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Functional Network Connectivity during Rest and Task: Comparison of Healthy Controls and Schizophrenic Patients

Mohammad R. Arbabshirani, Vince D. Calhoun

Abstract*— Functional connectivity examines temporal statistical dependencies among distant brain regions by means of seed-based analysis or independent component analysis (ICA). Spatial ICA also makes it possible to investigate functional connectivity at the network level, termed functional network connectivity (FNC). The dynamics of each network (ICA component) which may consist of several remote regions is described by the ICA time-course of that network; hence FNC studies statistical dependencies among ICA time-courses. In this paper, we compare comprehensively FNC in the resting state and during performance of an auditory oddball task in 28 healthy subject and 28 schizophrenic patients on relevant (non-artifactual) brain networks. The results show abnormalities both in the resting state and during the task but also the difference of the two states. Moreover, our results suggest that using data both in the resting-state and during the task can better separate the two groups. It is demonstrated that for three pairs of networks, the FNC of the healthy controls resides within a confined region of the correlation space whereas patients behave more sparsely. This can be used to discriminate the two groups based on partitioning the correlation space during the resting state and the task data.

I. INTRODUCTION

Schizophrenia is among the most prevalent mental disorders affecting about 1% of the population worldwide. This devastating chronic disease is usually characterized by disintegration in perception or expression of reality. Schizophrenic patients usually experience a combination of auditory hallucinations, paranoid or bizarre delusions, poor or nonexistent social functioning or disorganized speech and thinking. Economically, schizophrenia imposes huge cost to the society. While early diagnosis of this disease can significantly improve the treatment and reduce the costs [1], no clinical test currently exists for schizophrenia. The patient's self-reported experiences and observed behavior over the longitudinal course is the basis for diagnosis which makes it a difficult task due to the overlap of symptoms with other mental disorders.

Advances in neuroimaging technologies in the past two decades have opened a new window into the structure and functionality of healthy human brain as well as many brain disorders such as schizophrenia. It has been shown that schizophrenia impairs multiple cognitive systems including memory, attention and executive function [2]. Structural and functional abnormalities have been widely reported in patients with schizophrenia [3, 4].

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M. R. Arbabshirani (marbabshirani@mrn.org, phone: 505-272-5028) and V. D. Calhoun (vcalhoun@mrn.org) are with Department of ECE, University of New Mexico, Albuquerque, NM 87131, USA and The Mind Research Network, Albuquerque, NM 87106, USA.

Using functional connectivity methods, researchers have shown disrupted functional integration in schizophrenic patients [5]. Functional connectivity (FC) is defined as correlation (or other kinds of statistical dependency) among spatially remote brain regions [6]. FC analysis documents interactions among brain regions during a task as well as during rest. Two widely used FC approaches are: (a) seed-based analysis [7-10] and (b) spatial independent component analysis (ICA) [11, 12]. In the seed-based approach, individual seed voxels from predefined brain regions of interest (ROI) are chosen and the cross correlation of other voxels' time courses with the selected seeds then computed, to derive a correlation map. This map can then be thresholded to identify voxels showing significant FC with the seed voxels.

An alternative approach is based on 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. ICA estimates maximally independent components using independence measures based on higher-order statistics. 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 [11, 12]. 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 [13] although the task can result in a subtle modulation of the spatial patterns [14]. The dynamics of the BOLD signal within a single component is described by that component's time course. Regions contributing significantly within a given component are strongly functionally connected to each other.

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) [15] and measures the statistical dependencies among brain functional networks. Each functional network may consist of multiple remote brain regions. Spatial components resulting from sICA are maximally spatially independent but their corresponding time-courses can show a considerable amount of temporal dependency. This property of sICA makes it an excellent choice for studying FNC, which can be studied by analyzing these weaker dependencies among sICA time courses. These dependencies can be analyzed by correlation methods [15] or algorithms such as Dynamic Causal Modeling or Granger causality.

Most of the FNC research has been focused on either resting-state or task data but not both. In this research we compare FNC in the resting-state and during auditory oddball task (AOD) between 28 healthy controls and 28 schizophrenic patients.

II. Material and Methods

One session of resting-state and one session of auditory oddball task fMRI data were collected from 28 healthy and 28 schizophrenic patients. Participants gave written, informed, IRB approved consent at Hartford Hospital and were compensated for their participation. Schizophrenia was diagnosed according to the DSM-IV TR criteria 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. Patients were slightly older than controls (SZ age = 39.7 ± 10.1; HC age = 31.2 ± 10.9). All but three patients and one control were right handed. Healthy participants were free of any DSM-IV TR Axis I disorder or psychotropic medication. All participants were scanned during both an auditory oddball task and at rest with eyes open while fixating on a cross hair. The auditory oddball task consists of detecting an infrequent target sound within a series of regular and different sounds. The task consisted of one runs of auditory stimuli presented to each participant by a computer stimulus presentation system (http://nilab.psychiatry.ubc.ca/vapp) via insert earphones embedded within 30-dB sound attenuating MR compatible headphones. The standard stimulus was a 500-Hz tone, the target stimulus was a 1,000-Hz tone, and the novel stimuli consisted of nonrepeating random digital noises (e.g., tone sweeps, whistles). The target and novel stimuli each occurred with a probability of 0.10; the standard stimuli occurred with a probability of 0.80.

Scans were acquired at the Olin Neuropsychiatry Research Center at the Institute of Living/Hartford Hospital on a Siemens Allegra 3T dedicated head scanner equipped with 40 mT/m gradients and a standard quadrature head coil. The transaxial functional scans were acquired using gradient-echo echo-planar-imaging with the following parameters (repeat time (TR) = 1.50 s, echo time (TE) = 27 ms, field of view = 24 cm, acquisition matrix = 64 × 64, flip angle = 70 °, voxel size = 3.75 × 3.75 × 4 mm^3, slice thickness = 4 mm, gap = 1 mm, 29 slices, ascending acquisition). The auditory oddball task consisted of a 8 min runs and the resting state scan consisted of a 5 min run.

The raw fMRI data were first preprocessed. Then prepossessed resting state and AOD data from both healthy control and patients groups were analyzed with on group ICA. Subject specific spatial maps and time-courses were computed for rest and AOD conditions using back reconstruction. Next, FNC analysis was performed on the subject specific ICA time-courses. Finally, we analyzed the output from the FNC analysis.

Prior to the ICA, dimensionality of data 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 [16]. 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 [11] 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).

As mentioned before, significant temporal correlation can exist among the sICA TCs. Prior to computing correlations, ICA TCs were filtered. There are reports that show task related and other interesting information resides in lower frequencies while noise and artifacts contributes mostly to the higher frequency contents of the TCs [17]. A bandpass Butterworth filter with cut of frequencies at 0.017 Hz and 0.15 Hz was applied to the ICA TCs. Then FNC was computed between each pair of networks (ICA components) by calculating correlation between the two IC time courses.

For all FNC analyses, correlations were transformed to z-scores using Fisher's transformation ($z = \text{arctanh}(r)$). Then, robustness of maximum lagged correlation between each pair of TCs was tested separately for rest and task using t-tests. Finally, to determine the significant differences of rest versus task, paired t-tests were conducted on the two groups. The cut-off p-value for all of the tests was set at $p<0.05$ and was corrected for multiple comparisons using the false discovery rate (FDR) method.

III. Results

Figure 1 shows spatial maps of the selected IC components. Correlation matrices in rest and task for healthy controls and patients along with the correlation differences (rest-aod) and two sample t-test during rest and task between the two groups are shown in Figure 2. In all of the figures, black circles indicate pairs that survived t-test with p-value threshold of 0.05 corrected for false discovery rate.

The correlation difference matrix in Figure 2C shows that in 9 pairs, the difference in correlation (rest-aod) is significant in the healthy groups whereas none of the pairs are significant in the patients group. Interestingly four of the significant pairs include the default mode network (DMN). Figure 2D indicates that there are differences between the two groups both during the resting state and during the AOD task. The pairs surviving the two sample t –test are 8 and 5 for rest and task respectively. Moreover, just two of the significant pairs are common in both states. Again, DMN is involved in 3 out of 5 significant pairs during the task. We also performed two sample t-tests on the correlation difference (rest-aod) between the two groups. Two pairs (#17 and #20) and (#18 and #19) survived the test. Along with the average correlation comparison, we also compared 3 pairs of networks for each subject (illustrated in Figure 3). The first pair includes left and right fronto-parietal networks. These networks are highly lateralized and show strong positive connectivity both during rest and task. Figure 3A demonstrates that for healthy controls the FNC during rest and task is limited in range to a small region of the correlation space. The demonstrated region includes 23 controls and just 4 patients. This pattern repeats for the other pair of networks consists of the frontal and the visual networks. Again the range is limited mostly to negative values for both during rest and task for healthy controls but patients tend to behave more sparsely and 24 of them reside out of the specified region. This is shown in Figure 3B. FNC between the two visual networks in illustrated in Figure 3C. 24 of the healthy controls have positive FNC value for both the resting state and during the AOD task compared to just 12 patients following this rule.

IV. Discussion and conclusions

In this paper we studied the FNC during resting state and during AOD task between the healthy controls and schizophrenic patients. The results show several interesting abnormalities in the patients group. First of all, the differences between the two groups during rest and task were shown. It is interesting that more pairs in the resting state are significantly different between the two groups compared to the AOD task. This suggests using resting state data for classification purposes. Another interesting point is the FNC differences between rest and task. Figure 2c shows that the difference is not significant for none of the pairs of networks in the patient group whereas 9 pairs survived the t-test in the controls group. It can be inferred that schizophrenic patients not only behave abnormally in resting-state and during the task, the FNC differences between to two states are also abnormal. In other words, schizophrenic brains behave more similarly to the resting-state when performing the AOD task. The behavior of the DMN and the left fronto-parietal network are particularly abnormal in the patient groups.

We also demonstrated that the FNC values are much more variable in the patients group compared to the healthy controls. As shown in Figure 3, FNC values are confined to a particular region of the correlation space while patients tend to behave more sparsely. This also suggests that using both the resting state and the task data can improve the separability of the two groups. The FNC between the visual network and the frontal network is negative for both the resting state and during the task for most of the healthy controls, whereas, most of the patients show positive FNC in one or both of the states.

It can be concluded that using both the resting state and the task data reveals new information about the functionality of the brain especially for the schizophrenic patients. Also we predict better classification rate when using both rest and task data.

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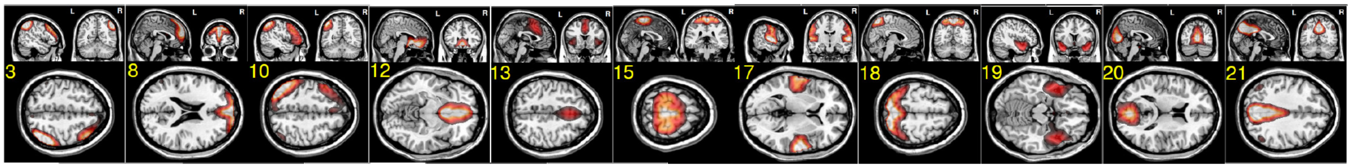

Figure 1. Spatial maps of selected ICA components

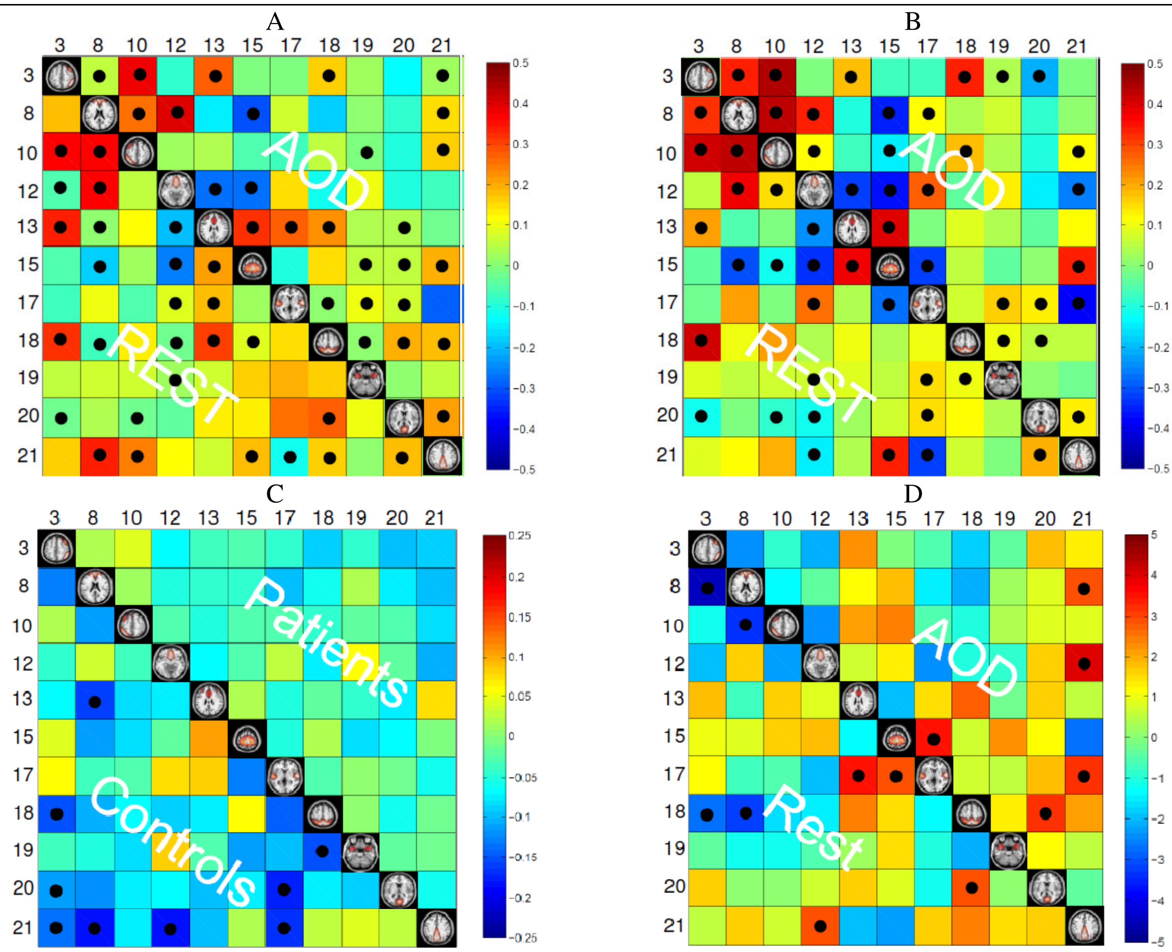

Figure 2. A)FNC in rest and task in healthy controls B) FNC in rest and task in patients C) FNC difference (rest-aod) in controls and patients D) Two sample t-test between the two groups during rest and during the task. Black circles show the pairs surviving the t-test with 0.05 p-value threshold corrected for FDR.

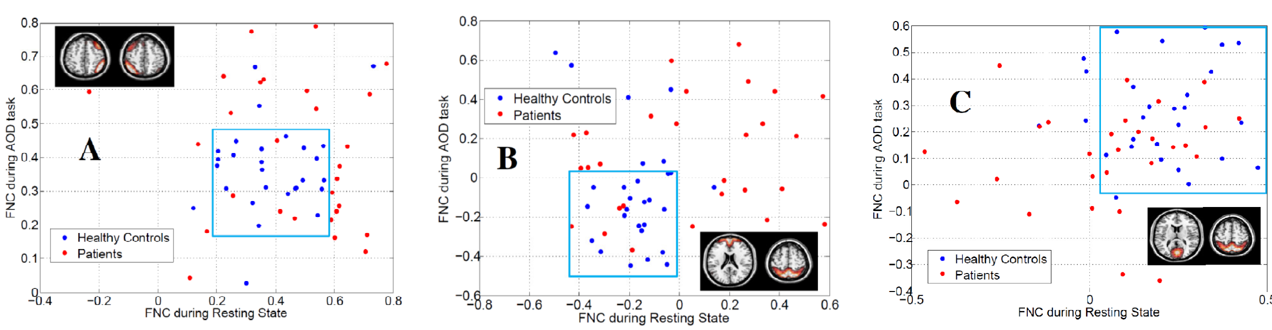

Figure 3. FNC for three pairs of networks during rest (horizontal axis) versus during task (vertical axis) for all the subjects. Most of the healthy subjects (blue circles) reside in a confined region of the FNC space (light blue square) whereas patients (red circles) behave more sparsely out of the shown region.