Diagnosis of Schizophrenia using Multivariate Analysis of Brain MR Images

Sushrutha Bharadwaj, M1, Anand Prem Rajan2
1&2School of Biosciences and Technology, VIT University, Vellore - 632014, India
1Department of Medical Electronics, Dayananda Sagar College of Engineering, Bengaluru, India - 560078

Abstract- Current laboratory procedures for the diagnosis of Schizophrenia are more subjective methods i.e. based on symptom profiles. Neural correlates do not provide sufficiently useful criteria. The existing univariate image analysis procedures are sub-optimal for the identification of specific neural correlates of schizophrenia. This paper aims at developing a mathematical tool for the diagnosis of schizophrenia using multivariable analysis of brain MR images. To identify the correlative pattern of gray matter differences between schizophrenics and healthy controls, Multivariate Linear Model (MLM) and Voxel based Morphometry (VBM) in Statistical Parametric Mapping (SPM) are used. Five images each of patients and controls are acquired and subject to multivariate analysis. The perceivable differences between the brain anatomies of the two groups are extracted and the regions of interest are recorded using the Talairach and Tournoux atlas. The pattern of the Eigen image is characterized by positive loadings indicating gray matter decline in the patients as well as the negative loadings reflecting gray matter increase in the patients. A learning algorithm using Support Vector Machines (SVM) is proposed and a classifier model is to be built. The differences extracted from the multivariate results have to be input to the model. When a random image is then input to the model, it has to accurately classify the incoming image as schizophrenic or a healthy one. The accuracy is predicted to be around 80%. These findings suggest that the multivariable analysis of brain images could be an effective method for the diagnosis of schizophrenia.

Keywords: Multivariate analysis, Schizophrenia, Statistical Parametric Mapping, Support Vector Mapping, Voxel Based Morphometry

I. INTRODUCTION

Current operational diagnostic systems for major psychiatric disorders such as schizophrenia are based solely on clinical manifestations and associated psychosocial impairments [1-3]. There is no single objective approach for the diagnosis of schizophrenia. No laboratory test for schizophrenia currently exists. Current image analysis approaches based on univariate methods have been found to be sub-optimal to identify potential specific neural correlates for schizophrenia. Researchers are now looking towards multi-variable analysis methods for an efficient objective analysis of the disease. Current research focuses on developing a clinical diagnosis procedure for schizophrenia. In univariate analysis the time series of each voxel in the brain is separately modeled and tested statistically for a condition of interest, usually in the framework of the General Linear Model [4-5].

In contrast, multivariate analysis considers the measurement of signals from many locations simultaneously. It is based on finding those patterns of the brain across many voxels which are characteristic of Schizophrenics versus controls to find perceivable characteristics of schizophrenics using MR images. Support vector machine (SVM) is a data classification algorithm that has been increasingly employed as a multivariate method for brain response classification [6]. SVM procedures can reveal coherent brain activations for individual subjects. The research intends to build a classifier using SVM that mathematically classifies a random image as a schizophrenic or a control.

II. METHODS

The block diagram of figure 1 shows a series of processes that are employed in statistical analysis that are used in this research. MR images of the subjects were acquired and pre-processing algorithms were applied on the images. Statistical analysis of the images was performed using Statistical Parametric Mapping software. The Multivariate Methods toolbox was used to process and extract multiple features from the images. These features were used by the Support Vector Machine tool to design a learning algorithm which learns about the differences in the images of schizophrenics and controls. Finally, a random image input to the algorithm will be classified as a schizophrenic or a normal image.

IMAGE ACQUISITION AND ANALYSIS

For experimental purpose, five images each of schizophrenic patients and healthy controls were acquired using MRI technique. The patients were recruited from National Institute of Mental Health and Neuro Sciences (NIMHANS), Bangalore, India. All the subjects were of same age, sex, education and had similar socio-economic status. Most importantly, all the patients were right handed and anti-psychotic naïve.

The MRI images were acquired using a 3.0 Tesla Philips (Achieva R2 release) MRI scanner. T1 weighted
three-dimensional magnetization prepared rapid acquisition gradient echo sequence was performed yielding a total of 165 slices in the sagittal plane. The imaging parameters were: TR = 8.1 ms; TE = 3.7 ms; Nutation angle = 8°; Field of view = 256mm; Slice thickness = 1mm without any inter slice gap; NEX = 1; Matrix size = 256*256; Voxel size = 1mm X 1mm X 1mm.

Figure 1: Basic flow of processes for multivariate analysis

Image analysis was performed using the Statistical Parametric Mapping (SPM) 5 software developed by Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK (http://www.fil.ion.ucl.ac.uk/spm). This software was implemented in MATLAB 7.01 (Mathworks Inc., Sherborn, MA, USA).

Image processing and analysis was performed according to the standard VBM protocol [7]. The first step is to realign the data to ‘undo’ the effects of subject movement during the scanning session. The spatial normalization involved transforming MRI images of all the subjects to a template that approximated the stereotactic space of Talairach and Tournoux [8]. The spatially normalized images were resliced to a final voxel size of 1x1x1 mm3 and partitioned into gray matter, white matter, cerebrospinal fluid, and other compartments. Modulated segments of gray matter were finally smoothed with a FWHM Gaussian kernel.

Statistical parametric mapping entails the construction of spatially extended statistical processes to test hypotheses about regionally specific effects [9]. Statistical parametric maps (SPMs) are image processes with voxel values that are, under the null hypothesis, distributed according to a known probability density function, usually the Student’s T or F distributions. We analyze each and every voxel using any standard (univariate) statistical test. The resulting statistical parameters are assembled into an image - the SPM. SPMs are interpreted as spatially extended statistical processes by referring to the probabilistic behavior of Gaussian fields [10-13]. In the present research, statistical t-test was conducted on the two groups of data and the results were estimated. These results were then used for multivariate analysis. The regional differences in gray matter volume were preserved in these results.

MULTIVARIATE ANALYSIS

Next, we extracted the gray matter distribution that differed most between schizophrenics and healthy controls. We used the MLM (Multivariate Linear Model) Package for this analysis (MMtoolbox, SHFJ-CEA, Orsay, France, http://www.madic.org/download/MMTBx/). The general format of the multivariate protocol is shown in (1)

\[
[Ds, u, Nvox] = \text{MM} \left( \text{argfile}, \text{typeAnal} \right) \tag{1}
\]

where \(Ds\) – Eigen values; \(u\) – Eigen vector; \(Nvox\) – Total number of voxels considered; \(\text{TypeAnal}\) – Type of analysis.

The standard way of using the MM package is to first perform a standard spm analysis that will provide a first apriori model, the corresponding estimated parameters and residual sum of square images. The temporal filter or the normalization chosen is of great importance for meaningful interpretation of the MM results. The MLM method is based on singular value decomposition of the matrix \(Z\), where \(Y\) is the data, \(X\) is the linear model, and \(\Sigma\) represents the temporal covariance matrix of the data [14].

\[
Z = (X'\Sigma X)^{-1/2}X'Y \tag{2}
\]

The MM toolbox analyses the results of SPM analysis and computes the dispersion matrix using the beta and Eigen images as shown in figure 2. By default, the package computes up to five Eigen images. Since
there is no temporal covariance for VBM data, the matrix $X'\Sigma X$ was simplified to $X'Y$. This matrix was then decomposed into an Eigen image (Figure 3) that represents the variance between the data and a set of regressors.

$$ (Subject1-time-dim + subject2-time-dim + \ldots + subjectN-time-dim) \times common-space-dim $$

This can also be considered as one Eigen image per subject (or region of interest). More often, the MM is performed on a matrix with dimension given in (5):

$$ (Subject1-space-dim + subject2-space-dim + \ldots + subjectN-space-dim) $$

### III. RESULTS AND DISCUSSION

The results obtained are particularly important for characterizing the difference between a group of patients and a group of healthy controls. The gray matter increase in figure (3) is indicated by the positive loadings which can also be noted in the Eigen values in figure 4 indicating an increase in gray matter in the corresponding regions of schizophrenics’ brains. Alternatively, the negative loadings in Eigen images indicate a decrease in gray matter in schizophrenics. This observation is very useful in differentiating between a schizophrenic brain and a normal brain.
IV. CONCLUSION

In the current paper, SPM and MM toolbox have been used to differentiate schizophrenia from healthy control subjects using multivariate analysis methods applied on MR images. Perceivable differences between the two groups of images are extracted. The positive and negative loadings in the Eigen images obtained using multivariate analysis algorithm relate to the gray matter changes in the brain that are particular to the Schizophrenia images.

The future work focuses on extracting the perceivable differences from the results of multivariate analysis and to build a classifier model using Support Vector Machines (SVM). When a random image is input to the model, it is intended to mathematically classify it as either schizophrenic or a healthy control.

LIBSVM, a library of support vector machines has been found to be a powerful tool for building a classifier model. It can be found at http://www.csie.ntu.edu.tw/~cjlin/libsvm. The accuracy of classification is also expected to be high compared to other classification models. Further elaboration of these methods may contribute for effective clinical diagnosis of schizophrenia.

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