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Identification of Alzheimer's Disease using Functional Connectivity Measures

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Abstract: ***Alzheimer's disease (AD) is a gradual neuro cognitive disorder caused by the damage of brain cells over a certain period of time. One non-invasive and efficient technique to investigate AD is to use functional magnetic resonance imaging (fMRI). Functional connectivity is a change in the functional connections between brain regions when an activity takes place. The correlation value gives the strength of functional connectivity. Pearson's correlation method was used to calculate the correlation coefficient between two time series. Mutual information which denotes the information successfully transmitted through a channel was also considered. In this paper, these two measures are compared and their performance and suitability is assessed for fMRI connectivity modelling based on the classification accuracy. Machine learning techniques such as support vector machine (SVM) is employed for connectivity analysis and classification of Alzheimer's from control population.***

Keywords: ***Alzheimer's Disease, Functional Magnetic Resonance Imaging, Functional Connectivity, Pearson's Correlation Coefficient, Mutual Information, Machine Learning.***

I. INTRODUCTION

Alzheimer's disease (AD) is a primary progressive degenerative disease of the central nervous system which affects people of age 65years and above [1]. It results in gradual loss of memory and other cognitive functions of the brain. It is the most common cause of dementia. As the disease progresses a distinct pattern of brain damage is noticed. The cause of Alzheimer's disease is poorly understood. At present there is no treatment for Alzheimer's to stop or reverse its progression. People affected with the disease increasingly rely upon others for assistance placing a burden on the caregiver.

To study any neurological disorder, it is essential to know the structural and functional changes in the brain. Hence, to image the structure and function of the brain, neuroimaging or brain imaging techniques are employed. Over the years, functional magnetic resonance imaging (fMRI) has been used in the field of medicine and disease diagnosis.

fMRI measures brain activity by detecting changes associated with blood flow. This approach is based on the fact that cerebral blood flow and neuronal activation are coupled i.e., oxygenated blood and deoxygenated blood have different magnetic properties. It is a non-invasive technique and has better spatial and temporal resolution. Hence, fMRI is preferred over other techniques.

Brain connectivity is a pattern of structural connections of statistical associations or causal interactions between distinct regions within a nervous system. It has been categorized into structural, functional and effective connectivity. Structural connectivity is the anatomical connections between brain regions. Functional connectivity refers to the temporal correlation in the activity of two brain regions that share similar functional properties. Unlike structural connectivity, functional connectivity is highly time-dependent. Effective connectivity is the influence of one brain region exerting on another.

A method has been proposed for exploring the variations in the functional brain network in AD patients using complex network theory [2]. Pearson's correlation method was used to determine the functional connectivity and a support Vector Machine (SVM) is used as a classifier. In the proposed approach it is claimed that the average classification accuracy for obtaining the eigenvalue for clustering coefficient and transitivity is 93.45% and the average global efficiency is 63.18%.

Univalent and bivalent brain functional connectivity measures has been used for connectivity modelling and for classifying autistic individuals from the healthy controls [3].

Machine learning classification has been employed using RCESVM and it was observed that bivalent measure produced a better classification accuracy.

In [4] brain state classification has been accomplished between PCE (Prenatal cocaine exposure) individuals and healthy controls. Features such as voxel intensities, obtained from fMRI data were fed as inputs to RCE-SVM classifier. The classification accuracy obtained was 90.3%.

Support vector machine (SVM) and graph theoretical approaches has been used to understand functional brain network variations in patients with Alzheimer's disease (AD) [5]. The graph measures were considered as the discriminating features and were fed to different feature selection algorithms to choose most significant features.

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Patients with AD were accurately classified from healthy control subjects with a classification accuracy of 100%.

The objective of this paper is to classify individuals as Alzheimer's or healthy control population based on functional connectivity analysis. Pearson's Correlation and Mutual information is used to determine the functional connectivity between the various brain regions. Using the obtained values, the top significant features are considered for further classification. Machine learning techniques such as RCE-SVM were used for the purpose of classification. The classification accuracy obtained for both the measures has been compared to determine the measure suitable for functional connectivity analysis.

Machine learning is the area of computer science in which the computers learn automatically without being explicitly programmed. Machine learning algorithms is categorized as supervised or unsupervised. Supervised machine learning algorithms apply information that has been learnt in the past to new data using labelled examples to estimate the future results. While unsupervised machine learning algorithms are used when the information required to train is neither classified nor labelled. Support vector machine (SVM) is a supervised learning mechanism used for linear classification and regression.

In this study, the proposed machine learning classification employs recursive cluster elimination-based support vector machine (RCE-SVM) classifier. RCE-SVM is a wrapper technique that has better classification accuracy and wide applicability.

II. METHODOLOGY

A. Data Acquisition and Pre-Processing

In this work, the fMRI data used was acquired from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database [6]. ADNI is a multisite longitudinal study employing imaging, clinical, bio-specimen and genetic biomarkers in healthy elders as well as in individuals with early mild cognitive impairment (EMCI), late MCI (LMCI) and Alzheimer's disease (AD). The objective of ADNI has been to test whether serial neuroimaging and other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and AD. Table 1 provides the demographics of the subjects used by us.

A total of 64 subjects were considered from phase-1 of the database: 35 control subjects and 29 AD patients. Resting-state fMRI data was acquired on 3T Philips MR scanners using a T2* weighted single shot echo planar imaging (EPI) sequence with 48 slices and the following parameters: slice thickness = 3.3mm, repetition time (TR) = 3000ms, echo time (TE) = 30ms, flip angle (FA) = 80°, voxel size = 3.3125 × 3.3125 × 3.3125 mm3, and 140 temporal volumes in each run. Field of view (FOV) parameters were the following: Right-Left (RL) = 212mm, Anterior-Posterior (AP) = 198.75mm, and Foot-Head (FH) = 159 mm. Anatomical images were obtained using magnetization-prepared rapid gradient echo (MPRAGE) sequence for overlay and localization (TR = 6.8ms, TE = 3.1ms, voxel size: 1.11 × 1.11 × 1.2 mm3, FA = 9°, FOV: RL = 204mm, AP = 253mm, FH = 270mm).

The raw fMRI data was subjected to standard resting-state fMRI data preprocessing steps such as normalization to MNI space, realignment, detrending, regressing out nuisance covariates such as six head motion parameters, white-matter signal and cerebrospinal fluid signal using SPM8 and DPARSF [7] toolboxes in a MATLAB environment. Mean fMRI timeseries were then extracted from 200 functionally similar brain regions of interest obtained through spectral clustering (cc200 template, [8]).

Table-I: Basic Demographics

Variable		Control	AD
Age, years	*Mean*	74.5	73.1
	Median	73.8	74.5
	SD	5.9	7.4
	Range	20.5	30.6
Gender, No. of subjects	*Male*	15	13
	Female	21	16

B. Functional Connectivity

Functional connectivity is the connectivity between the various brain regions having similar functional properties. It is the temporal correlation between spatially remote neurophysiological events. Functional connectivity is used for discovering statistical patterns.

In this study, functional connectivity is determined using the Pearson's correlation coefficient (PCC) [3]. PCC is a measure of the linear correlation between two variables. It is the best method of measuring the strength association between variables because it is based on the method of covariance. Pearson's correlation coefficient varies from -1 to +1. A positive correlation indicates that the two variables increase and decrease together, negative correlation implies that as one variable increases the other decreases and vice versa and finally a result of zero shows that there is no relationship between the variables.

PCC is given by the covariance of two variables divided by the product of their standard deviations.

$$\rho_{X,Y} = \frac{cov\,(X,Y)}{\sigma_X\,\sigma_Y} \qquad (1)$$

Equation 1 gives Pearson's correlation coefficient, where cov is the covariance and σ_X and σ_Y is the standard deviation. In this study, PCC is computed between the time series of every pair of brain regions, for all the subjects. For each subject there are 200 different brain regions (as per cc200 template) and each region has a time series of length 130. The PCC computation yields a 200x200 correlation coefficient matrix per subject. In this matrix, (i, j) corresponds to the functional connectivity between brain regions i and j which indicates that the two brain regions are functionally connected with the strength specified by the correlation value.

The mutual information denotes the information transmitted through a channel successfully. It measures the strength of brain functional connectivity. The mutual information for two random variables X and Y is defined as:

$$I(X, Y) = \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} f_{XY}(x, y) \log \frac{fXY(x,y)}{fX(x)fY(y)} dxdy \quad (2)$$

Over the years, mutual information (MI) has been used as an alternative measure for measuring functional connectivity as it not only measures the linear association between two-time series but also non-linear relationships. It denotes the information transmitted on the brain links. It has been proved that mutual information is a powerful measure in quantifying the association between any two fMRI temporal response waveforms [10]. In this study, similar to Pearson's correlation co-efficient mutual information is computed between the time series of every pair of brain regions, for all the subjects. MI computation yields a 200x200 matrix per subject.

Once the connectivity matrices have been obtained, statistical analysis is performed. In neuroimaging, we are interested to know the difference in the brain regions between the disease populations in comparison to the healthy controls. The objective is to compare the values between the two groups. 2-sample t-test is performed to determine the significant connectivity paths in the correlated data.

The 2-sample t-test determines if the two-population means are equal. It is applied to compare whether the average difference between any two groups is significant or has occurred by chance. T-tests are so called because the test results are based on the t-values. The sample data from the two groups is fed as the input to 2-sample t-test that gives the tvalue. The formula for computing the 2-sample t-test is given by

$$t = \frac{\overline{X_1} - \overline{X_2}}{S} \quad (3)$$

In equation (3), numerator indicates the difference of mean value of the first and the second group respectively and S indicates standard error of mean (SE).

The resultant matrix obtained after performing 2-sample ttest is a matrix of zeros and ones. One implies that the corresponding (i,j) connectivity path is statistically significant and zero implies that the connectivity path has occurred by chance.

C. Machine Learning

Traditionally, algorithms are a set of instructions which are explicitly programmed for the computers to solve a given problem. Using machine learning algorithms, computers train on data inputs and statistical techniques are used to output values that fall within a specific range. One such machine learning algorithm is a support vector machine (SVM). SVM developed by Vapnik is a supervised learning approach which has been broadly employed for categorization in various fields. In the previous study [4] it was shown that using distinguishing features, which have statistically different values for the classes being considered improvises SVM-based classification. Hence for this purpose, filtering and wrapper techniques have been used. Filtering techniques make use of statistical methods such as t-tests to obtain the significant features. Wrapper methods that include RFE and RCE eliminate features iteratively to reduce the prediction error. Hence, RCE-SVM is referred to as a classifier.

RCE-SVM combines a clustering method and SVM to identify and rank those gene clusters for classification. The main steps depicting RCE-SVM algorithm is as shown in the flowchart in Fig 1. The important steps of this algorithm are clustering step, SVM scoring step and RCE step. For all the 64 subjects (29 Alzheimer's and 35 control population) the input features were divided into two parts. The first part was taken as training data and the second part was used as testing data. In the clustering step, K-means algorithm is employed to group the training data into N clusters. Initially, the total number of clusters was made equal to number of features and successively reducing them by 20% until the remaining number of clusters were two. The N value obtained after every iteration becomes the initial value for RCE-SVM loop. SVM scoring step, involves scoring of clusters based on their ability to distinguish between the two classes. Training data was randomly separated into 6 subsets of same sizes for the purpose of scoring the clusters. The linear SVM was trained using 5 out of the 6 subsets. Performance of the SVM was estimated with the remaining subset. The clustering and cross validation processes was repeated 100 times to obtain various partitions. Classification accuracy was computed for all the 100 repetitions with the testing data. The average value of calculated accuracy, considering the repetitions and the folds, was assigned as the score for the cluster. In the RCE step lowest 20% of low scoring clusters were eliminated. The remaining features were integrated and the value of N was decreased by 20%. Clustering step, SVM scoring step and RCE step were repeated iteratively. After each iteration, performance was evaluated and lesser number of features were analyzed the previous iterations. The entire procedure was repeated until the number of clusters was 2. The complete separation of testing data and training data eliminates bias in performance accuracy.

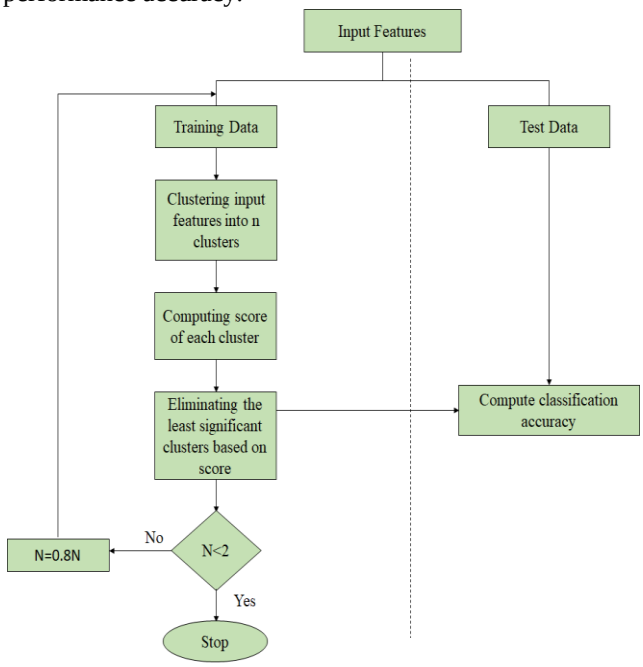

Fig. 1. Flowchart of RCE-SVM

III. RESULTS

The two functional connectivity measures PCC and MI is used to perform classification. Table 2 depicts the different classification accuracies that were obtained for both connectivity measures at different iterations. It can be inferred from the table and also from Fig 2 that PCC gives better classification accuracy in comparison with mutual information.

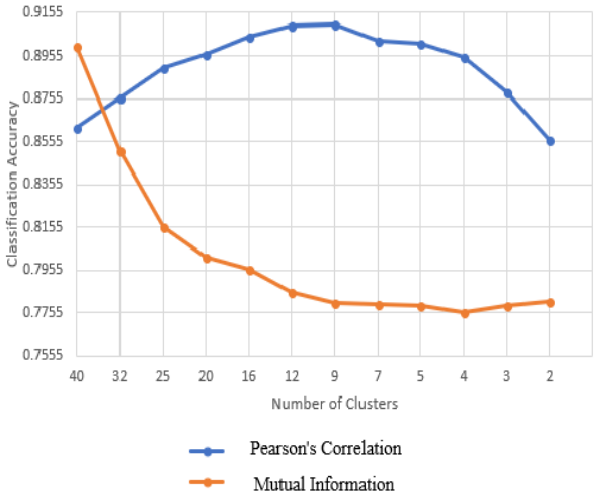

Fig. 2. Graph of classification accuracy vs number of clusters.

This could be because of PCC having more generality but less specificity in comparison with MI. This also means PCC can detect a wide range of associative relationships between two random variables. Whereas MI is more selective in modelling bivariate relationships. In other words, MI could not have modelled Alzheimer's and healthy controls differences well because of its specificity.

Table-II: SVM Results

Iterations	Clusters	Pearson's Correlation	Mutual information
1	40	0.86153	0.89984375
2	32	0.875938	0.85140625
3	25	0.89	0.81578125
4	20	0.895938	0.8015625
5	16	0.904375	0.795625
6	12	0.909375	0.7853125
7	9	0.910156	0.78015625
8	7	0.9025	0.7796875
9	5	0.901406	0.77890625
10	4	0.8946	0.775625
11	3	0.878594	0.77875
12	2	0.85625	0.78078125

IV.CONCLUSION

The purpose of this paper was to compare the performance of two brain functional connectivity measures, Pearson's correlation and Mutual information and determine the measure suitable for connectivity analysis. Machine learning technique was used to perform classification of individuals with Alzheimer's from healthy controls using the two functional connectivity measures. The measure which results in higher classification accuracy represents more comprehensive characterization of the underlying neuroscience of Alzheimer's. RCE-SVM classification showed that Pearson's correlation co-efficient resulted in a better classification accuracy compared to mutual information and hence this proves to be more suited for the analysis of fMRI functional connectivity.

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http://adni.loni.usc.edu/wpcontent/uploads/how_to_apply/ADN I_Acknowledgement_List.pdf

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Chaitra N, currently working as an Assistant professor in the Department of ECE, BNM Institute of Technology has over 12 years of experience in teaching and industry together. She did her B.E from BMS College of Engineering and Master's from RV College of Engineering, Bangalore. She was a topper for her branch in both under and post-graduation studies and received Gold medal from VTU for securing first rank in M.Tech (Digital Communications). Currently she is pursuing Ph.D under VTU in the area of image processing and pattern classification. She has over 15 publications in reputed international conferences and journals.

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