Functional Classification of Schizophrenia Using Feed Forward Neural Networks

Madiha J. Jafri, Vince D. Calhoun

Abstract—**In medicine, the nature of an illness is often determined through behavioral or biological markers. The process of diagnosis becomes difficult when dealing with mental disorders since they rely primarily on behavioral markers. Schizophrenia is an example of a complex mental disorder that relies on aberrant behavior such as auditory hallucinations, dampening of emotions, paranoia, etc. This research is an attempt to determine a biological marker for schizophrenia through the use of functional magnetic resonance imaging (fMRI). In this paper, we propose a method of classification of schizophrenia and healthy controls, using a neural network approach and functional brain 'modes' estimated from resting state data using independent component analysis. A reliable technique for discriminating schizophrenia based upon fMRI would be a significant advance and may also provide additional information about the biological implications of mental illness.**

I. Introduction

ACCORDING to the National Institute of Mental Health (NIMH), Schizophrenia is the most chronic and disabling of the severe mental disorders. The disease affects some of the most highly evolved functions in humans such as perception, memory, attention, cognition, and emotion. The cognitive symptoms of schizophrenia, which include difficulties with attention, memory, and problem solving, can create significant barriers to a normal and productive life. Finding treatments for these symptoms has been hampered by a lack of scientific consensus on which cognitive impairments should be targeted for research and what tools are best for measuring them.

Extensive research is being performed on data from structural and functional magnetic resonance imaging (MRI) at the Olin Neuropsychiatry Research Center (ONRC) in Hartford, CT. Work discussed in this paper specifically focuses on functional MRI (fMRI) data collected from both healthy controls and patients diagnosed with schizophrenia. FMRI scans were collected at the ONRC. Although there has been much work showing difference in the fMRI of schizophrenic patients and healthy controls in task-related scans, this research focuses on "resting state" scans, in which the subject is requested to lay still for five minutes in the scanner with his/her eyes closed, not to think of one thought in particular and not to fall asleep. Resting state scans are useful because they do not confound performance with brain activity [3][16]. There is also an additional advantage of using resting state scans since collection of the data is easier and quicker than typical cognitive paradigms.

One of the most popular multivariate methods to analyze fMRI data is independent component analysis (ICA). ICA is a statistical and computational technique for revealing hidden factors that underlie sets of random variables, measurements, or signals. The ICA of the random variable x consists of finding a linear transformation $s = A^{-1}x$ so that the components s are as independent as possible [13][22].

Feed forward neural networks were used to analyze spatial ICA components extracted from subjects' resting state fMRI data and to classify the subjects as either patients or healthy controls. Artificial neural networks are computational systems whose architecture and operation are inspired from the knowledge about biological neural cells (neurons) in the brain. In this paper, the neural networks are trained using the classic back propagation algorithm, which derives its name from the fact that error signals are propagated backward through the network on a layer-by-layer basis. Therefore, in a three layer neural network (input, hidden, and output layers), the weights of the network are uploaded starting with the hidden to output weights, followed by the input to hidden weights, with respect to the sum of square error.

The next few sections will introduce the detailed design of the classification project, describe the fMRI image acquisition and processing, and show the results. Finally we discuss possible future work to improve classification results further.

II. Research Design

The following sub-sections show the step-by-step procedure performed for effective classification:

A. Data Collection and Pre-Processing:

Data from thirty-eight patients with Schizophrenia and thirty-one healthy controls was drawn from ongoing studies, with written subject consents, at the ONRC. Healthy controls were required to not have a history of psychiatric illness, while the patients were required to meet the DSM-IV criteria for schizophrenia or schizoaffective disorder.

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M. J. Jafri is with the Olin Neuropsychiatry Research Center at the Institute of Living in Hartford, CT 06012 USA (phone: 860-545-7894; fax: 860-545-7797; e-mail: mjafri@harthosp.org).

V. D. Calhoun is an Associate professor in the department of Psychiatry at Yale University, and is also the Director of the Medical Image Analysis Laboratory at the Olin Neuropsychiatry Research Center at the Institute of Living in Hartford, CT 06012 USA (e-mail: vince.calhoun@yale.edu).

The following fMRI scans were collected using a 3.0 Tesla Siemens Allegra scanner at the ONRC.

1) A sagittal scout scan [spin echo (SE), repeat time (TR)=500 ms, echo time (TE)=9ms, field of view (FOV)=24cm, Matrix=256×256, flip angle (FA)=8°, slice thickness (ST)=5mm].

2) A T1-weighted anatomic scan (SE, TR=700ms, TE=12ms, Matrix=256×256, FA=8°, ST=5mm)

3) Functional scans (gradient-echo echo-planar-imaging, TR=1s, TE=30ms, FOV=24cm, Matrix=80×80, FA=60°, ST=5mm). Acquisition of all scans took approximately 30 minutes.

Before performing statistical analysis, subject data was pre-processed using SPM2 (available at: http:/www.fil.ion.ucl.ac.uk/ spm/ software/ spm2/). Pre-processing included realignment, normalizing and smoothing of all subject images. Images were realigned using INRIalign, a motion correction algorithm unbiased by local signal changes. Data were spatially normalized into the standard Montreal Neurological Institute space, and spatially smoothed with a 10×10×10 mm^3 full width at half-maximum Gaussian kernel. The data (originally acquired at 3.44×3.44×4mm^3) was re-sampled to 3.5×3.5×4.5 mm^3, resulting in 53×63×41 voxels.

B. ICA Algorithm:

Figure 1 illustrates the principle of ICA of fMRI. Two sources are presented along with their representative hemodynamic mixing functions. In the fMRI data, these sources are assumed to be mixed by their mixing functions and added to one another. The goal of ICA is then to unmix the sources using some measure of statistical independence.

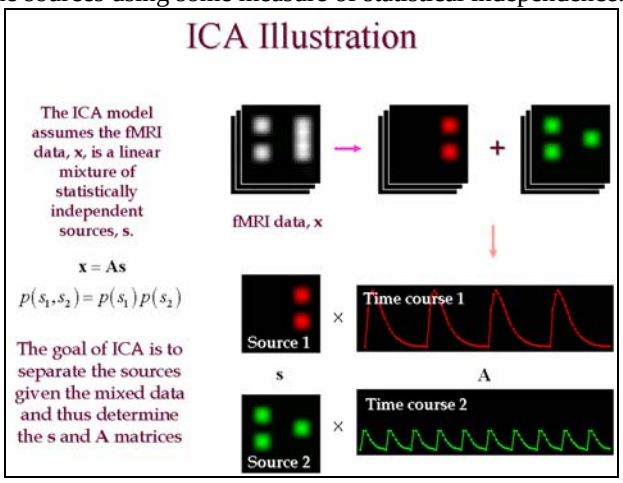

Figure 1: ICA Illustration of Source separation using mixing matrices

While standard ICA techniques are useful for analyzing single subjects, the Group ICA of fMRI toolbox (GIFT), extends the functionality of ICA to multiple subjects and sessions, allowing for group inferences. This software is available for download at http://icatb.sourceforge.net with a detailed tutorial and references to over 20 successful publications resulting from the use of GIFT for analysis [6].

C. Data Extraction:

The Infomax ICA algorithm in GIFT was used to estimate thirty components [20]. Resting state scans are useful since they do not confound performance with brain activity. In addition, multiple groups have been able to analyze resting state networks using ICA, due to their consistency across subjects [5], [1].

For each of the 69 subjects, images for each of the above components were loaded into MATLAB and voxels where the variance among controls and among patients was the least while the mean difference between patients and controls was the maximum needed to be extracted. Therefore half of the 69 subjects (20 patients, 15 controls) were taken to analyze differences in voxels between patients and controls. Complete dataset (all 69 subjects) was not used because this would provide too much *a priori* knowledge about the dataset before classification. We included more patients than controls in the dataset due to the greater variability in the patient data [19].

Once the top 500 significant voxel locations were determined from the sample, data from these voxel locations was extracted and saved from all 69 subjects. This data was then sent to the Neural Network for training and testing as explained in the next section.

D. Neural Network Design

A three layer Neural network was created with 500 nodes in the first (input) layer, 1 to 50 nodes in the hidden layer, and 1 node as the output layer. We varied the number of nodes in the hidden layer in a simulation in order to determine the optimal number of hidden nodes. This was to avoid over fitting or under fitting the data. Due to hardware limitations, ten nodes in the hidden layer were selected to run the final simulation. Figure 2 shows the design of the Feed Forward Neural networks used in this research.

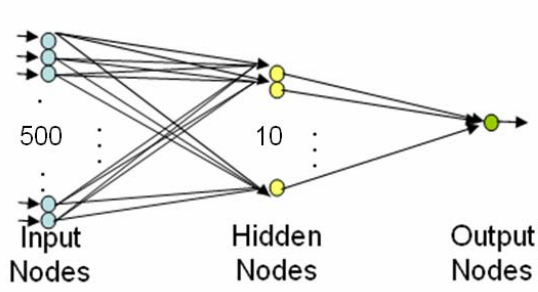

Figure 2: Feed Forward Neural Network

The 500 data points extracted from each subject were then used as inputs of the neural networks. The output node resulted in either a 0 or 1, for control or patient data respectively. Since the nodes in the input layer could take in values from a large range, a transfer function was used to transform data first, before sending it to the hidden layer, and then was transformed with another transfer function before sending it to the output layer. In this case, a tan sigmoid transfer function was used between the input and hidden layer, and a log sigmoid function was used between

the hidden layer and the output layer.

The weights in the hidden node needed to be set using "training" data. Therefore, subjects were divided into training and testing datasets. Out of the 69 subjects, 2 random patients and 2 random controls were selected as "test data", while the rest of the dataset was used for training. Training data was used to feed into the neural networks as inputs and then knowing the output, the weights of the hidden nodes were calculated using back propagation algorithm. 120 trials were performed on the same Neural Network, selecting 65 subjects randomly every time for re-training and 4 remaining subjects for testing to find accuracy of Neural network prediction.

III. Results

Seven components (resting state networks) were used in the classification algorithm (see figure 3). The following components were identified as being blood oxygen level dependent (BOLD) related resting-state networks:

1. Component 19- Default Mode: Activations were observed in the posterior parietal cortex at the occipito-parietal junction, along the mid-line in the precuneus and posterior cingulated cortex, and in the frontal pole [3], [1], 4].
2. Component 21-Parietal: Activations were observed in the parietal lobe, separated by central sulcus from the frontal lobe, and the parieto-occipital sulcus from the occipital lobe [1, [14].
3. Component 23- Lateral and Medial Visual Cortical Areas: These include areas located in Calcarine sulcus bilaterally as well as medial and lateral extrastriate regions such as the lingual gyrus and the occipital pole, extending laterally towards the occipito-temporal junction [3][14].

4/5. Components 27/28- Dorsal Visual Stream: The lateralized activations were primarily seen in the dorsal visual stream including left and right lateral occipital complex and inferior parietal cortex, bilateral intraparietal suclus as well as right and left-middle superior frontal gyri [3][14].

6. Component 29- Medial frontal: Activations can be observed between the inferior and superior frontal suclus and in front of the precentral sulcus [2,22].
7. Component 30- Temporal: Activations in this component include Heschl's gyrun, planum polare and planum temporale, the lateral superior temporal gyrus and the posterior insular cortex [2,22 [7]].

Figure 4 shows a histogram of components and voxel selections. The x-axis values correspond to the seven component numbers selected and mentioned previously. Interestingly, most of the selected voxels came from component 19, or the Default Mode component. The next dominant component was 29, or the Medial frontal component.

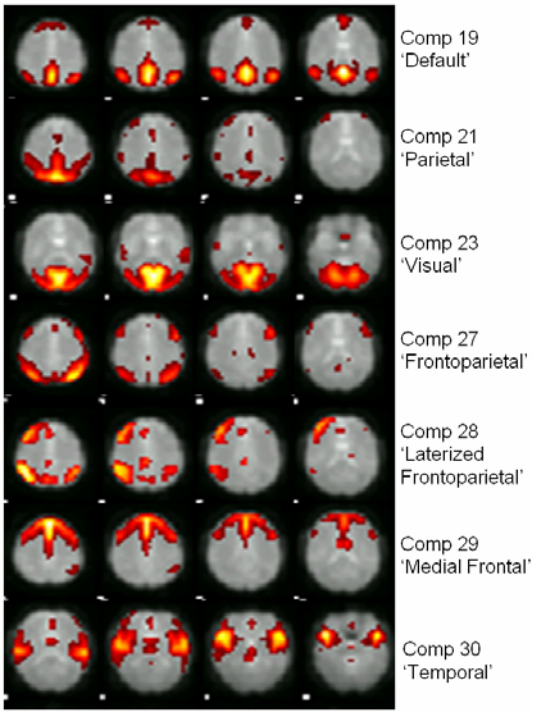

Figure 3 Components Representing Various Modes

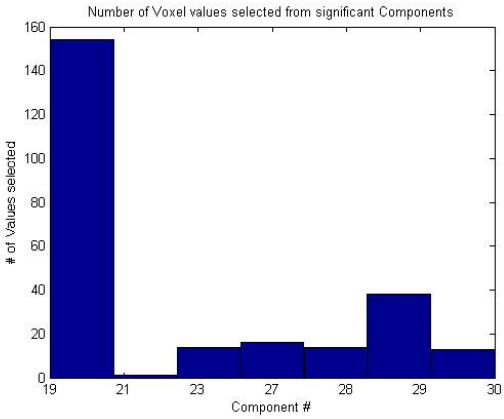

Figure 4: Voxel Selection by Component

Figure 5 shows a histogram of the resulting accuracies from 120 NN predictions. As seen in the figure, the overall mean accuracy for the 120 trials was 75.6%. There were more trials with an accuracy between 0.75 and 1 (or 75% and 100%), than values between 0 to 0.75.

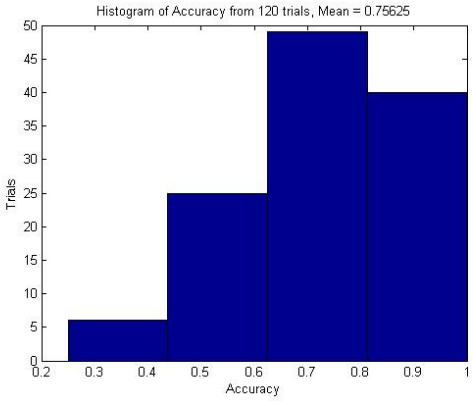

Figure 5: Accuracy Results from 120 Trials

IV. Conclusion

Several classification techniques have been previously used on fMRI data; however, classification of schizophrenic patients and controls using resting state data poses several obstacles due to lack of a task-related event, which may show significant differences in the activation levels of healthy controls from patients. Classification was also performed using the timecourses' normalized power spectral densities from images of all subjects as well as relating the correlation values of the timecourses from each of the 7 selected components for each subject. The results and repeated trials from both of the above implemented methods yield lesser accuracy than the method mentioned in this paper. The current classification mean of around 76% is also promising and may be further increased with larger sample sizes and additional variables which likely contribute to the heterogeneity of schizophrenia. Furthermore, this research takes into consideration all sub-types of Schizophrenia, under DSM-IV criteria. Therefore, further sub-classification of individual schizophrenia types should improve accuracy as well. This classification technique may also be used for prediction of other brain disorders as well as to determine the effectiveness of cognitive remediation as treatment on schizophrenic patients.

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