Detecting Volumetric Changes in fMRI Connectivity Networks in Schizophrenia Patients

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***Abstract*— There is a growing interest in identifying neuroimaging-based biomarkers for schizophrenia. Previous studies have shown both functional and structural brain abnormalities in schizophrenia patients. One main category of these findings consists of volumetric abnormalities in brain structure in different cortical and subcortical structures in patients' brain. However there has been little work investigating changes in the brain's functional volumes. Nor has there been work studying differences in brain networks as opposed to single regions. In this study, we investigated the volumes of functional networks as potential biomarkers. Independent component analysis was used to decompose fMRI images into maximally independent spatial maps and corresponding time-courses. Volume of functional networks was computed from subject-specific back reconstructed spatial maps. The results show that different nodes of the default-mode network exhibit volumetric abnormalities in schizophrenia patients. Interestingly these networks are larger in patients compared to controls.**

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. Also, discovering biomarkers can help us better understand the effects of the disease in the brain which can result in more effective drugs.

The human brain has a well-identified structural and functional anatomy. Advances in neuroimaging technologies in the past two decades have provided insight into the structure and function of the healthy human brain as well as many brain disorders such as schizophrenia. Schizophrenia is among the most prevalent mental disorders affecting about 1% of the population worldwide [2]. This devastating, chronic heterogeneous disease is usually characterized by disintegration in perception of reality, cognitive problems and chronic course with lasting impairment [3]. Multiple structural and functional brain abnormalities are widely reported in patients with schizophrenia [4-6]. Volumetric structural abnormalities measured by magnetic resonance imaging (MRI) are the main category of these studies [7-13]. Neuroimaging studies using MRI have documented reductions in gray matter (GM) volume accompanied by proportionate increases in ventricular cerebrospinal fluid (CSF) volume. Also some studies showed volumetric abnormalities in subcortical structures such as thalamus and hippocampus [8, 14].

Using functional connectivity methods, researchers have shown disrupted functional integration in schizophrenia patients [15-19]. Functional connectivity (FC) is defined as correlation (or other kinds of statistical dependency) among spatially remote brain regions [20]. There are also few researches on the abnormalities of the shape of functional networks [21-23]. There has been little work looking at functional volumes in single brain regions but no previous work investigating volume of functional networks. Each functional network may consist of multiple remote brain regions working together for performing specific tasks. Most of previous works reported abnormalities in default-mode network (DMN) [24]. The default mode network consists of several brain regions including parts of medial prefrontal cortex, medial parietal cortex, lateral parietal cortex, lateral temporal cortex, precuneus cortex anterior/posterior cingulated cortex (ACC/PCC). The default-mode network is hypothesized to support higher mental faculties including understanding others' mental states, self-referential behavior, moral reasoning, recollection and imagining the future.

In this study we investigate the volume of functional networks as potential biomarker for schizophrenia. Our dataset consist of fMRI data from healthy controls and schizophrenia patients. Independent component analysis (ICA) will be used to decompose the dataset into independent spatial maps and corresponding time-courses. We hypothesize that schizophrenic patients suffer from volumetric abnormalities in functional networks. To investigate this idea we will compare volumes of several well-known functional networks between the two groups.

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II. PROCEDURE

Participants consisted of 67 healthy controls and 55 chronic schizophrenia outpatients all of whom gave written, informed, IRB approved consent at Hartford Hospital and were compensated for their participation. Schizophrenia or bipolar disorder was diagnosed according to the criteria in the DSM-IV on the basis of a structured clinical interview administered by a research nurse and review of the medical file. Exclusion criteria included any participants with auditory or visual impairment, mental retardation (full scale IQ < 70), traumatic brain injury with loss of consciousness greater than 15 min, presence or history of any neurological illness. Participants were also excluded if they met criteria for alcohol or drug dependence within the past 6 months or produced a positive (assessed by urine toxicology screen on the day of scanning).

Two runs of 244 stimuli were presented to the participant using a custom presentation package (http://nilab.psychiatry.ubc.ca/vapp/) and an MRI compatible sound system (Magnacoustics). The stimuli consisted of nontarget stimuli (1-kHz tones, 75% probability), target stimuli (1.5-kHz tones, 12.5% probability), and nonrepeating random digital noises (e.g., tone sweeps, whistles, 12.5% probability). The stimulus duration was 200 ms with a 1,800 ms interstimulus interval. Participants were instructed to respond as quickly and accurately as possible with their right index finger every time the target tone occurred and not to response to nontarget tones or novel stimuli.

The system diagram for functional data analysis is illustrated in Figure 1. Data were preprocessed using SPM5 software (http://fil.ion.ucl.ac.uk), motion corrected, spatially normalized into standard MNI space and slightly subsampled to voxel size $3 \times 3 \times 3$ mm^3, resulting in $53 \times 63 \times 46$ voxels. Next, spatial smoothing with a $10 \times 10 \times 10$ mm^3 FWHM Gaussian kernel was performed.

Functional dataset was analyzed using ICA. ICA is 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 [25]. 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). Depending on data matrix formation, one can perform either temporal or spatial ICA on fMRI data. Spatial ICA (sICA) is the predominant ICA approach used for fMRI data [26-28]. SICA decomposes fMRI data into a set of maximally spatially independent maps and their corresponding time-courses. Each thresholded sICA map may consist of several remote brain regions forming a brain functional network. Spatial ICA generates consistent spatial maps while modeling complex fMRI data collected during a task or in the resting-state although the task can result in a subtle modulation of the spatial patterns [23].

Prior to the ICA, data dimensionality was reduced at two levels using principal component analysis (PCA). First at the subject level, dimensionality was reduced to 80. Then reduced data from all subjects and all sessions were concatenated together and put through another reduction step. The number of components for the second level reduction was estimated to be 20 by minimum description length (MDL) criterion [29]. This is also the number of IC components. Note the MDL is a data driven approach, so it is not dependent on whether data are collected at rest or during a task.

Infomax group sICA [26] was conducted to decompose the aggregated data into components using GIFT software (http://icatb.sourceforge.net/). SICA applied to fMRI data identifies temporally-coherent networks (TCNs) by estimating maximally independent spatial sources, referred to as spatial maps (SMs) and their corresponding time courses (TCs). Control and patient data were analyzed in one group ICA instead of two separate ICAs so that a tighter comparison between rest and task could be performed without additional variability induced due to trying to match components from separate ICA analyses.

In order to estimate subject-specific SMs and TCs, a back-reconstruction approach based on PCA compression and projection was used [28]. Subject-specific TCs were reconstructed separately for rest and task. Spatial maps were reconstructed and converted to Z values for each of the subjects. All of the components were visually inspected and the non-artifactual components were selected.

III. RESULTS

From the 19 ICA components, 9 components were selected as non-artifactual, relevant networks. Figure 2 illustrates the spatial maps of the selected IC components. These networks are: auditory network (IC #13), frontal-parietal networks (IC #4 and 6), default-mode networks (IC #1, 10 and 17), visual networks (IC #11 and 15) and motor network (IC # 16). Volumes of these 9 networks were compared between the two group using two sample t-test. The false discovery rate p-value threshold of 0.05 was used to identify significant differences. Figure 3 illustrate the mean volume of different functional networks for both groups. Table 1 summarizes the significant differences. Interestingly all three significant functional networks are parts of DMN.

IV. DISCUSSION AND CONCLUSIONS

We investigated whether functional volumetric abnormalities exist in schizophrenia patients or not. Using group ICA, the functional dataset was decomposed into spatial maps and associated time-courses. Three functional networks show significant volumetric differences between the groups. All these networks include regions from DMN. Surprisingly, mean volumes of these three functional networks are larger in the patients.

It should be noted that functional data was collected during an auditory oddball task. Functional networks are cognitive-state dependent [23, 30] and the difference between patients and controls can be more or less in other cognitive-states or in the resting-state.

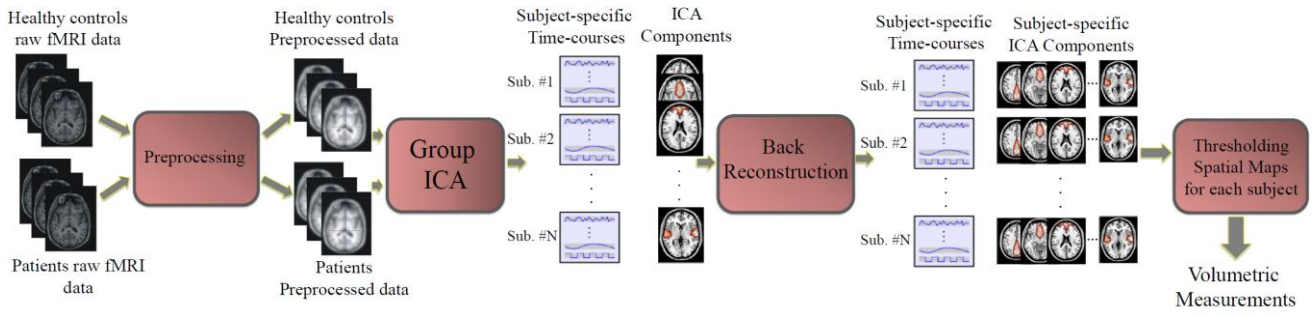

Figure 1: System diagram of functional data analysis

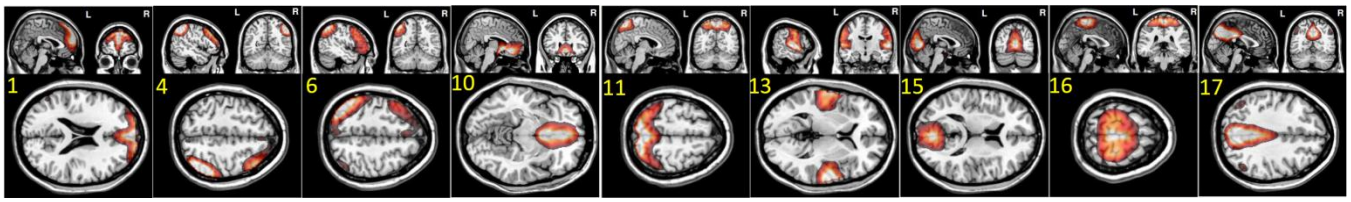

Figure 2. Nine selected independent components

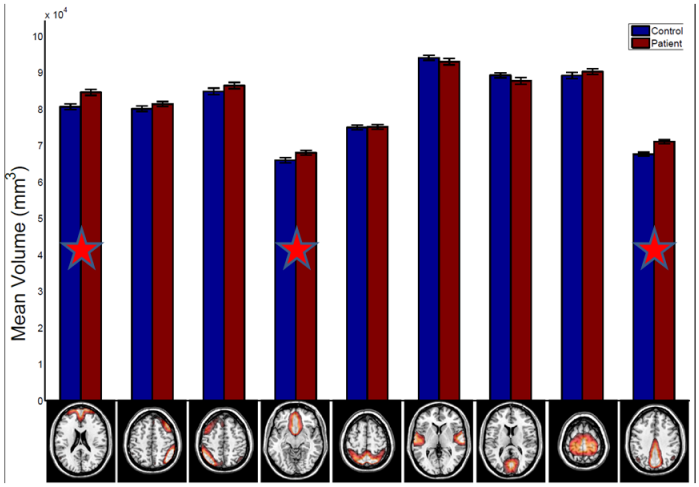

Figure 3. Mean volume of functional networks (in cc) for both groups. Black bars show the standard error of the mean. Red stars indicate networks that survived two-sample t-test between the two groups (FDR corrected p-value of 0.05).

Table 1. Significant functional volumetric differences between patients and controls

Functional Network	Volume (mm^3) mean±std Controls	Volume (mm^3) mean±std Patients	P-value
IC 17	67620.8±4194.48	71053.2±3836.86	**7.85E-06**
IC 1	80653.0±6542.44	84588.0±5946.35	**7.92E-04**
IC 10	65954.5±5632.33	68033.1±4798.30	**3.22E-02**

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