0	150
	Total	300

Deviance Table

Source	DF	Seq Dev	Contribution	Adj Dev	Adj Mean	Chi-Square	P-Value
Regression	4	54.143	13.02%	54.143	13.5358	54.14	0.000
Mean FT33	1	23.848	5.73%	41.537	41.5369	41.54	0.000
Mean DWT33	1	27.963	6.72%	3.464	3.4640	3.46	0.063
mean DWT44	1	2.281	0.55%	2.230	2.2305	2.23	0.135
Gender	1	0.051	0.01%	0.051	0.0512	0.05	0.821

Term	Coef	SE Coef	95% CI	Z-Value	P-Value	VIF
Constant	-8.69	3.13	(-14.83, -2.55)	-2.78	0.006	
mean ft44	-18.00	3.15	(-24.17, -11.82)	-5.71	0.000	1.59

APPENDIX F

Nested ANOVA: Mean ft coronal versus Targets, Gender

Analysis of Variance for Mean ft coronal

Source	DF	SS	MS	F	P
Targets	1	0.0295	0.0295	27.526	0.034
Gender	2	0.0021	0.0011	0.627	0.535
Error	296	0.5062	0.0017		
Total	299	0.5379			

Nested ANOVA: Mean ft Sagittal versus Targets, Gender

Analysis of Variance for Mean ft Sagittal

Source	DF	SS	MS	F	P
Targets	1	0.0240	0.0240	151.291	0.007
Gender	2	0.0003	0.0002	0.193	0.824
Error	296	0.2432	0.0008		
Total	299	0.2676			

APPENDIX G

Figure G. 1: Comparison plot of single view and combination view of CII.

The figure shows the difference between the means of CII (Energy + Entropy) by group and gender. 0 is for normal controls (NC), and 1 is for AD patients. The mean for the single view (Left side) shows that there is a difference among the groups NC and AD, and among the Males and females. The combination of multi-view showed similar results; however, the differences between the NC and AD groups are much pronounced. In both cases, the mean among males from NC and females for AD are closer together.

APPENDIX G (CONT.)

Figure G. 2: Correlation Comparison Plot single view vs. combination view.

The figure represents the means of a single view (left side), and by groups, 0 represents normal controls (NC), and 1 represents AD group. The right side shows the means for the combination of multi-views (axial, sagittal, and coronal views). The images depict a clear difference among the groups' means for both cases where the NC has a lower mean in both instances. In the comparison between single and multi-view, there is also a difference between the average values; the combination view resulted in lower means for both AD and NC groups.