Accurate Classification of Schizophrenia Patients based on Novel Resting-State fMRI Features

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***Abstract*— There is a growing interest in automatic classification of mental disorders such as schizophrenia based on neuroimaging data. Most previous studies considered structural MRI, diffusion tensor imaging and task-based fMRI for this purpose. However, resting-state fMRI data has not been used much to evaluate discrimination of schizophrenia patients from healthy controls. Resting data are of great interest, since they are relatively easy to collect, and not confounded by behavioral performance on a task. In this study, we extract two types of features from resting-state fMRI data: functional network connectivity features that capture inter-network connectivity patterns and autoconnectivity features capturing temporal connectivity of each brain network. Autoconnectivity is a novel concept we have recently proposed. We used minimum redundancy maximum relevancy to select features. Classification results using support vector machine shows that combining these two types of features can improve the classification on a large resting fMRI dataset consisting of 195 patients with schizophrenia and 175 healthy controls. We achieved the accuracy of 85% which is very promising.**

I. Introduction

Population studies show that lifetime prevalence of all psychotic disorders is as high as 4% (http://www.nimh.nih.gov/statistics/SMI_AASR.shtml). These disorders can impair normal life significantly and impose huge societal cost [1]. Clinically, the patient's self-reported experiences and observed behavior over the longitudinal course of the illness constitute the basis for diagnosis. The overlapping symptoms of mental disorders and the absence of standard biologically-based clinical tests make differential diagnosis a challenging task. Early diagnosis of these diseases can significantly improve treatment response and reduce associated costs [2].

Advances in neuroimaging technologies in the past two decades have opened a new window into the structure and function of the healthy human brain as well as illuminating many brain disorders such as schizophrenia. Schizophrenia is among the most prevalent mental disorders affecting about 1% of the population worldwide [3]. This devastating, chronic heterogeneous disease is usually characterized by disintegration in perception of reality, cognitive problems and chronic course with lasting impairment [4]. Multiple structural and functional brain abnormalities are widely reported in patients with schizophrenia [5, 6].

Recently, there is a growing interest in designing prognostic/diagnostic tools based on neuroimaging and other data that display high accuracy and robustness [7]. The relatively small amount of research on MRI-based classification of schizophrenia patients can be divided into three categories based on the type of discriminating features used: structural-based[8-11], functional-based [12-14] or combination of structural and functional features [15].

In recent years, spontaneous modulation of blood oxygenation level-dependent (BOLD) signal during the resting condition has found fruitful clinical applications [16]. Resting-state fMRI (rfMRI) experiments are less prone to multi-site variability, allow a wider range of patients to be scanned and make it possible to study multiple cortical systems from one dataset [16].

Functional connectivity (FC) is defined as correlation (or other kinds of statistical dependency) among spatially remote brain regions. Using functional connectivity methods, researchers have shown disrupted functional integration in schizophrenia patients [17, 18]. There is growing interest in studying FC among brain functional networks. This type of connectivity, which can be considered as a higher level of FC, is termed functional network connectivity (FNC) [19] and measures the statistical dependencies among brain functional networks during rest and task [20, 21]. Each functional network may consist of multiple remote brain regions. FNC abnormalities in schizophrenia patients has been shown by several studies [22].

We used another novel feature which will be called "autoconnectivity" hereafter. Autoconnectivity captures the correlation of a time-series with its lagged version. If that time-series represents the temporal pattern of a brain network, then autoconnectivity is connectivity of that network with itself.

Extracting brain functional networks and their corresponding time-course is the first step to extract both types of proposed features. We used spatial independent component analysis (ICA) for this purpose. ICA, a multivariate data-driven method which as a blind source separation method, can recover a set of signals from their linear mixtures and has yielded fruitful results with fMRI data [23, 24]. ICA estimates maximally independent components using independence measures based on higher-order statistics. Compared to general linear model approaches, ICA requires no specific temporal model (task-based design matrix), making it ideal for analyzing resting

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state data [25]. Spatial components resulting from spatial ICA are maximally spatially independent but their corresponding time-courses can show a considerable amount of temporal dependency.

The purpose of this study is to design accurate classifier for schizophrenia patients using features from resting-state fMRI data. In our previous work [26], we showed that resting-state FNC features can be used to classify schizophrenia patients from healthy controls. In this study we use both FNC and autoconnectivity features and test in on much larger dataset compared to our previous works.

II. MATERIAL AND METHODS

A. Dataset

For this study we used data from a large imaging study including 195 patients with schizophrenia and 175 healthy volunteers were recruited that were matched for age, gender, handedness, and race distributions. All patients included in the study had been diagnosed with schizophrenia based on the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-I/P) (First, Spitzer, Gibbon, & Williams, 2002a). Imaging data for six of the seven sites was collected on a 3T Siemens TIM Trio System and on a 3T General Electric Discovery MR750 scanner at one site. Resting state fMRI scans were acquired using a standard gradient-echo echo planar imaging paradigm: FOV of 220×220 mm (64×64 matrix), TR = 2 sec, TE = 30 ms, FA = 77^0, 162 volumes, 32 sequential ascending axial slices of 4 mm thickness and 1 mm skip. Subjects had their eyes closed during the resting state scan.

B. Quality Control

We performed rigid body motion correction using the INRIAlign toolbox in SPM to correct for subject head motion. All subjects that had SFNR < 150 and a maximum root mean squared translation > 4 mm were excluded from further analysis. This excluded a total of 56 subjects, resulting in 314 subjects (163 HC and 151 SZ) for subsequent analysis. For the retained subjects, we performed slice-timing correction to account for timing differences in slice acquisition. Then the fMRI data were despiked using AFNI's 3dDespike algorithm to mitigate the impact of outliers. The fMRI data were subsequently warped to a Montreal Neurological Institute (MNI) template and resampled to 3 mm^3 isotropic voxels. Instead of Gaussian smoothing, we smoothed the data to 6 mm full width at half maximum (FWHM) using AFNI's BlurToFWHM algorithm which performs smoothing by a conservative finite difference approximation to the diffusion equation.

C. Group Independent Component Analysis:

All of the preprocessed functional data from both control and patient groups were analyzed using spatial group independent component analysis (GICA) framework as implemented in the GIFT software [27]. Spatial ICA decomposes the subject data into linear mixtures of spatially independent components that exhibit a unique time course profile. A subject-specific data reduction step was first used to reduce 162 time point data into 100 orthogonal directions of maximal variability using principal component analysis. Then subject reduced data were concatenated across time and a group data PCA step reduced this matrix further into 100 components along directions of maximal group variability. One hundred independent components were obtained from group ICA using the *infomax* algorithm. 47 intrinsic connectivity networks (ICNs) were selected for final processing using the procedures described in our earlier work [28]. The subject specific Time-courses (TCs) corresponding to the ICNs selected were detrended, orthogonalized with respect to estimated subject motion parameters, and then despiked.

D. Extracting Functional Network Connectivity Features

For each subject, we computed the functional network connectivity, referred to as FNC, by computing pairwise Pearson correlation using the processed ICA time-courses. We selected 47 ICNs, resulting in 1081 FNC features for each subjects.

E. Extracting Autoconnectivity Features

Autoregressive of model order one (AR1) were fit to each ICA time-series for each subject. Assuming x_t represents an ICA time-course. The purpose of AR1 modelling is finding α in the below equation:

$$x_t = \alpha x_{t-1} + w_t \quad (1)$$

Maximum likelihood was used to estimate the AR1 coefficient (α). This produced 47 autoconnectivity features for each subject.

F. Feature selection

In total we extracted 1128 features for each subject (47+1081). The high number of features compared to the subjects in our dataset can cause curse of dimensionality problem. To avoid this problem we used minimum redundancy maximum relevancy (MRMR) feature selection method. This methods tries to maximize the mutual information between the selected features and class labels while minimize the mutual information among the selected features.

G. Classification

Over the last 15 years following the work by Cortes et al. (Cortes and Vapnik, 1995), SVM has proven useful in many machine learning and pattern recognition analysis problems. Moreover, when data classes are heterogeneous with few training samples, SVMs appear to be especially beneficial (Melgani and Bruzzone, 2004). This binary classifier aims at finding a hyperplane that maximizes the margin between the two classes. SVM is able to fit non-linear classifiers by a incorporating a method called kernel trick. Non-linear SVM maps the data to a higher dimensional space where the data is linearly separable. The projection of that hyperplane in the original feature space is then non-linear. There are several kernel functions that can be used in non-linear SVM. In this study we used linear SVM along with non-linear SVM with radial basis function (RBF) and polynomial kernels.

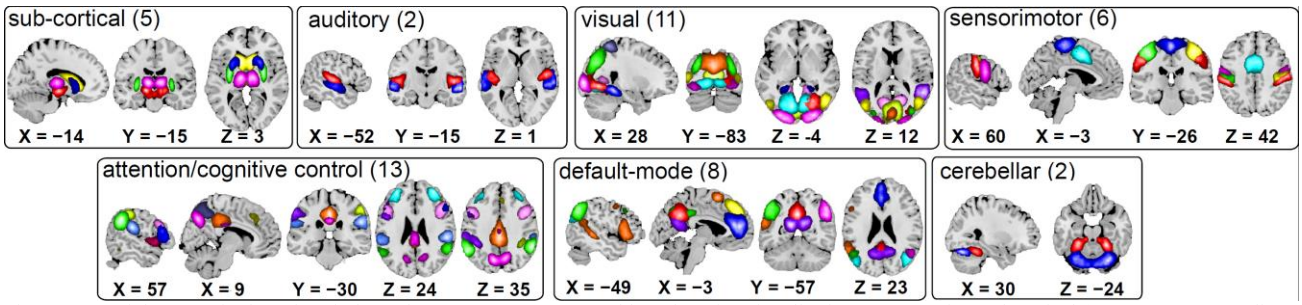

Figure 1. Spatial maps of selected 47 independent components grouped based on functionality into 7 categories: subcortical (5 components), auditory (2 components), visual (11 components), sensorimotor (6 components), attention/cognitive control (13 components), default-mode network (8 components) and cerebellar (2 components).

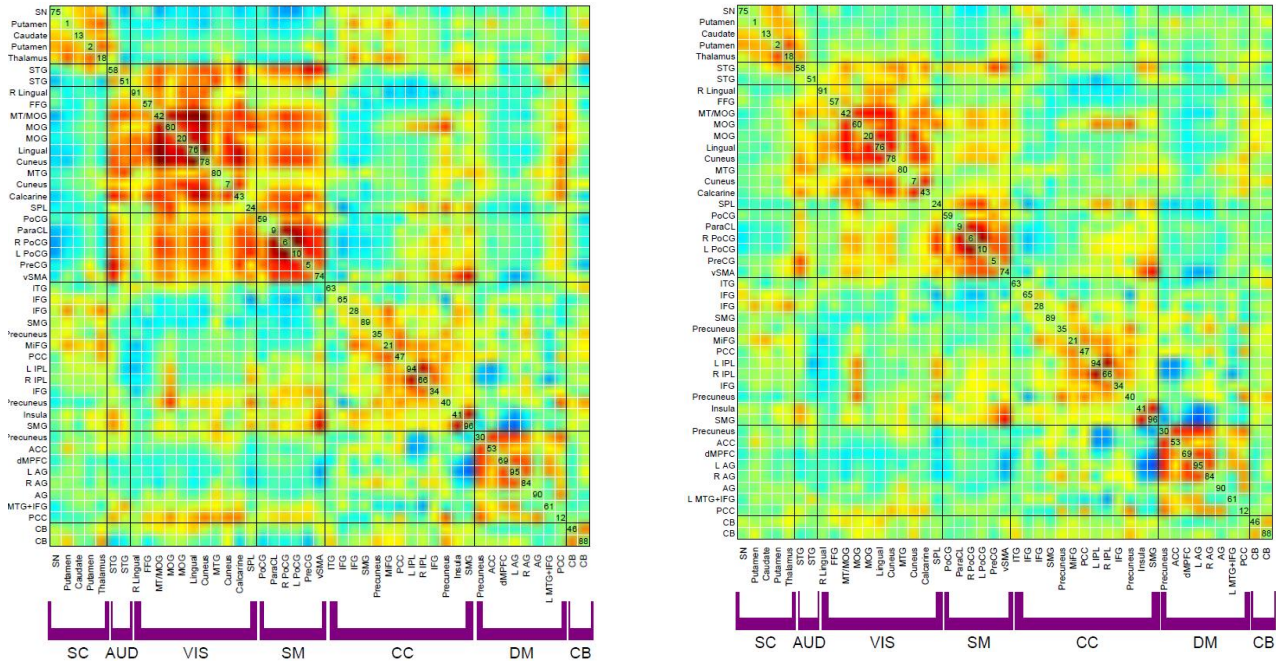

Figure 2. Mean of FNC grouped by functionality of brain networks for healthy controls (left) and schizophrenia patients (right)

H. Cross-validation

We used 10 fold cross validation to calculate the generalized error of the classifier. In each run 10 subjects were set aside for testing and the rest were used for training. A leave-one out method was used inside the training set to find the optimal value for SVM hyperparameters along with optimal number of features to be selected by MRMR feature selection approach.

III. RESULTS

Of these 100 ICA components, 47 components were identified as resting-state networks using the procedures described in our earlier work (Allen et al., 2012; Allen et al., 2011). ICA spatial maps were broadly categorized based on anatomical proximity and prior knowledge of their function into the following sub-categories: subcortical (SC), auditory (AUD), visual (VIS), somatomotor (SM), a heterogeneous set of regions involved in various attentional and cognitive control processes (CC), default-mode (DMN), and cerebellar (CB) networks. These resting-state networks are illustrated in Figure 1.

1081 FNC features and 47 autoconnectivity feature were extracted for each subject. The group average FNC features are illustrated in Figure 2. Autoconnectivity features are averaged for each functional group and are illustrated in figure 3. We performed classification first for FNC and autoconnectivity separately and then for their combination. Features were demeaned and normalized by the variance to make them comparable. Table 1 summarizes the results.

IV. DISCUSSION

In this study we proposed a classification approach for discriminating schizophrenia patients from healthy controls based on two types of resting-state features: functional network connectivity and autoconnectivity. Adding novel autoconnectivity features to FNC features improved the classification performance significantly. Our results show that using these features can result in a robust and accurate

classifier with about 88% overall accuracy which is very promising.

TABLE 1: Classification Results

Feature \ Accuracy	Overall Accuracy	Sensitivity	Specificity
FNC	83.7%	81.4%	85.9%
Autoconnectivty	80.2%	78.1%	82.2%
FNC +Autoc	**88.21%**	**86.7%**	**89.5%**

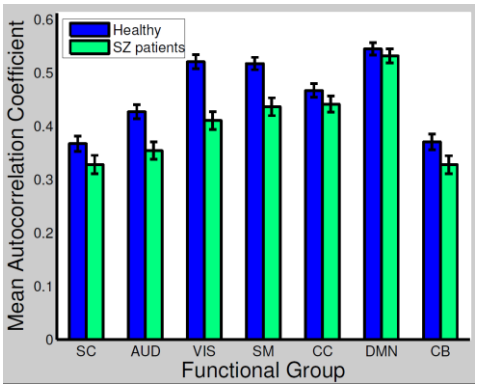

Figure 3. Average autoconnectivity Features for healthy controls and schizophrenic patients averaged for each brain functional group (Figure 1). Standard error values are illustrated for each bar. Note that number of autoconnectivity features are 47 but we are showing just the average for each functional group here.

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