A Comparative Study of Neuroimaging and Pattern Recognition Techniques for Estimation of Alzheimer's Disease

Saima Farhan, Muhammad Abuzar Fahiem, Fahima Tahir, Huma Tauseef

Department of Computer Science, Lahore College for Women University, Lahore, Pakistan
itisab@gmail.com

Abstract: Alzheimer's disease is known to be a major cause of death around the globe and according to Alzheimer's association report (2013), the death percentage of the disease has increased to 68% since year 2000. Early detection of the disease is crucial in order to help the patients, relatives and care givers to cope with the situation and to help the practitioners discover new drugs. For this reason, there is an imperative need for automated techniques to be developed in order to detect the disease well before irreversible loss is made. In recent years, neuroimaging combined with machine learning techniques have been studied for the detection of Alzheimer's disease. The diagnosis process may be strengthened by incorporating genetic information, as genetics also play a key role in onset and progression of this disease. A comparative study of different neuroimaging techniques is being reported in this paper. In addition, the contribution of research community in this domain is studied and a comprehensive comparative study is conducted. Keeping in mind the shortfalls of the study conducted, we have designed a classification framework that is helpful in processing data from heterogeneous sources, in order to gain benefit of complementary information present in multiple data sources. Our research work is focused on brain images and genetic data as biomarkers for the detection of Alzheimer's disease, with a primary focus on improving the prediction accuracy. The research work will be beneficial in assisting practitioners for the interpretation of medical images and diagnosis of certain diseases. It will also aid in uncovering the underlying reasons of the disease, and ultimately in helping discover appropriate drugs. The proposed framework will play a vital role in the domain of Computer Aided Diagnostics and Preventive Studies.
[Farhan S, Fahiem MA, Tahir F, Tauseef H. **A Comparative Study of Neuroimaging and Pattern Recognition Techniques for Estimation of Alzheimer's Disease**. *Life Sci J* 2013;10(7s):1030-1039] (ISSN:1097-8135). http://www.lifesciencesite.com. 166

Keywords: Alzheimer's disease, Brain Imaging, Pattern Recognition, Image Analysis, Genetic Data.

1. Introduction

Alzheimer's disease (AD) is a neuro-degeneration disorder that progressively declines individual's memory and cognitive skills. It is a major form of dementia (Boss, 2000; Hebert et al., 2001) that is incurable and unpreventable up till now. AD affects size, structure and function of the brain. It begins in hippocampus which processes memories and cerebral cortex which is responsible for thought processing and decision making. The cognitive domains that are impaired in AD are memory, language, functional abilities, problem solving, perceptual skills, orientation, constructive abilities and attention. In last stages of the disease, individual are unable to function mentally, socially and physically and are totally dependent on the care givers.

The disease mostly effect people of 65 years and above and the risk of being effected doubles every five years. In addition to age, other risk factors are environment and genetics that play a role in onset and progression of this disease. AD affects 5% over the age of 65 and 20 % over the age of 80. The proportion of the population above 65 years of age is increasing with time, hence is the chances of AD. Around 60 to 80 percent of the dementia cases come under the category of AD (Hebert et al., 2003). It is considered to be one of the major causes of death around the globe. Deaths from heart disease have decreased by 16%, breast cancer by 2%, prostate cancer by 8%, stroke by 23% and HIV by 42% whereas deaths by AD increased 68% since year 2000 (Alzheimer's association report, 2013).

Alzheimer's is a challenge of the 21st century that affects individual's mental and social health. It is considered to be the most costly disease. The number of Alzheimer's patients is growing every year and it is estimated that by 2050, every 1 of 85 persons will suffer from AD (Brookmeyer, et al., 2007). Currently the worldwide estimation of Alzheimer's patients is 36 million and with increase in life expectancy this figure will shoot up to more than 115 million people by the year 2050. One million people in Pakistan are estimated to be suffering from AD.

The main causes for AD are the accumulation of Beta amyloid (βA) and Tau (τ) proteins in the brain (Thompson et al., 2007) which block the communication of nerve cells making them die. The two forms of AD (Blennow, 2006), are autosomal dominant familial AD and Sporadic AD. Autosomal dominant familial AD is known to be genetically

inherited. The genes responsible for this type of AD are amyloid precursor protein (APP), presenilin 1 and presenilin 2. Researchers agree that almost all early-onset Alzheimer's disease, a condition that occurs in 30s, 40s and 50s, is inherited. Sporadic AD is caused by a gene called APOEε4. The presence of this allele increases the risk of a person for development of AD. Sporadic AD is also known as late-onset Alzheimer's disease, as it occurs after 65 years of age.

The clinical diagnosis of AD includes investigating patient history, collateral history from relatives and clinical observations. Test that is widely used for evaluation of cognitive decline is Mini-Mental State Examination (MMSE). MMSE combine with Clinical Dementia Rate (CDR) scale and family/caregivers interviews are used to evaluate and track a subject's cognitive decline. Although these tools are beneficial in monitoring one's cognitive impairment level, but these techniques are time consuming and cannot capture the earlier changes in brain that can be an indicator for the development of AD. Scientists have agreed that brain changes take place almost 20 years before clinical symptoms can be observed. So there is an immense need of image-based analysis techniques for detecting brain changes much earlier than irreversible neuronal loss is made (Fox and Schott, 2004).

The ultimate diagnosis of Alzheimer's can only be done by postmortem of the brain after death. Because AD is detected at a late stage, the current practices and procedures can only slow down its progression. For this reason, researchers are interested to develop reliable and early detection methods of AD in order to improve preventive and curing treatments. It will be especially beneficial for those suffering from Mild Cognitive Impairment (MCI), not to develop AD in the near future.

The major issue at the moment is that there is no cure for Alzheimer's. There is an immense need to devise automated approaches for early diagnosis and detection of AD as it may aid experts to prescribe medications that can at least slow down the progression of the disease. The possibility of early diagnosis may also help the patient and the patient's family to develop coping techniques.

The rest of the paper is organized as follows: A comprehensive literature survey is presented in section 2. Section 3 provides a comparative study of different neuroimaging techniques and the work done in the domain of neuroimaging and pattern recognition for the purpose of AD identification. Keeping in mind the advantages and disadvantages of various techniques we have proposed a framework in section 4. Section 5 provides discussion and the paper concludes in section 6.

2. Literature Survey

The modern way of neuroimaging techniques have enabled researchers to analyze and quantify different structures and functions of the brain. These imaging techniques aid in the detection of AD. Moreover, genetics also has significant impact on the onset and progression of this disease. For this reason genetic aspects of AD can also be incorporated in the detection of AD. In this section an in-depth literature study is conducted to comprehend existing techniques and practices in the neuroimaging and pattern recognition based disease detection and DNA analysis. Shortfalls and limitations of the existing techniques are considered while designing a new framework for the diagnosis of AD.

2.1 Brain Imaging

Modern imaging techniques have played variety of roles in the study of AD. There are a number of safe and recognized techniques for brain imaging that are helpful in evaluating various aspects of the neuroanatomy, pathology, physiology and chemistry of the brain with great reliability. These methods are extremely beneficial as they provide a way for non-invasive in vivo study of the brain. Such techniques can be used for the measurement of local neuronal activity of the living human brain and can be broadly classified as structural imaging techniques and functional imaging techniques (Fantini et al, 2001).

The AD affected individuals have changes in the size, structure and function of the brain. The anatomical changes can be captured through structural imaging which provides a way to get quantitative information about the anatomy of the brain. Atrophy is a late feature in the progression of AD and structural neuroimaging assessment is based on features like atrophy. Therefore, it is crucially required to develop new methodologies for early and precise recognition of AD at the prodromal stages. Structural modalities that are widely used for Alzheimer's study include Computed Tomography (CT) (Lopez et al., 1995; Jobst, Barnetson, & Shepstone, 1998) and Magnetic Resonance Imaging (MRI) (Davatzikos et al. 2008; Klöppel et al., 2008).

Functional imaging techniques provide information about cerebral metabolic activity inside the brain which helps to understand physiological function of the brain from image-based data. It also enables to identify pathologic anomalies in internal tissues of the brain. The changes in cerebral metabolic activity can be noticeable before structural and anatomical variations are seen. Functional modalities include functional Magnetic Resonance Imaging (fMRI) (Wagner, 2000), Magnetoencephalography (MEG), Electroencephalography (EEG), Positron Emission Tomography (PET) (López et al., 2011; Ramírez et al.,2009) and Single-Photon Emission Computed Tomography (SPECT) (Stoeckel et al.,

2001).

The exact conclusion about the disease cannot be done until after the death, when an autopsy can be done to check the changes in the brain. But advanced brain imaging have proved to be a useful tool in this regard and is set as an industry standard for the diagnosis of the disease at this time. These imaging modalities provide a large amount of information. But this large amount of information is not knowledge. Having more data is only one half of the equation. There is an immense need for the design of such models and algorithms that can face the challenge posed by this ocean of data. The analysis of this wealth of data to extract meaning patterns is by itself challenging, considering the computation time and dimensionality of imaging data.

2.2 Pattern Recognition

Pattern recognition is a branch of artificial intelligence that involves the design of new algorithms for recognition of complex patterns, with its application in handwriting recognition, speech recognition, fingerprint recognition, biometrics, stock market analysis, medical diagnosis and many more. The focus of our research is medical diagnosis, and the aim being to classify neuroimages into healthy subjects and AD.

For meaningful interpretation of brain images, these images pass through a number a phases. Vast research has been carried out to extract meaningful information from neuroimages. The image processing steps for such images may include whole brain extraction, image registration, segmentation, feature extraction and classification. The description of each step is provided in the following text.

2.2.1 Whole Brain Extraction

Also known as "skull stripping", whole brain extraction separates non-brain voxels from brain voxels to prepare it for image analysis. A number of techniques are available for whole brain extraction including Multi Atlas Propagation and Segmentation (MAPS) (Leung, et al., 2011), Brain Extraction Tool (BET) (Smith, 2002), Hybrid Watershed Algorithm (HWA) (S´egonne et al., 2004) and Brain Surface Extractor (BSE) (Sandor & Leahy, 1997).

2.2.2 Automated Registration

Registration allows the alignment of multiple images by finding their spatial correspondence, so that they share a common coordinate system. (Hajnal et al., 2001). Techniques used for automated registration are atlas based registration (Wolz et al., 2010), intensity/voxel based registration (Ashburner & Friston, 2000) and feature based registration (Maintz et al., 1996).

2.2.3 Anatomical Segmentation

Segmentation describes the process of dividing the image into anatomically defined regions and assigning labels to each region. Some common segmentation techniques used in literature are brain atlas generation (Mazziotta et al., 2001), multi atlas segmentation (Lotjonen et al., 2010), automatic segmentation (Kovacevic et al., 2002) and shape-based segmentation (Tsai et al., 2003).

2.2.4 Feature Selection

Feature selection is the process of defining a subset of features from the available images that can be helpful in design of effective learning models. Main objective of feature selection algorithms is to derive relevant features which along with the classification technique increase performance and predictive power of the system. Features that are used for AD can be broadly classified as region based features (Chupin et al., 2009), voxel based features (Klöppel et al., 2008) and vertex based features (Querbes et al., 2009).

2.2.5 Classification

A number of classifiers have been designed so far including Linear Discriminant Analysis (LDA) (Fisher, 1936), Support Vector Machines (SVM) (Vapnik and Lerner, 1963), Neural Networks (NN) (Savio et al., 2009) and Principle Component Analysis (PCA) (Lopez et al., 2011) to name a few. These classifiers perform well on medical images, as well as in other pattern recognition domains.

2.3 Brain Imaging and Pattern Recognition

A number of pattern recognition based methods on the advanced brain imaging have been applied for Alzheimer's study. The key to pattern recognition for Alzheimer's is the extraction of features from a variety of neuroimaging techniques and then its classification. A large number of techniques exist in literature for extraction of features. Similarly an enormous number of classification methods can be found in literature that can perform with high accuracy.

MRI being a non-invasive method and showing high potential in characterizing AD is widely used for AD studies to quantify gray and white matter integrity with high reproducibility (Unal et al., 2011). Many studies based on image analysis have shown that hippocampal/cortical volume changes during AD (Pennanen et al., 2004).

Early methods used for diagnosis of AD used volumetric measurements and were based on manual extraction of region of interest (ROI). The problem with such methods is that they do not show high sensitivity and specificity in diagnosis of Alzheimer's individuals. Such limitations are overcome by the use of voxel based morphometry (VBM).

VBM is a whole brain unbiased objective technique, for detecting group differences in the density or volume of the brain matter. Such techniques come under the umbrella of univariate

models, and are widely used. (Patil and Yardi, 2011) performed a quantitative volumetric study on Mild Cognitive Impairment (MCI) and AD subjects to show that the changes in mean values of Grey Matter (GM), White Matter (WM), Cerebrospinal Fluid (CSF) and total volume of brain can be used as discriminative feature between AD and MCI. Although VBM methods are used for detecting group differences, they are of limited use for classifying individuals.

The limitations of the ROI and VBM methods are overcome by multivariate approaches which deal whole image as an observation. Recent investigations are focused on the use of high dimensional pattern classification methods that considers relations between different brain regions. While these techniques perform well, high dimensionality of the features and small number of samples as well as label ambiguity arises as major issues for medical images. The first problem is also known as 'curse of dimensionality'.

An image based classification method is proposed by (Ye, et al., 2011) for classification of AD subjects using MRI scans. The technique is based on dimensionality reduction using non-linear manifold learning and semi-supervised classifier is used to cater class label issues. An automatic unsupervised classification method for effectively differentiating AD subjects from normal aging is proposed by (Long and Wyatt, 2010). They used symmetric log-domain diffeomorphic demons algorithms to compute the pair wise registration of MR scans. The Riemannian distance between them, calculated using its deformation field, is used in spectral embedding algorithm, to project images on low dimensional space. Quick shift clustering algorithm is finally applied for partitioning images into classes.

To isolate MRI's that shows symptoms of AD, (Bagcl & Bai, 2007) used different types of wavelets for feature extraction and different SVM kernel functions for classification. It was shown that for classification, Gabor wavelets achieve better results than Daubechies wavelets. (Patil & Yardi, 2011) presented a technique for feature extraction and classification of MRI into those showing AD, MCI or Cognitively Normal subjects. Before feature extraction, 3D MRI is normalized using Voxel Based Morphometric (VBM) analysis, spatial filtering and slice averaging into a 2D MRI slice. Features are extracted using Discrete Wavelet Transform (DWT) and Feed Forward Artificial Neural Network is used for classification.

MRI as biomarker for AD detection has been proven in many studies, but MRI as diagnosis tool for MCI is a more challenging problem and has been paid less attention. In case of functional imaging further investigation is required, especially in case of MCI. Functional modalities such as PET and SPECT measure the brain metabolic activity by the use of a radioactive tracer, which is injected in the body. The movement of the nuclear medicine is monitored in the body and hence abnormalities are identified (Wong et al., 2002). PET and SPECT images are used in a number of studies for the successful classification of AD, using a variety of classifiers. PET images are used with discriminant analysis (Higdon et al., 2004) and a boosting classifier (Silveira and Marques, 2010) which is a mixture of simple classifiers, for the successful classification of AD from normal subjects. (Kosugi et al., 2003) used neural networks with both PET and SPECT scans for the same purpose. Nearest Mean Classifier (NMC) (Stoeckel et al., 2001) and Fisher Linear Discriminant (FLD) (Fung and Stoeckel, 2007) are used with SPECT scans, for diagnosis of normal subjects versus AD patients.

2.4 Genetics

The root cause for AD is unidentified; however the role genes play in the onset and progression of this disease cannot be ignored. Genetics information can be used successfully for detecting the onset and development of AD. From a genetic perspective, AD is a heterogeneous disorder with both familial and sporadic forms. Both forms share the same pathological features.

2.4.1 Genes Implicated in Familial Alzheimer's Disease

Early onset of AD that occurs in 30's, 40's and 50's of an individual life's, is mostly inherited (Dawbarn & Allen, 2007). It has been shown that this type of AD is a direct cause of a number of different gene mutations on particular chromosomes. The genes involved are amyloid precursor protein (APP) on chromosome 21, Presenilin 1 on chromosome 14 and Presenilin 2 on chromosome 1. The mutations of genes cause formation of abnormal proteins, which forms a basis of AD; for example, increased production of Aβ peptides.

2.4.2 Genes Implicated in Sporadic Alzheimer's Disease

The other form of AD is sporadic and usually occurs after 65 years of age. The major risk factor for late-onset AD is age (Rocca et al., 2004), but other factors like genetic, lifestyle and environment also play their roles. A genetic risk factor has been identified which appears to increase the risk for developing the disease. The APOE gene on chromosome 19 is the only one so far shown to be associated with the development of sporadic AD (Dawbarn & Allen, 2007). Apolipoprotein E (APOE) gene comes in three forms or alleles; APOE ε2, APOE ε3 and APOE ε4. The most common of these is APOE ε3, which has a neutral effect, while ε2 allele has a neuro-protective effect. APOE ε4 is involved in Aβ

deposition tangles formation. Carriers of APOE ε4 allele are at a higher risk of developing AD than those who do not have an APOE ε4.

Neuroimaging techniques have enabled us to study the brain in vivo and analyze and quantify its structures. Some neuroimaging techniques like PET can be used to study the accumulation of amyloid in the brain tissues and its correlation to genetics. Genome wide association studies have been able to identify a number of genes that are either directly responsible for the disease onset or may increase the chances of an individual to develop AD. More research is this area is still required. Research in combining imaging and genetic risk factors can definitely increase the prediction accuracy of the disease.

3. Comparative Study

With the advancements in neuroimaging technology and the development of new imaging techniques, search for precise, cheap and noninvasive techniques have been significantly elevated. In this section we have compared various neuroimaging techniques considering its different aspects. Among these the most imperative attributes are spatial and temporal resolution of an imaging technique. Spatial resolution determines to which degree the measured activity is localized within the brain. Temporal resolution refers to how closely the timing of neuronal activity can be estimated from measured data. Functional imaging techniques can be further classified as direct or indirect. Techniques that measure neuronal activity directly through electrical or magnetic effects of brain activity are called direct methods in contrast to indirect methods that rely on hemodynamic data. All techniques have relative strengths and limitations which make them appropriate or inappropriate in various conditions. A complete comparison of available neuroimaging techniques are presented in Table 1.

A comprehensive literature survey of AD identification using high dimensional pattern classification methods have been presented in Table 2. Extensive research has been carried out using either one of the neuroimaging modalities or a combination of more than one. In addition to neuroimages, some have also incorporated the risk genes and CSF values in an effort to increase the prediction accuracy. In different works, the data sets have been divided in multiple groups for the purpose of classification. The most common of these groups is cognitively normal (CN) and Alzheimer's patients (AD). Others may be mild cognitive impairment (MCI) which is a prodromal stage of AD. An effort has also been made to see the conversion from MCI to AD, but there is still a lot of research to be carried out. Results have been reported in the form of accuracy, specificity and sensitivity.

4. Proposed Framework

We have proposed a framework that is capable of dealing with heterogeneous data. The main driving force for the design of the proposed framework is to gain benefit of complementary information present in different data sources for the purpose of classification. The proposed framework makes use of image processing and pattern recognition techniques to help practitioners identify the disease from neuroimages at an earlier stage before irreversible loss to brain has occurred. The diagnosis process is strengthened by incorporating genetic data that leads to improvement in the prediction accuracy. Minimizing heterogeneous disparity between brain imaging and DNA structure provides a relation that is helpful for effective diagnosis of the disease.

The framework we proposed consists of analysis of brain images and genetic data and is presented in Figure. 1. Brain images are preprocessed after which features are extracted from it. Gene data analysis is done and gene mutations or the genes that play as risk factors for development of AD are extracted. Features extracted from different data sources are then used for the formulation of feature set. Once the feature set is ready it is fed to the classifier for possible classification as Alzheimer's effected or cognitively normal individual.

5. Discussion

We have discussed a number of neuroimaging, image processing and pattern recognition techniques. All have their associated pros and cons. For automated analysis and classification of neuroimages, spatial resolution is an important aspect which cannot be ignored. Neuroimaging techniques like PET with high spatial resolution are preferred. PET imaging technique is also capable to capture the metabolic activity deep inside the brain as opposed to MEG and EEG. Similarly we need to know the anatomical structures of the brain to identify the regions of interest. For this purpose MRI is considered to be the best. The datasets including MRI, PET images and genetic data, used for evaluation of our framework, are obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI). In the domain of image processing and pattern recognition, we have studied various classifiers. But the challenge is that of higher dimensionality of the input data. Our proposed framework tries to capture only those features from input set that contribute to a greater degree in the classification task. The classifier is tuned in such a way that it can process heterogeneous features from multiple data sources.

Table 1: Comparison of Neuroimaging Techniques

Neuroimaging Technique	CT	MRI	fMRI	MEG	EEG	PET	SPECT
Type	Structural	Structural	Functional	Functional	Functional	Functional	Functional
Direct/indirect	-	-	Indirect	Direct	Direct	Indirect	Indirect
Invasiveness	No	No	No	No	No	Yes	Yes
Spatial resolution	Low	Good	Good/excellent (3-6 mm)	Good/excellent (5 mm)	Reasonable/good (10 mm)	Good/excellent 4 mm	Good (6 mm)
Temporal resolution	-	-	Reasonable (4-5 s)	Excellent (< 1 ms)	Excellent (< 1 ms)	Poor (~30-40 s)	Poor (>60 s)
Radioactivity	No	No	No	No	No	Yes (0.5-2.0 mSv)	Yes (3.5-12.0 mSv)
Radioactive Tracer	No	No	No	No	No	15O , 13N , 11C, 18F, 82Rb, PiB	133Xe, 99mTc-HMPAO, 99mTc-ECD, 123I-IMP (diffusible)
Radiation exposure	Yes	No	No	No	No	No	No
Cost	Low	Low	Moderate	Moderate	Low	High	Moderate
Magnetic susceptibility	No	Yes	Yes	Yes	No	No	No
Claustrophobic	No	Yes	Yes	Yes	No	Yes	Yes
Require extra session for MRI	Yes	-	No	Yes	Yes	Yes	Yes
Stimuli based	No	No	Yes	Yes	Yes	Yes	Yes
Measures	Tissue density	Hemoglobin in the blood	Haemodynamic response (Blood oxygen level)	Neuromagnetic field	Neuroelectrical potentials	Haemodynamic response (CBV, CBF, rOEF, glucose Metabolism)	Haemodynamic response (CBF)
Limitations	-Bone artifacts-May increase risk of cancer -Unable to differentiate tissue types accurately -Unable to visualize the posterior fossa clearly -Measures only anatomy	-Artifacts from non-ferromagnetic metallic objects -Measures only anatomy	- Artifacts from non-ferromagnetic metallic objects -Temporal resolution is limited by the reaction of the body - Expensive, space consuming and immobile scanner -Subjects are not allowed to move at all while being scanned	-Can only measure cortical signals and not those deep inside the brain -Overall brain imaging is beyond its reach -Prone to background noise -Has to be housed in a highly magnetically shielded room -Highly immobile	-Can only measure cortical signals and not those deep inside the brain -Overall brain imaging is beyond its reach -Exerts pressure on subject's head and causes headache -Require application of conductive paste to the skin of head -Background noise can cause significant amount of artifacts -Signal depends on geometrical and electrical properties of brain and skull	-Resolution limited by blood flow -Requires separate session for structural MRI -Repeated scanning is not possible due to use of radioactive tracers	-Resolution limited by blood flow -Requires separate session for structural MRI -Repeated scanning is not possible due to use of radioactive tracers -Lower spatial and temporal resolution

Table 2: Review of Recent Studies Investigating the Potential of Neuroimaging Data and Pattern Recognition Techniques

Reference	Biomarkers			Preprocessing			Neuroimaging Feature			Classifier		Results			
	Imaging Modality	Genetics	CSF	Registration/ spatial normalization	Segmentation	Intensity Normalization	Type	Extraction Technique	Reduction/ Selection Technique	Type	Name	Group	Accuracy (%)	Specificity (%)	Sensitivity (%)
Segovia et. Al., 2012	PET	×	×	√	×	√	ROI	GMM	Gaussian with higher heights	Supervised	Linear SVM	CN vs. AD	87.50	86.60	88.42
												CN & MCI vs. MCIc & AD	78.91	90.88	50.00
											SVM RBF	CN vs. AD	90.63	90.72	90.53
												CN & MCI vs. MCIc & AD	78.41	90.88	48.31
							Score vectors	PLS	Truncating feature vector		Linear SVM	CN vs. AD	87.50	90.72	84.21
												CN & MCI vs. MCIc & AD	76.92	88.42	49.15
											SVM RBF	CN Vs. AD	86.46	90.72	82.11
												CN & MCI vs. MCIc & AD	76.18	92.98	35.59
Ye et. Al., 2008	MRI	√	×	-	-	-	ROI & Voxel based tensor	Tensor factorization	MKL		RKDA	CN vs. AD	-	89.50	95.00
											SVM		-	85.00	94.50
Silveira & Marques, 2010	PET	×	-	√	×	√	Voxel intensities	-	-	Supervised	AdaBoost	CN vs. AD	90.97	-	-
												CN vs. MCI	79.63		
												MCI vs. AD	70.00		
Stoeckel et. Al., 2001	SPECT	×	×	√	×	√	Voxel intensities	-	-	Supervised	NMC	CN vs. AD	84.8	-	-
											PFLD		89.9		
Patil & Yardi, 2011	MRI	×	×	√	√	-	DWT coefficients	Daubechies wavelet	-	Supervised	Feed forward back propagation ANN	CN vs. AD	74	-	-
								Haar wavelet					67		
Long & Wyatt, 2008	MRI	×	×	√	√	-	WM	-	Spectral embedding algorithm	Unsupervised	Quick shift clustering	CN vs. AD	94.67	-	-
							GM						97.33		
Ye et. Al., 2011	MRI	×	×	√	√	-	Morphological features	Ravens maps	Non linear manifold learning technique	Semi-supervised	Linear laplacian SVM	cMCI vs. ncMCI	56.1	40.8	94.1
Kloppel et al., 2008	MRI	-	-	√	√	-	GM from whole brain	-	-	Supervised	Linear SVM	CN vs. AD	95.6	94.1	97.1
							GM of antero-medial lobe VOI						94.1	97.1	91.2
Illan et. Al., 2010	SPECT	×	×	√	-	√		ICA	-	Supervised	Linear SVM	CN vs. AD	84.81	87.80	81.58
											Quadratic SVM		87.34	92.68	81.58
											RBF SVM		89.87	95.12	84.21
											Polynomic SVM		88.61	92.68	84.21
Illan et. Al., 2011	PET	×	×	√	-	√	Image projection coefficients	PCA	Image projection	Supervised	PCA- RBF kernel	CN vs. AD	88.24	88.64	87.70

Table 2: Review of Recent Studies Investigating the Potential of Neuroimaging Data and Pattern Recognition Techniques (Contd.)

Reference	Biomarkers			Preprocessing			Neuroimaging Feature			Classifier		Results			
	Imaging Modality	Genetics	CSF	Registration/ spatial normalization	Segmentation	Intensity Normalization	Type	Extraction Technique	Reduction/ Selection Technique	Type	Name	Group	Accuracy (%)	Specificity (%)	Sensitivity (%)
											PCA-Linear kernel		82.35	70.45	95.12
								ICA			ICA- RBF kernel		87.06	86.36	87.80
											ICA-Linear kernel		75.29	59.09	92.68
Filipovych et. Al., 2012	MRI	√	×	√	√	-	Local volumetric measurements of GM, WM, & CSF	-	-	Supervised	Non-linear SVM with Gaussian kernel	MCIc vs. MCInc (Predictor)	AUC=0.779	-	-
							SNP				Linear SVM				
Zhang et. Al., 2011	MRI & PET	-	√	√	√	√	Volume of GM in each ROI for MRI & average intensity in each ROI for PET & CSF	-	T-test statistics	Supervised	Weighted combination of multiple kernels- linear SVM	CN vs. AD	93.2	93.3	93
												CN vs. MCI	76.4	66	81.8
Salas-Gonzalez et. Al., 2010	PET	×	×	√	×	√	Factor loadings	Factor analysis	T-student test	Supervised	Multivariate GMM with linear discriminant function	CN vs. AD	92.00	-	-
												CN vs. MCI	83.00	-	-
												CN vs. MCI-AD	79.00	-	-
											Multivariate GMM with quadratic discriminant function	CN vs. AD	89.00	-	-
												CN vs. MCI	80.00	-	-
												CN vs. MCI-AD	76.00	-	-
											Linear SVM	CN vs. AD	92.00	-	-
												CN vs. MCI	86.00	-	-
												CN vs. MCI-AD	85.00	-	-
Chaves et. Al., 2012	SPECT	×	×	√	×	√	Voxel based features	PCA & PLS	Association rule mining	Supervised	Linear SVM	CN vs. AD	91.75	95.12	89.29
	PET	×	×	√	×	√	Voxel based features	PCA & PLS	Association rule mining		RBF SVM	CN vs. AD	90	90.67	89.33
Padilla et. Al., 2012	SPECT	×	×	×	×	√	Voxel intensities	FDR	NMF	Supervised	SVM with bounds of confidence	CN vs. AD	91.42	92.30	90.56
	PET	×	×	×	×	√	Voxel intensities	FDR	NMF		SVM with bounds of confidence	CN vs. AD	86.59	85.36	87.50

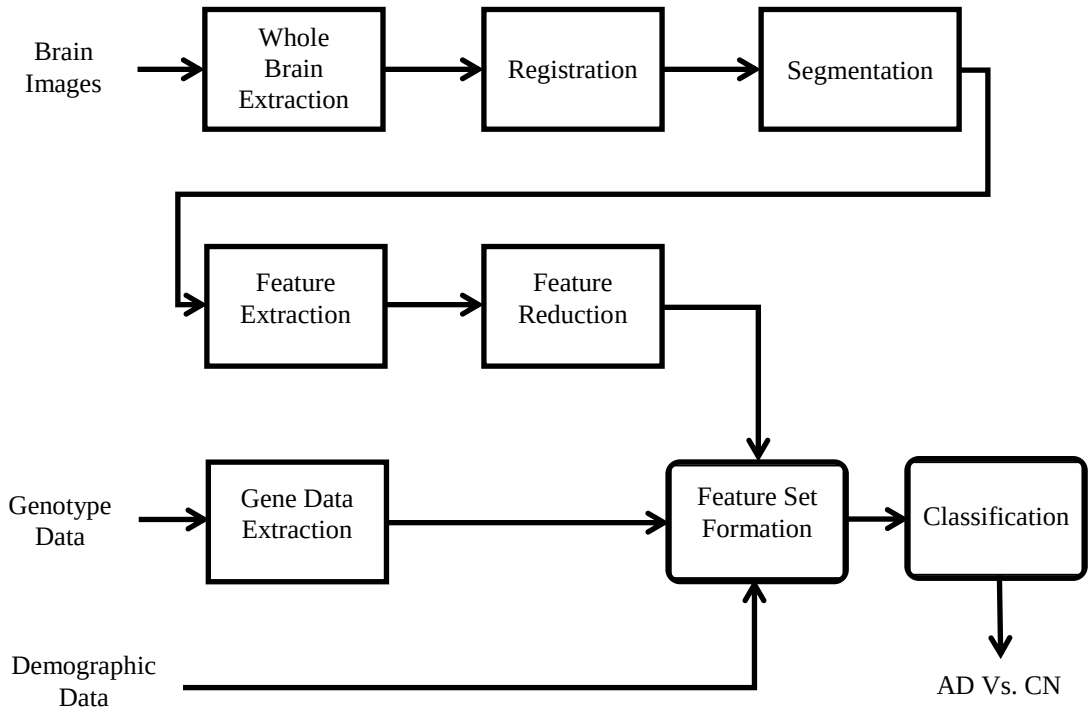

Figure 1: Proposed framework for Pattern Recognition based Classification of Alzheimer's Disease and Cognitively Normal Individuals

6. Conclusion

The proposed research work is focused on the design of a classifier, based on image processing and pattern recognition techniques, where data sources are heterogeneous in nature. The predictive power of the classifier is enhanced by integrating features from structural and functional neuroimages. The classification process is further strengthened by incorporating genetic data. This research supports the process of correct identification of people who are in early stages of Alzheimer's development as no clinical symptoms are visible in initial stages of AD. The research work also improves and contributes in the visual assessment procedure of neuroimages conducted by the medical practitioners. The proposed framework is beneficial for early estimation of AD, which in turn will benefit AD patients, their relatives/care givers and medical practitioners in particular and the whole community in general.

Corresponding Author:
Dr. Muhammad Abuzar Fahiem
Department of Computer Science
Lahore College for Women University, Lahore, Pakistan
E-mail: itisab@gmail.com

References

1. Alzheimer's Association, Alzheimer's disease facts and figures. Alzheimer's and Dementia, 2013; 9(2): 208-245.
2. Ashburner J, Friston KJ. Voxel-based morphometry—the methods. Neuroimage 2000; 11(6): 805-821.
3. Bagci U, Bai L. A comparison of daubechies and gabor wavelets for classification of MR images. IEEE International Conference on Signal Processing and Communications 2007;676-679.
4. Blennow K., de Leon M, Zetterberg H. Alzheimer's disease. Lancet 2006; 368:387–403
5. Boss MA. Diagnostic approaches to Alzheimer's disease. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease 2000; 1502(1): 188-200.
6. Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM. Forecasting the global burden of Alzheimer's disease. Alzheimer's and Dementia 2007; 3(3):186-191.
7. Chaves R, Ramírez J, GóRriz JM, Puntonet CG. Association rule-based feature selection method for Alzheimer's disease diagnosis. Expert Systems with Applications 2012.
8. Chupin M, Gérardin E, Cuingnet R, Boutet C, Lemieux L, Lehéricy S, Benali H, Garnero L, Colliot O. Alzheimer's Disease Neuroimaging Initiative. Fully automatic hippocampus segmentation and classification in Alzheimer's disease and mild cognitive impairment applied on data from ADNI. Hippocampus 2009;19(6):579–587.
9. Davatzikos C, Fan Y, Wu X, Shen D, Resnick SM. Detection of prodromal Alzheimer's disease via pattern classification of magnetic resonance imaging. Neurobiology of aging 2008; 29(4): 514-523.
10. Dawbarn D, Allen SJ. (editors). Neurobiology of Alzheimer's disease. Oxford University Press, New York, 3rd edition. 2007.
11. Fantini S, Aggarwal P, Chen K, Franceschini MA. Monitoring brain activity using near-infrared light. American laboratory 2001; 33(20):15-17.
12. Filipovych R, Gaonkar B, Davatzikos C. A Composite Multivariate Polygenic and Neuroimaging Score for Prediction of Conversion to Alzheimer's Disease. IEEE International Workshop on Pattern Recognition in NeuroImaging (PRNI) 2012;105-108.
13. Fisher RA. The use of multiple measurements in taxonomic problems. Annals of Human Genetics 1936; 7(2):179-188.
14. Fox NC, Schott JM. Imaging cerebral atrophy: normal ageing to Alzheimer's disease. The Lancet 2004; 363(9406): 392-394.
15. Fung G, Stoeckel J. SVM feature selection for classification of SPECT images of Alzheimer's disease using spatial information. Knowledge and Information Systems 2007; 11(2): 243-258.
16. Hajnal JV, Hawkes D J, Hill DLG. (editors). Medical image registration 2001. CRC Press.
17. Hebert LE, Scherr PA, Bienias JL, Bennett DA, Evans DA. Alzheimer disease in the US population: prevalence estimates using the 2000 census. Archives of neurology 2003; 60(8): 1119.
18. Higdon R, Foster NL, Koeppe RA, DeCarli CS, Jagust WJ, Clark CM, Barbas NR, Arnold SE, Turner RS, Heidebrink JL, Minoshima S. A comparison of classification methods for differentiating fronto-temporal dementia from Alzheimer's disease using FDG-PET imaging. Statistics in Medicine 2004; 23(2):315-326.
19. Illán IA, Górriz JM, Ramírez J, Salas-Gonzalez D, López MM, Segovia F, Chaves R, Gomez-Rio M, Puntonet CG. 18F-FDG PET imaging analysis for computer aided Alzheimer's diagnosis. Information Sciences 2011; 181(4):903-916.
20. Illán IÁ, Górriz JM, Ramírez J, Salas-Gonzalez D, López M, Segovia F, Padilla P, Puntonet CG. Projecting independent components of SPECT images for computer aided diagnosis of Alzheimer's disease. Pattern Recognition Letters 2010;31(11): 1342-1347.

21. Jobst KA, Barnetson LP, Shepstone BJ. Accurate prediction of histologically confirmed Alzheimer's disease and the differential diagnosis of dementia: the use of NINCDS-ADRDA and DSM-III-R criteria, SPECT, X-ray CT, and Apo E4 in medial temporal lobe dementias. International Psychogeriatrics 1998; 10(3): 271-302.
22. Klöppel S, Stonnington CM, Chu C, Draganski B, Scahill RI, Rohrer JD, Fox NC, Jack Jr. CR, Ashburner J, Frackowiak RSJ. Automatic classification of MR scans in Alzheimer's disease. Brain 2008;131(3): 681–689.
23. Kosugi Y, Uto K, Hagiwara R, Kosaka N, Abe A, Kameyama M, Momose T. Neural networks for cerebral diagnosis using PET and SPECT. IEEE EMBS Asian-Pacific Conference on Biomedical Engineering 2003;24-27.
24. Kovacevic N, Lobaugh NJ, Bronskill MJ, Levine B, Feinstein A, Black SE. A robust method for extraction and automatic segmentation of brain images. Neuroimage 2002; 17(3): 1087.
25. Leung KK, Barnes J, Modat M, Ridgway GR, Bartlett JW, Fox NC, et al. Brain MAPS: an automated, accurate and robust brain extraction technique using a template library. Neuroimage 2011; 55:1091–108.
26. Long X, Wyatt C. An automatic unsupervised classification of MR images in Alzheimer's disease. IEEE Conference on Computer Vision and Pattern Recognition (CVPR) June, 2010; 2910-2917.
27. López M, Ramírez J, Górriz JM, Álvarez I, Salas-Gonzalez D, Segovia F, Chaves R, Padilla P, Gómez-Río M. Principal component analysis-based techniques and supervised classification schemes for the early detection of Alzheimer's disease. Neurocomputing 2011;74(8): 1260-1271.
28. Lopez OL, Becker JT, Jungreis CA, Rezek D, Estol C, Boiler F, DeKosky ST. Computed tomography--but not magnetic resonance imaging--identified periventricular white-matter lesions predict symptomatic cerebrovascular disease in probable Alzheimer's disease. Archives of neurology 1995, 52(7):659.
29. Lotjonen JM, Wolz R, Koikkalainen JR, Thurfjell L, Waldemar G, Soininen H, Rueckert D. Fast and robust multi-atlas segmentation of brain magnetic resonance images. NeuroImage 2010; 49: 2352–2365.
30. Maintz JA, van den Elsen PA, Viergever MA. Comparison of edge-based and ridge-based registration of CT and MR brain images. Medical image analysis 1996; 1(2): 151-161.
31. Mazziotta J, Toga A, Evans A, Fox P, Lancaster J, Zilles K, Woods R, Paus T, Simpson G, Pike B, Holmes C, Collins L, Thompson P, MacDonald D, Iacoboni M, Schormann T, Amunts K, Palomero-Gallagher N, Geyer S, Parsons L, Narr K, Kabani N, Goualher GL, Boomsma D, Cannon T, Kawashima R, Mazoyer B. A probabilistic atlas and reference system for the human brain: International Consortium for Brain Mapping (ICBM). Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences 2001; 356(1412):1293-1322.
32. Padilla P, López M, Górriz JM, Ramírez J, Salas-González D, Álvarez I. NMF-SVM Based CAD Tool Applied to Functional Brain Images for the Diagnosis of Alzheimer's Disease. IEEE Transactions on Medical Imaging 2012; 31(2): 207-216.
33. Patil MM, Yardi AR. Classification of 3D Magnetic Resonance Images of Brain using Discrete Wavelet Transform. International Journal of Computer Applications 2011; 31(7): 23-27.
34. Patil MM, Yardi AR. VBM based MR Imaging Volumetric Analysis of AD and MCI. International Journal of Computer Applications 2011; 13(2): 42-46.
35. Pennanen C, Kivipelto M, Tuomainen S, Hartikainen P, Hänninen T, Laakso MP, Hallikainen M, Nissinen A, Helkala EL, Vainio P, Vanninen R, Partanen V, Soininen H. Hippocampus and entorhinal cortex in mild cognitive impairment and early AD. Neurobiology of Aging 2004; 25(3):303–310
36. Querbes O, Aubry F, Pariente J, Lotterie JA, Démonet JF, Duret V, Puel M, Berry I, Fort JC, Celsis P. Alzheimer's Disease Neuroimaging Initiative. Early diagnosis of Alzheimer's disease using cortical thickness: impact of cognitive reserve. Brain 2009;32 (8):2036–2047.
37. Ramirez J, Górriz J, López M, Salas-Gonzalez D, Álvarez I, Segovia F, Puntonet C. Early detection of the alzheimer disease combining feature selection and kernel machines. Advances in Neuro-Information Processing 2009;410-417.
38. Rocca WA, Hofman A, Brayne C, Breteler MMB, Clarke M, Copeland JRM, Dartigues J-F, Engedal K, Hagnell O, Heeren TJ, Jonker C, Lindesay J, Lobo A, Mann AH, Molsa PK, Morgan K, O'Connor DW, Droux Ad. S, Sulkava R, Kay DWK, Amaducci L. Frequency and distribution of Alzheimer's disease in Europe: a collaborative study of 1980-1990 prevalence findings. Annals of Neurology 2004; 30(3):381-390.
39. S´egonne F, Dale AM, Busa BE, Glessner BM, Salat BD, Hahn BHK, A BF. A hybrid approach to the skull stripping problem in MRI. NeuroImage 2004; 22:1060–75.

40. Salas-Gonzalez D, Górriz JM, Ramírez J, Illán IA, López M, Segovia F, Chaves R, Padilla P, Puntonet CG. Feature selection using factor analysis for Alzheimer's diagnosis using F-FDG PET images. Medical physics 2010; 37: 6084.
41. Sandor S, Leahy R. Surface-based labeling of cortical anatomy using a deformable atlas. IEEE Trans on Medical Imaging 1997; 16(1):41–54.
42. Savio A, García-Sebastián M, Hernández C, Graña M, Villanúa J. Classification results of artificial neural networks for alzheimer's disease detection. Intelligent Data Engineering and Automated Learning-IDEAL 2009; 641-648.
43. Segovia F, Górriz JM, Ramírez J, Salas-Gonzalez D, Álvarez I, López M, Chaves R. A comparative study of feature extraction methods for the diagnosis of Alzheimer's disease using the ADNI database. Neurocomputing 2012; 75(1): 64-71.
44. Silveira M, Marques J. Boosting Alzheimer disease diagnosis using PET images. IEEE 20th International Conference In Pattern Recognition (ICPR) 2010; 2556-2559.
45. Smith SM. Fast robust automated brain extraction. Human Brain Mapping 2002; 17(3):143-155.
46. Stoeckel J, Malandain G, Migneco O, Koulibaly PM, Robert P, Ayache N, Darcourt J. Classification of SPECT images of normal subjects versus images of Alzheimer's disease patients. In Medical Image Computing and Computer-Assisted Intervention–MICCAI 2001, Springer Berlin Heidelberg, 666-674.
47. Thompson PM, Hayashi KM, Dutton RA, CHIANG MC, Leow AD, Sowell ER, Zubicaray GD, Becker JT, Lopez OL, Aizenstein HJ, Toga AW. Tracking Alzheimer's disease. Annals of the New York Academy of Sciences 2007; 1097(1): 183-214.
48. Tsai A, Yezzi JA, Wells W, Tempany C, Tucker D, Fan A, Willsky WEGA. A shape-based approach to the segmentation of medical imagery using level sets. IEEE transactions on medical imaging 2003; 22(2): 137-154.
49. Unal Y, Kocer HE, Akkurt HE. Automatic Diagnosis of Intervertebral Degenerative Disk Disease Using Artificial Neural Network. In 6th International Advanced Technologies Symposium (IATS'11) 2011; 16-18.
50. Vapnik VN, Lerner A. Pattern recognition using generalized portrait method. Automation and Remote Control 1963; 24(6):774-780.
51. Wagner AD. Early detection of Alzheimer's disease: An fMRI marker for people at risk?. Nature neuroscience 2000; 3:973-974.
52. Wolz R, Aljabar P, Hajnal JV, Hammers A, Rueckert D. LEAP: learning embeddings for atlas propagation. Neuroimage 2010; 49:1316–25.
53. Wong KP, Feng D, Meikle SR, Fulham MJ. Segmentation of dynamic PET images using cluster analysis. IEEE Transactions on Nuclear Science 2002; 49(1): 200-207.
54. Ye DH, Pohl KM, Davatzikos C. Semi-supervised Pattern Classification: Application to Structural MRI of Alzheimer's Disease. IEEE International Workshop on Pattern Recognition in NeuroImaging (PRNI) 2011; 1-4.
55. Ye J, Chen K, Wu T, Li J, Zhao Z, Patel R, Bae M, Janardan R, Liu H, Alexander G, Reiman E. Heterogeneous data fusion for Alzheimer's disease study. In Proceedings of the 14th ACM SIGKDD international conference on Knowledge discovery and data mining August 2008;1025-1033.
56. Zhang D, Wang Y, Zhou L, Yuan H, Shen D. Multimodal classification of Alzheimer's disease and mild cognitive impairment. Neuroimage 2011; 55(3): 856-867.

6/27/2013