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# CLASSIFICATION OF SCHIZOPHRENIC AND CONTROLS USING FMRI DATA

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***Abstract-*** Schizophrenia is currently diagnosed based upon symptoms and there is no quantitative, biologically based technique as yet. Classification of individuals into schizophrenia and control groups based on fMRI data is thus of great interest to support psychiatric diagnoses. I applied an automated technique fMRI data obtained during Sternberg Item Recognition Paradigm task. The validity of the technique was tested with holdout method and the detection performance varied between 98.92% and 100% applying different holdout iterations. The findings suggest that the proposed data reduction algorithm is effective in classifying individuals into schizophrenia and control groups and useful as a diagnostic tool. Functional Magnetic Resonance Imaging (fMRI) technology enables medical doctors to observe brain activity patterns that represent the execution of subject tasks, both physical and mental. Independent component analysis applied to functional magnetic resonance imaging (fMRI) data has been fruitful in grouping the data into meaningful spatially independent components.

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***Keywords –*** Classification, Euclidean distance, fMRI, ICA, schizophrenia.

## I. INTRODUCTION

Over the past decade, functional Magnetic Resonance Imaging (fMRI) [1] has emerged as a powerful instrument to collect vast quantities of data about activity in the human brain. The automated classification of fMRI images of Brain helps doctors to accurately classify the schizophrenic patients and healthy controls. The objective of this work is to identify biomarkers predictive of schizophrenia based on fMRI data collected for both schizophrenic and non-schizophrenic subjects performing a simple Sirp task in the scanner. Statistical parametric mapping (SPM) is the dominant tool for analysis of functional brain data acquired from medical imaging modalities such as positron emission tomography (PET) and functional magnetic resonance imaging and is aimed at identification of functionally specialized brain regions. SPM is a voxel based hypothesis driven method that examines regionally specific responses on the basis of standard inferential statistics.

Independent component analysis (ICA) is a statistical method used to discover hidden features from a set of measurements or observed data such that the sources are maximally independent. Typically, it assumes a generative model where observations are assumed to be linear mixtures of independent sources, and unlike principal component analysis (PCA), which uncorrelates the data, ICA works with higher-order statistics to achieve independence. Independent component analysis applied to functional magnetic resonance imaging (fMRI) data has been fruitful in grouping the data into meaningful spatially independent components. I propose an automated way to classify schizophrenic and healthy patients. The total error is minimized based upon the Euclidean distance between the group mean images and the images to be classified. Using holdout approach, results indicate an average sensitivity and specificity of 99% and 100% respectively. In summary, I show that using features derived from fMRI data

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with ICA and a supervised classification approach, one can objectively separate diagnostic groups.

Given the limited accepted capability of genetics to diagnose schizophrenia, functional MRI (fMRI) is gaining importance and becoming a more widely used innocuous technique with the potential to help diagnose schizophrenic patients, among other neurological illnesses. There is great potential in the development of methods based on fMRI as a biologically based aid for medical diagnosis, given that current diagnoses are based upon imprecise and time-consuming subjective symptom assessment. In this thesis, I propose a method to discriminate among two input classes, healthy controls (class 1, HC) and schizophrenia patients (class 2, SZ) using fMRI data collected while subjects are performing the Sternberg Item Recognition Paradigm **(**SIRP1) task, a scanning procedure. Initial feature extraction is performed using group independent component analysis (ICA), which is a data-driven approach that extracts maps of regions that exhibit intrinsic functional connectivity. I present a methodology to automatically and objectively discriminate between healthy controls, and schizophrenia patients. The challenges one faces in the use of fMRI for classification are twofold: first one is the high dimensionality of the input feature space, and the second one is the reduced sample set size available.

## II. BACKGROUND

### *A. Functional magnetic resonance imaging*

Functional MRI [1] is a non-invasive technique for studying brain activity. During the course of an fMRI experiment, a series of brain images are acquired while the subject performs a set of tasks. Changes in the measured signal between individual images are used to make inferences regarding task-related activations in the brain. fMRI has provided researchers with unprecedented access to the brain in action. Functional Magnetic Resonance Imaging (fMRI) technology enables medical doctors to observe brain activity patterns that represent the execution of subject tasks, both physical and mental. In general, each subject exhibits his own

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activation pattern for a given task, whose intensity is affected by the physiology of the subject's brain, the usage of medications, and the parameters of the scanner used for image acquisition. Since it is possible to co-register the resulting activation map to a standard brain, all activation patterns from the different individuals can be analyzed in terms of consistency on the brain sections or brain coordinates where the activation is observed. The technology that enables us to observe visually the spatial-temporal behaviour of the brain activation during a normal routine is based on the Blood-Oxygen- Level Dependent principle (BOLD**)**. An fMRI scanner measures the value of the fMRI signal (BOLD response) at all the points in a three dimensional image. While the importance of modeling brain connectivity and interactions became widely recognized in the current fMRI-analysis literature, practical applications of the proposed approaches such as dynamic causal modeling, dynamic Bays nets were usually limited to interactions analysis among just a few known brain regions believed to be relevant to the task or phenomenon of interest.

*B. Independent Component Analysis*

Because of the high dimensionality of fMRI data, a data reduction scheme is typically applied prior to ICA. The dimensionality of the data in fMRI is determined by the repeat time (TR) parameter. This can be changed from scan to scan and has no relationship to the number of sources in the brain. We assume that more time points are acquired than the number of brain sources, an assumption justified for many fMRI experiments. ICA has only recently been applied to fMRI data. It has proved promising, but there is a need to study the properties of ICA as applied to fMRI data.

A typical ICA model assumes that the source signals are not observable, are statistically independent, and are non-Gaussian, with an unknown but linear mixing process. Consider an observed M-dimensional random vector denoted by $x = (x1, \ldots, x_M)^T$, which is generated by the ICA model:

$$x = As$$

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where s = [s1, s2, . . . $s_N$]$^T$ is an N-dimensional vector whose elements are assumed independent sources and $A_{M\times N}$ is an unknown mixing matrix. Typically M >= N, so A is usually of full rank. The goal of ICA is to estimate an unmixing matrix $W_{N\times M}$ such that y is a good approximation to the true sources given by:

$$y = Wx$$

Popular approaches for performing ICA include maximization of information transfer, which is equivalent to maximum likelihood estimation, maximization of non-Gaussianity, mutual information minimization. Both Principal (PCA) and Independent Component analysis (ICA) are transformations that rely on statistics of the given data set. PCA is based on the information given by the second order statistics, whereas ICA goes up to high order statistics. Therefore the result obtained by ICA is assumed to be more meaningful than the one gained by PCA. However ICA better works on the data that have been already preprocessed by PCA. Thus ICA is often perceived as an extension of PCA. PCA and especially ICA have recently become popular tools in various fields, e.g. blind source separation, feature extraction, telecommunication, finance, text document analysis, seismic monitoring and many others.

*C. Infomax*

Infomax [2] maximizes the information transfer from the input to the output of a network using a non-linear function. A majority of applications of ICA to fMRI use Infomax since the sources of interest in this case are super Gaussian in nature and the algorithm favors separation of super-Gaussian sources. However, the artifacts present in fMRI data typically have sub-Gaussian distributions. Z-scores for Infomax were higher than the other algorithms for the task-related source, indicating that Infomax achieves a higher contrast to noise ratio. Repeated runs showed that the changing initial random condition does not change results significantly. Infomax is much slower than the other algorithms listed in the toolbox.

GIFT is an application developed in MATLAB 6.5 that enables group inferences from fMRI data using Independent Component Analysis (ICA)[3]. A GIFT is used to run single subject and

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single session analysis as well as group analysis. ICA has been successfully applied to single subject and single session analyses. Group analysis of fMRI is important to study specific conditions within or between groups of subjects. The GIFT contains an implementation of ICA for analyzing the fMRI data. ICA has been successfully used to analyze single-subject fMRI datasets and, recently, for multisubject analysis [4].

*D. The Sternberg Item Recognition Paradigm (SIRP)*

A typical SIRP is a continuous performance, choice reaction time task that requires working memory (WM). Subjects are asked to memorize a set of target digits. They are then presented with probes (single digits) and respond by indicating whether the probe is a target (a member of the memorized set) or a foil (not a member of the memorized set). The number of targets can be varied to provide a range of working memory load conditions.

This version of the SIRP task consisted of three working memory loads, where subjects were shown a memory set of 1, 3 or 5 target digits in red, followed by a series of probe digits in green. For each run, two memory sets for each of the three load conditions, were presented. Each condition had three portions: learn, encode, and probe epochs. Subjects were asked to learn the sets of red digits and instructed to press with their index finger if the green probe digit matched one of the targets and with their middle finger if it did not.

## III. EXPERIMENTAL SETUP

Figure 1 shows the block diagram of the processing system for the classification of Healthy Controls and Schizophrenia Patients. First fMRI images are given as input to the system. Those input images are preprocessed using SPM. Then these preprocessed images are fed to GIFT for feature extraction.

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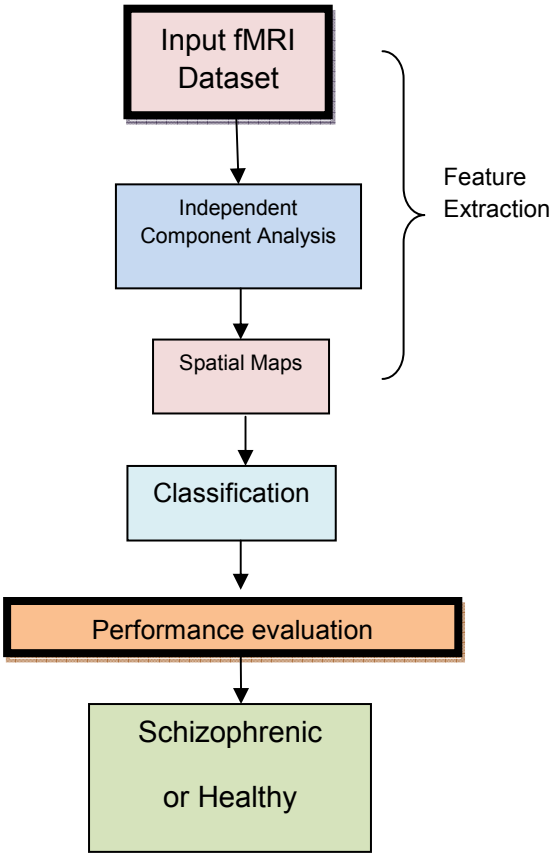


Figure 1 The processing system for classifying schizophrenic vs. healthy

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GroupICA is applied on the preprocessed dataset and spatial maps are constructed [4]. The independent components extracted from GroupICA are fed the classifier for further processing. Classification procedure is applied on the ICs. Mean image for each group is calculated first. Then Euclidean distance is found out between the individual and each group's average image. A given image was classified as belonging to a group if the distance between that image, was less than that between the other two groups.

*A. Image Acquisition*

The scans were acquired on 1.5T Siemens scanner. Healthy comparison subjects and schizophrenic/ schizoaffective male and female adults between the ages of 18 and 70 were recruited for this study. All subjects had regular hearing levels (no more than a 25 db loss in either ear), had sufficient eyesight or were correctable to be able to see visual display, were fluent in English, and were able to perform the cognitive tasks in this study. No female subjects were pregnant and female subjects of childbearing potential received a urine or blood pregnancy test before the MRI. There could be no contradictions to MRI scanning including a cardiac pacemaker, metal fragments in eye, skin, body; heart valve replacement, brain clips, venous umbrella, being a sheet-metal worker or welder, aneurysm surgery, intracranial bypass, renal, aortic clips; prosthetic devices such as middle ear, eye, joint, or penile implants, joint replacements; hearing aid, neurostimulator, insulin pump; shunts/stents, metal mesh/coil implants; metal plate/pin/screws/wires, or any other metal implants; permanent eyeliner or permanent artificial eyebrows or significant claustrophobia.

Control subjects were excluded if they had a current or past history of a major neurological, psychiatric, medical illness; previous head injury; substance or alcohol dependence; and IQ less than 75 (as measured by the North American Adult Reading Test

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(NAART)); if they were using migraine treatments; or if a first degree family member had a diagnosis of a psychotic illness. Subjects with schizophrenia or schizoaffective disorder meeting DSM-IV criteria were allowed in the study; schizophreniform subjects were excluded. Subjects were excluded if they had a current or past history of a major medical illness; previous head injury or prolonged unconsciousness; or substance and/or alcohol dependence. Patients were also excluded if they currently had an IQ less than 75 as measured by the NAART. Subjects were required to be clinically stable with no significant changes in their psychotropic medications in the previous two months

B. Preprocessing

Data were preprocessed using the Statistical Parametric Mapping software package, SPM5. Data were Slice Timed, spatially smoothed with a 8 mm3 full width at half-maximum Gaussian kernel, spatially normalized into the standard Montreal Neurological Institute space.

C. Independent Component Analysis

GroupICA was used to decompose all the data into twenty-four components using the GIFT software. For each participant, the two runs were concatenated and then reduced from temporal dimensions using principal component analysis (PCA) on all in-brain voxels.

Dimension estimation, to determine the number of components, was performed using the minimum description length criteria, modified to account for spatial correlation [7,8]. Data from all subjects were then concatenated and this aggregate data set reduced to 39 temporal dimensions using PCA, followed by an independent component estimation using a neural network algorithm which attempts to minimize the mutual information of the network outputs.

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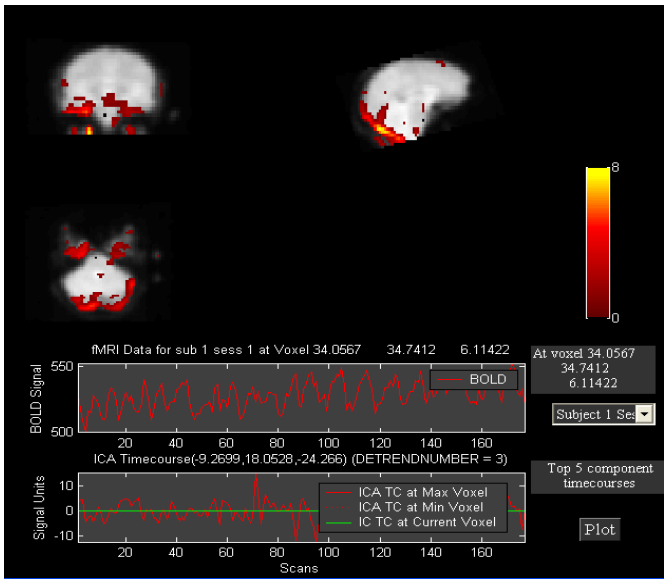


Figure 3.21 Orthogonal view of IC

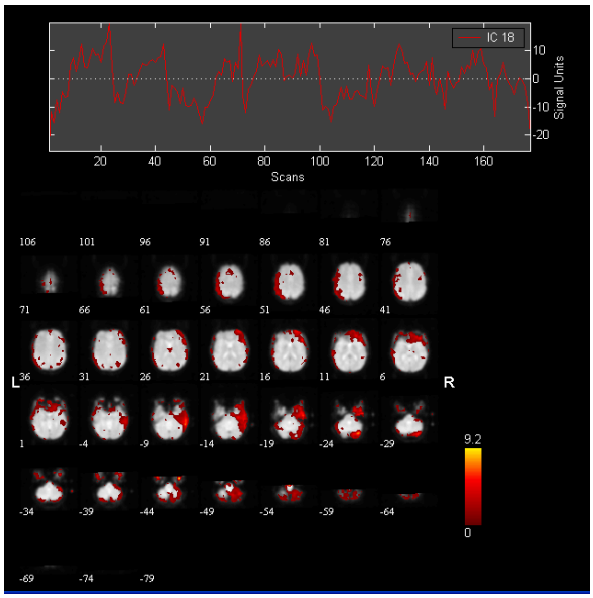


Figure 3.22 Spatial map of Schizophrenia Patient

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*D. Classification*

A classification algorithm is developed. Voxels from the entire brain were initially included in the algorithm. A mean image was computed for each group, and the Euclidean distance between an individual's brain image and each group's images was computed. A given image was classified as belonging to a group if the distance between that image, was less than that between the other two groups. In order to validate the classification procedure, a holdout approach was used in which whole dataset is divided into training set and a testing set and the process was repeated for training and testing sets. The detailed algorithm is as follows:

1. Define the groups as gschizo, gcont
2. Compute group average images avgsch, avgh and tschizo and thealthy
3. Compute the pair-wise difference
{Cont - schizo, schizo - cont}
4. For each participant, and for each group,
 a) Compute Euclidean distance between group mean voxels and participant voxels and
 b) Classify as
 cont if Dcont,i < Dschizo,i
 schizo if Dschizo i < Dconti
5. Compute sum of all false positive and false negative classification errors
6. Once the classifier is developed, then apply holdout approach.

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## IV. RESULTS

I have achieved 100% accuracy for classifying Schizophrenic patients. I have used the classification algorithm as shown in system development section and used the holdout method to validate the classifier. This classifier shows average sensitivity of 98.92% and average specificity of 100%.

Accuracy of the classifier= Number of predictions/ Total number of predictions

= 59/60

= 98.33 %

Accuracy for iterations 1, 3 =100%

Average Accuracy of the classifier = (100 + 98.33 + 100)/ 3

= 99.4433%

Error Rate for iteration1, 3 =00%

Error rate for iteration 2=1/60=1.67%

Average Error Rate= 0.5555%

The Table 1 and Table 2 shows the results of classification for the test sets.

Table 1. Results of classification : Holdout 1, 3

| | Patients with schizophrenia | |
|---|---|---|

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| | Positive | Negative | |
|---|---|---|---|
| Positive | True Positive (TP) = 30 | False Positive (FP) = 00 | → Positive predictive value = TP / (TP + FP) = 100% |
| Negative | False Negative (FN) = 00 | True Negative (TN) = 30 | → Negative predictive value = TN / (FN + TN) =100% |
| | Sensitivity = TP / (TP + FN) = 100% | Specificity = TN / (FP + TN) = 100% | |

Table 1. Results of classification: Holdout 2

| | **Patients with schizophrenia** | | |
|---|---|---|---|
| | **Positive** | **Negative** | |
| Positive | True Positive (TP) = 29 | False Positive (FP) = 00 | → Positive predictive value = TP / (TP + FP) = 100% |
| Negative | False Negative (FN) = 01 | True Negative (TN) = 30 | → Negative predictive value = TN / (FN + TN)=96.77% |

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| | | | |
|---|---|---|---|
| | Sensitivity = TP / (TP + FN) =96.67% | Specificity = TN / (FP + TN) = 100% | |

*D. Discussion*

Our approach attempts to overcome several challenges associated with the use of brain imaging to study mental illness. I incorporate automated feature extraction to identify spatially distinct and employ a supervised classification algorithm to distinguish two groups. FMRI results involving schizophrenia suffer from large variability. Independent Component Analysis is proved to be more consistent and robust, hence improving the ability to develop reliable biomarkers for disease classification. Spatial masks were created for automated feature identification following the ICA fMRI decomposition. Classification accuracy was validated using a hold approach and an average sensitivity of 99% and specificity of 100% was obtained. The identification of a quantitative measure for disease classification is very much needed. A recent task of classification for bipolar disorder, schizophrenia and healthy controls shows the results of average sensitivity 90% and specificity 95%. Controls were correctly classified 95% of the time, schizophrenia patients 92%, and bipolar patients 81o%. The sensitivity of the tests examined ranged from 28% to 73% whereas the specificity was from 67% to 90%. My results suggest it may be possible to utilize fMRI data to improve diagnostic decision-making. A potential limitation of the current study is that all patients were on medication at the time of testing. Additional studies will be required to determine whether a medication effect is present or not.

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