Computer aided diagnosis of Alzheimer's disease: A review

A. Monisha Bharathi
Dept. of Computer Applications
Bharathiar University
Coimbatore, India
moniarul90@gmail.com

R. Rajeswari
Dept. of Computer Applications
Bharathiar University
Coimbatore, India
rrajeswari@rediff.com

***Abstract*— Alzheimer's disease is a neurodegenerative disease which causes memory loss and cognitive decline. Early detection of this disease is essential for effective treatment. Computer aided diagnosis is a tool which is based on medical imaging. It is used to output to assist radiologists in the interpretation of images by improving the accuracy and consistency of diagnosis. It is also used to reduce the image reading time. It is very helpful for physicians to detect the Alzheimer's disease. In this paper, various computer aided diagnosis methods which are used in the diagnosis of Alzheimer's diseases are examined. This paper provides a detailed overview of the methods used in the diagnosis of Alzheimer's disease.**

Keywords—Computer Aided Diagnosis, Alzheimer's Disease, Feature Extraction, Feature Selection, Classification.

I. INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia. AD is a progressive neurodegenerative disorder first affecting memory functions and then gradually affecting all cognitive functions with behavioral impairment and eventually causing death [13, 16]. It has affected more than thirty million people worldwide. It is expected to affect sixty million people over the next 50 years due to the increase in life expectancy and aging of the population. There is no cure for Alzheimer's disease, but its early detection is essential for an effective treatment [5].

Many researchers have developed Computer Aided Diagnosis (CAD) systems that automatically diagnose AD before being detected by cognitive tests [1, 6]. CAD is more important in medical and clinical research. CAD is used for support decisions and it uses the scanned data from medical imaging. CAD system analyzes and evaluates the radiologist in a short period of time. It helps to improve the accuracy and efficiency of radiologists in medical diagnosis.

The scanned data of brain are stored in different formats such as MRI, fMRI, PET, SPECT. Magnetic Resonance Imaging (MRI) is used to produce high quality of two or three dimensional brain image structures using magnetic fields and radio waves. Functional Magnetic Resonance Imaging (fMRI) is non-invasive technique which is not involving the intrusion of instruments into the body. It allows indirect measurement of neuronal activity [17].

Positron emission tomography (PET) is a functional imaging technique which produces a three dimensional image of functional processes in the body. PET scanning is used to show blood flow, oxygen and glucose metabolism in the tissues of the working brain [3, 12]. Single-photon emission computed tomography (SPECT) acts like PET. It produces images that show how organs work and how blood flows to the heart. It shows the areas of brain which are active and which are less active [3, 11].

Diagnosis of Alzheimer's disease can be implemented by three stages which are: (a) Feature extraction, (b) Feature Selection and (c) Classification. These three stages have several algorithms that can be used for diagnosis. Feature Extraction involves in simplifying the large set of data accurately. Feature Extraction methods are transformative which reduces the dimensionality and describes the data with sufficient accuracy. Feature selection is the process of selecting a subset of relevant features. Feature selection techniques avoid many redundant or irrelevant features. Classification is the most important stage in CAD of AD. It can be categorized as (i) Supervised Classification and (ii) Unsupervised Classification. Supervised Classification is based on trained data. Unsupervised Classification does not make use of trained data.

The rest of this paper is organized as follows. Section 2 describes the main stages of CAD for AD. Section 3 describes various computer aided diagnosis techniques for Alzheimer's disease. Section 4 gives the conclusion.

II. MAIN STAGES OF CAD FOR AD

CAD for Alzheimer's disease consists of three stages: (a) Feature extraction, (b) Feature Selection and (c) Classification. Various techniques used for these three stages of CAD for AD are shown in figure 1. These stages play a vital role in efficient and early diagnosis of AD.

Feature extraction is a general term for the methods used to construct the combinations of variables and describing the data with sufficient accuracy. Some of these methods are described here. Partial Least Square (PLS) is a method used for finding the fundamental relations between two matrices. It creates an orthogonal score vector which is also called latent vectors or components by maximizing the covariance between different set of variables [1]. Principal Component Analysis (PCA) is a non- parametric method used for extracting relevant information from confusing data sets. It generates an orthonormal basis vector which can maximize the scatter of all the projected samples [3]. Independent Component Analysis (ICA) is a computational method which is used for illuminating hidden factors that underlie sets of random variables. Lattice Independent Component Analysis (LICA) is a non-linear

alternative to ICA. It is based on the lattice independent discovered when dealing with noise robustness [4]. CONNectivity matrix linkage (CONN) is a hierarchical agglomerative clustering method which is used to capture information about the neighbourhood relationships in the input space to build clusters [16]. Factor Analysis is a method of statistical techniques which is used to represent a set of variables in terms of hypothetical smaller variables.

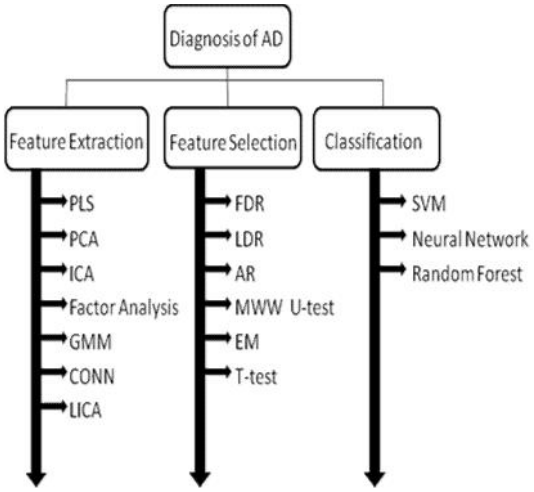

Fig. 1. Algorithms/Methods used for diagnosis

Feature selection, also known as variable or attribute or variable subset selection, is used to select the subset of relevant features. Fisher Discriminant Ratio (FDR) selects the most discriminant voxels and thus reduces the computational burden in the preliminary voxel selection stage. Linear Discriminant Analysis (LDA) is a method used for separating or characterizing two or more classes of objects or events. Association Rule (AR) is the most popular method which is used for discovering hidden relations between variables in the databases. The Expectation Maximization (EM) is a parameter estimation method which can fall into the general framework of maximum likelihood estimation. It is applied to the data which is considered to be incomplete, or hidden [11]. Mann–Whitney–Wilcoxon U-Test (MWW) is a novel based method used for a statistical test which can be helpful in the selection task [3].

Support Vector Machines (SVM) is a supervised learning method mainly used for classification. It can analyze data and recognize patterns [5]. The Random Forest (RF) is an ensemble classification method which is based on learning algorithms. It is used to construct a set of classifiers. It consists of many decision trees [17]. An artificial neural network (ANN) is a paradigm used for information processing which is inspiring by the way of biological nervous systems such as brain [3].

III. OVERVIEW OF VARIOUS CAD TECHNIQUES FOR AD

Segovia et al [1] have proposed an early diagnosis of Alzheimer's disease based on Partial Least Square algorithm for extraction of score vectors and selecting a number of scores as features. Finally diagnosis is done by Support Vector Machine (SVM) classifier. The authors have used 97 SPECT images for normal and AD patient. They have used 41 normal SPECT and 56 AD images from the image database.

Andrea Chincarini et al [2] have proposed local MRI analysis approach in the diagnosis of early prodromal Alzheimer's disease. The authors have used intensity and textural for features and template matching techniques for feature extraction of voxel of interest. SVM is used for classification.

Lopez et al [3] have proposed Principal Component Analysis (PCA) based techniques and supervised classification schemes for the early detection of Alzheimer's disease. Principal Component Discriminant methods are proposed as feature extraction and Linear Discriminant Analysis (LDA) or the Fisher Discriminant Ratio (FDR) is used for feature selection. Finally the classification is done by SVM classifier and Neural Network Classifier. The authors have used 53 AD images, 114 Mild Cognitive Impairment (MCI) images and 52 Normal Control images for their experiment.

Darya Chyzhyk et al [4] have proposed a Hybrid Dendritic computing with kernel- LICA applied to Alzheimer's disease detection in MRI. Here the authors have proposed Lattice Independent Component Analysis (LICA) and kernel Approach for feature extraction and SVM for Classification.

Illan et al [5] have proposed Bilateral symmetry aspects in Computer-aided Alzheimer's disease diagnosis by single-photon emission-computed tomography imaging. The authors have studied the brain symmetry and its usage for CAD of Alzheimer's disease. They have studied the symmetry of brain using machine learning based classifiers and have studied their relationship with AD. For this purpose they have used the eigen image decomposition of single-photon emission computed tomography images. The authors have used 97 images, out of which 41 are images of normal patient, 30 are perfusion deficit (AD1) images, 22 are moderate deficit (AD2) images and 4 are severe deficit (AD3) images.

Martinez-Murcia et al [6] have proposed Computer-aided diagnosis for Alzheimer's disease based on Mann-Whitney-Wilcoxon U-Test for selecting a voxel and factor analysis as feature extraction. Finally diagnosis is done by SVM classifier. Here the authors have used 96 SPECT images and 196 PET images.

Chaves et al [7] have proposed an association rule (AR)-based feature selection method for AD diagnosis. This rule based feature selection had enabled in solving the sample size problem in order to design a CAD system. They have proposed PCA or PLS for feature extraction and SVM as classifier. The authors have used 150 PET images, out of which 75 are control patient images and 75 are AD patient images.

Chaves et al [8] have proposed integrating discretization and association rule based classification for Alzheimer's disease diagnosis. The discretization method is used as feature extraction for selecting the mean intensity. Association rule method is used for classification.

Alexandre Savio et al [9] have proposed deformation based feature selection for Computer Aided Diagnosis of Alzheimer's disease. In this paper the authors have used the scalar deformation measures of CAD systems for AD. They have evaluated three supervised feature selection methods. They are Pearson's Correlation, Bhattacharyya distance, Welch's t-test. Final stage of diagnosis is performed by SVM classifier.

TABLE I. OVERVIEW OF VARIOUS METHODS ASSOCIATED WITH CAD FOR AD

Methods	Features	Feature Extraction	Feature Selection	Classification
Segovia et al	Out-of-bag error Score vector	Partial Least Squares	Fisher Discriminant Ratio	SVM
Andrea Chincarini et al	intensity and textural MRI-based features	template matching techniques		SVM
				Random Forest
Lopez et al	Voxel Selection	Principal Component Analysis	Fisher Discriminant Ratio (FDR)	SVM
			Linear Discriminant Analysis (LDR)	Neural Network
Darya Chyzhyk et al		Lattice Independent Component Analysis		SVM
		Kernel Approaches		
Illan et al	Eigen vector	Principal Component Analysis Symmetric		SVM
Martinez-Murcia et al	Voxel Selection	Factor Analysis	Mann–Whitney–Wilcoxon U-Test (MWW)	SVM
Chaves et al	Voxel Selection	Principal Component Analysis Partial Least Squares	Association Rule	SVM
Chaves et al	Mean Intensity	Discretization Method		AR
Alexandre Savio et al	Scalar Measures	Jacobian Determinant	(i) Pearson's correlation (ii) Bhattacharyya distance (BD) (iii) Welch's t-test (WT)	SVM
Salas-Gonzalez et al	Mean Intensity		Mean Image Standard Deviation Image	Quadratic Discriminant Linear discriminant function Mahalanobis distance SVM K nearest neighbour
Gorriz et al	Voxel intensities	Gaussian mixture model	EM	SVM
Illan et al	Voxel as Features	Principal Component Analysis		Kernel-SVM
		Independent Component Analysis		
Ramirez et al	Voxel Intensities	Sequential Minimal Optimization (SMO)	FDR	SVM
Segovia et al	Feature Vectors	Gaussian mixture model		SVM
	Score Vectors	Partial Least Squares		
Andres Ortiz et al	Voxel Intensities	CONNectivity matrix linkage clustering Algorithm and LVQ3	Fisher Discriminant Ratio (FDR)	SVM
Evanthia et al		Demographics Behavioral Head motion Volumetric measures Activation patterns Hemodynamics	Wrapper approach Filter approach	SVM Random Forest
Illán et al	Voxel selection	Component Based Analysis	Image Factorization	SVM
Alvarez Illan et al		Independent Component Analysis (ICA)		Kernel-SVM
Chaves et al	Voxel selection	Normalized Mean Square Error (NMSE)	t-test	SVM
Evanthia et al		Demographics Behavioral Head motion Volumetric measures Activation patterns Hemodynamics	Symmetrical Uncertainty	Random Forest

Salas-Gonzalez et al [10] have proposed two approaches to select set of voxels for the diagnosis of Alzheimer's disease. The first approach used by authors is based on selecting the voxels which have the greatest difference between controls and Alzheimer's disease. The second approach is based on selecting the voxels which not only have greatest difference between both modalities but also present lower dispersion. The authors have used 41 normal images, 20 possible AD images, 17 probable AD images, 1 certain AD images.

Gorriz et al [11] have proposed GMM based SPECT image classification for the diagnosis of Alzheimer's disease. The authors have used voxel intensities as features and Gaussian mixture model for feature extraction. The Expectation Maximization Algorithm is used as feature selection based on Gausssian result. Classification is done by SVM classifier. The authors have used 97 SPECT images, out of which 43 are normal images, 30 are possible AD images, 20 are probable AD images and 4 are certain AD images.

Illan et al [12] have proposed F-FDG PET imaging analysis for Computer aided Alzheimer's diagnosis. Here the authors have proposed PCA/ICA as feature extraction and voxel as features. SVM is used for performing the classification task. The authors have used 97 normal control images, 209 Mild Cognitive Impairment(MCI) images and 95 AD images.

Ramirez et al [13] have proposed Computer-aided diagnosis of Alzheimer's type dementia combining support vector machines and discriminant set of features. The authors have used Fisher Discriminant Ratio as feature selection and have used SVM as classifier. The authors have used 52 SPECT images of Patients. In that 23 are Normal control images, 13 are possible AD images, 12 are probable AD images and 4 are certain AD images.

Segovia et al [14] have proposed a comparative study of feature extraction methods for the diagnosis of Alzheimer's disease using the ADNI database. In this paper the authors have proposed two approaches. The first approach is to select the feature vectors and Gaussian mixture model for feature extraction. The second approach is to select the score vector and Partial Least Square method for feature extraction. Finally SVM is used for classification. The authors have used PET images for experiment results. In that they used 97 normal control images, 188 Mild Cognitive Impairment (MCI) images, 23 MCI converter images and 95 AD images.

Evanthia et al [15] have proposed a six stage approach for the diagnosis of the Alzheimer's disease based on fMRI data. The authors have categorized feature extraction into six stages. They are demographics, behavioral, head motion, volumetric measures, activation patterns, hemodynamics. Using these they have extracted the features and have used wrapper approach and filter approach for feature selection. SVM and Random forest are used for classification. The authors have also proposed a supervised method to assist the diagnosis and monitor progression of Alzheimer's disease using data from an fMRI experiment [17]. Here the authors have used the feature extraction methods which they have proposed in [15]. They have used symmetric uncertainty for feature selection and random forest for classification [17].

Andres Ortiz et al [16] have proposed Learning Vector Quantization(LVQ)-SVM based CAD tool applied to structural MRI for the diagnosis of the Alzheimer's disease. In this paper the authors proposed CONNectivity matrix linkage clustering Algorithm as feature extraction for clustering. LVQ is used for reduction of features and Fisher discriminant for feature selection. The classification is done by SVM. Here the authors have used 50 T1 weighted MRI images, out of which 25 are normal images and 25 are AD images.

Illan et al [18] has proposed Computer aided diagnosis of Alzheimer's disease using component based SVM. The image factorization is done by dividing the whole brain image into smaller subvolumes or components. The classification using SVM is done for each component. The authors have used 79 SPECT images of Patients. In that 41 are Normal control images, 20 are possible AD images, 14 are probable AD images and 4 are certain AD images.

Alvarez Illan et al [19] have proposed projecting independent components of SPECT images for computer aided diagnosis of Alzheimer's disease. The authors have used Independent Component Analysis for feature extraction and to reduce the feature space dimensionality. Classification is done by SVM. The authors have used 79 SPECT images of Patients. Out of these images 41 are Normal control images, 20 are possible AD images, 14 are probable AD images and 4 are certain AD images.

Chaves et al [20] have proposed SVM-based computer-aided diagnosis of the Alzheimer's disease using t-test NMSE feature selection with feature correlation weighting. Classification is done by SVM. Here the authors have used 79 SPECT images, out of which 41 are images of normal patients and 38 are images of AD affected patients.

IV. Conclusion

CAD tools help in early diagnosis of AD and help in slowing down the rapid progress of the disease. The main stages used in the CAD of AD are: feature extraction, feature selection and classification. In this survey, various algorithms and methods which are used in these stages of diagnosis are studied in detail. For every method a brief discussion and analysis are presented. This survey would enable the beginners in this research area to get an overview of the various techniques used in CAD of AD.

Acknowledgement

The authors are thankful to Bharathiar University for valuable support.

References

[1] F. Segovia , J.M. Gorriz, J. Ramirez, D. Salas-Gonzalez, I. Alvarez, "Early diagnosis of Alzheimer's disease based on Partial Least Squares and Support Vector Machine", Expert Systems with Applications 40 (2013), pp. 677-683.

[2] Andrea Chincarini, Paolo Bosco, Piero Calvini, Gianluca Gemme, Mario Esposito, Chiara Olivieri, Luca Rei, Sandro Squarcia, Guido Rodriguez, Roberto Bellotti, Piergiorgio Cerello, Ivan De Mitri, Alessandra Retico, Flavio Nobili, "Local MRI analysis approach in the diagnosis of early and prodromal Alzheimer's disease", NeuroImage 58 (2011), pp. 469-480.

[3] M. Lopez, J. Ramirez, J.M. Gorriz, I. Alvarez, D. Salas-Gonzalez, F. Segovia, R. Chaves, P. Padilla, M. Gomez-Rio, the Alzheimer's Disease

Neuroimaging Initiative, "Principal component analysis-based techniques and supervised classification schemes for the early detection of Alzheimer's disease", *Neurocomputing* 74 (2011), pp. 1260-1271.

[4] Darya Chyzhyk, Manuel Grana , Alexandre Savio, Josu Maiora, "Hybrid dendritic computing with kernel-LICA applied to Alzheimer's disease detection in MRI", Neurocomputing 75 (2012), pp. 72-77.

[5] Ignacio Alvarez Illan, Juan Manuel Gorriza, Javier Ramirez, Elmar W. Lang, Diego Salas-Gonzalez, Carlos G. Puntonet, "Bilateral symmetry aspects in computer-aided Alzheimer's disease diagnosis by singlephoton emission-computed tomography imaging", Artificial Intelligence in Medicine 56 (2012), pp. 191-198.

[6] F.J. Martinez-Murcia, J.M. Gorriz, J. Ramirez, C.G. Puntonet, D. Salas-Gonzalez, "Computer Aided Diagnosis tool for Alzheimer's Disease based on Mann-Whitney-Wilcoxon U-Test", *Expert Systems with Applications* 39 (2012), pp. 9676-9685.

[7] R. Chaves, J. Ramirez, J.M. Gorriz, C.G. Puntonet, "Association rule based feature selection method for Alzheimer's disease diagnosis", *Expert Systems with Applications* 39 (2012), pp. 11766-11774.

[8] R. Chaves, J. Ramirez, J.M. Gorriz, "Integrating discretization and association rule-based classification for Alzheimer's disease diagnosis", *Expert Systems with Applications* 40 (2013), pp. 1571-1578.

[9] Alexandre Savio, Manuel Grana, "Deformation based feature selection for Computer Aided Diagnosis of Alzheimer's Disease", *Expert Systems with Applications* 40 (2013), pp. 1619-1628.

[10] D. Salas-Gonzalez, J.M. Gorriza, J. Ramirez, I. Alvarez, M. Lopez, F. Segovia , C.G. Puntonet, "Two approaches to selecting set of voxels for the diagnosis of Alzheimer's disease using brain SPECT images", *Digital Signal Processing* 21 (2011), pp. 746-755.

[11] J.M. Gorriz, F. Segovia, J. Ramirez, A. Lassl, D. Salas-Gonzalez, "GMM based SPECT image classification for the diagnosis of Alzheimer's disease", *Applied Soft Computing* 11 (2011), pp. 2313-2325.

[12] I.A. Illan, J.M. Gorriz, J. Ramirez, D. Salas-Gonzalez, M.M. Lopez, F. Segovia, R. Chaves, M. Gomez-Rio, C.G. Puntonet, "F-FDG PET imaging analysis for computer aided Alzheimer's diagnosis", *Information Sciences* 181 (2011), pp. 903-916.

[13] J. Ramirez, J.M. Gorriz, D. Salas-Gonzalez, A. Romero, M. Lopez, I. Alvarez, M.Gomez-Rio, "Computer-aided diagnosis ofAlzheimer's type dementia combining support vector machines and discriminant set of features", *Information Sciences* 237 (2013), pp. 59-72.

[14] F. Segovia, J.M. Gorriz, J. Ramirez, D. Salas-Gonzalez, I. Alvarez, M. Lopez, R. Chaves, "A comparative study of feature extraction methods for the diagnosis of Alzheimer's disease using the ADNI database", *Neurocomputing* 75 (2012), pp. 64-71.

[15] Evanthia E. Tripoliti, Dimitrios I. Fotiadis, Maria Argyropoulou, George Manis, "A six stage approach for the diagnosis of the Alzheimer's disease based on fMRI data", *Journal of Biomedical Informatics* 43 (2010), pp. 307-320.

[16] Andres Ortiz, Juan M. Gorriz, Javier Ramirez , F.J. Martinez Murcia, "LVQ-SVM based CAD tool applied to structural MRI for the diagnosis of the Alzheimer's disease", *Pattern Recognition Letters* 34 (2013), pp. 1725-1733.

[17] Evanthia E. Tripoliti, Dimitrios I. Fotiadis, Maria Argyropoulou, "A supervised method to assist the diagnosis and monitor progression of Alzheimer's disease using data from an fMRI experiment", *Artificial Intelligence in Medicine* 53 (2011), pp. 35- 45.

[18] I.A. Illan, J.M. Gorriza, M.M. Lopez, J. Ramirez, D. Salas-Gonzalez, F. Segovia, R. Chaves, C.G. Puntonet, "Computer aided diagnosis of Alzheimer's disease using component based SVM", *Applied Soft Computing* 11 (2011), pp. 2376-2382.

[19] I. Alvarez Illan, J.M. Gorriz, J. Ramirez, D. Salas-Gonzalez, M. Lopez, F. Segovia, P. Padilla, C.G. Puntonet, "Projecting independent components of SPECT images for computer aided diagnosis of Alzheimer's disease", *Pattern Recognition Letters* 31 (2010), pp. 1342-1347.

[20] R. Chaves, J. Ramirez, J.M. Gorriz, M. Lopez, D. Salas-Gonzalez, I. Alvarez, F. Segovia, "SVM-based computer-aided diagnosis of the Alzheimer's disease using t-test NMSE feature selection with feature correlation weighting", *Neuroscience Letters* (2009).