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Investigation of relationships between fMRI brain networks in the spectral domain using ICA and Granger causality reveals distinct differences between schizophrenia patients and healthy controls

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ABSTRACT

Functional network connectivity (FNC) is an approach that examines the relationships between brain networks (as opposed to functional connectivity (FC) that focuses upon the relationships between single voxels). FNC may help explain the complex relationships between distributed cerebral sites in the brain and possibly provide new understanding of neurological and psychiatric disorders such as schizophrenia. In this paper, we use independent component analysis (ICA) to extract the time courses of spatially independent components and then use these in Granger causality test (GCT) to investigate causal relationships between brain activation networks. We present results using both simulations and fMRI data of 155 subjects obtained during two different tasks. Unlike previous research, causal relationships are presented over different portions of the frequency spectrum in order to differentiate high and low-frequency effects and not merged in a scalar. The results obtained using Sternberg item recognition paradigm (SIRP) and auditory oddball (AOD) tasks showed FNC differentiations between schizophrenia and control groups, and explained how the two groups differed during these tasks. During the SIRP task, secondary visual and cerebellum activation networks served as hubs and included most complex relationships between the activated regions. Secondary visual and temporal lobe activations replaced these components during the AOD task.

Introduction

Functional connectivity (FC) investigates relationships using the functional MRI (fMRI) activation patterns among individual voxels or regions (Biswal et al., 1995). A recent extension of FC called functional network connectivity (FNC) is a powerful way of characterizing distributed changes in the brain by examining the functional interactions among different correlated brain networks, usually identified using independent component analysis (ICA) (Jafri et al., 2008; Londei et al., 2006).

In order to quantify the strength of interactions between brain regions and to reveal directed interactions of activated brain areas, Goebel et al. (2003) proposed using the Granger causality test (GCT) on fMRI measurements of a selected region of interest. They employed a measure of linear influence between two time series presented by Geweke (1982). In addition to a simulation example, they also used the averaged time-course of voxels in a specified reference region in a Granger causality test with other time courses obtained from each single voxel in the functional volume of the brain. Three parameters (ratios of the variance of noise in the autoregressive (AR) and autoregressive moving average (ARMA) models) presented by Geweke (1982) were evaluated for each reference region chosen. The results revealed a directed influence exerted by the left lateral prefrontal cortex and premotor areas on the left posterior parietal cortex.

Van De Ven et al. (2004) proposed applying spatial ICA to decompose fMRI time series data into maximally independent signals and to find functionally connected brain regions within sensory and motor regions in the resting state fMRI data. They indicated that selecting seed voxels and correlating fMRI time courses of these with those of all other voxels is biased because the results only showed functional connectivity for that chosen brain region. The results

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showed that prefrontal and parietal areas were functionally connected during resting state and results were consistent in spatial, temporal and frequency parameters among subjects.

Londei et al. (2006) carried out a similar analysis to Goebel et al. (2003) except the Granger causality test was applied to the time-courses associated with ICA components (or networks). Three different parameters, first presented by Geweke (1982), were used to explain the causal relationships between ICA components based on the reduction of noise in an autoregressive model (Londei et al., 2006).

The results demonstrated the method as a promising approach to detect cognitive and causal relationships in neuroimaging data. It is proposed that spatial and temporal activities of fMRI data could be used first to extract components most correlated with the stimuli, which represented the independent functional activities. Then, GCT could be used to understand the dynamics of higher-order processes that are usually difficult to detect and analyze causal relationships of brain activity networks. The empirical demonstration included in the study was useful in terms of explaining the application of GCT on the ICA components but there was no spectral information present.

Spectral analysis of the FC with both task-activation functional MRI and resting state data were investigated by Cordes et al. (2001) using cross-correlation maps obtained from time courses of voxels. Contributions of low-frequency components and physiological noise were examined. Since only low sampling rates were used during regular fMRI image acquisitions, they applied multi-slice acquisitions with a faster sampling rate (TR = 0.4 s instead of TR = 2 s) to prevent aliasing and to better be able to observe the effect of physiological noise in the spectrum. It has been found that low-frequency fluctuations (<0.1 Hz) constituted more than 90% of the correlation coefficient spectrum. Physiological (respiratory, 0.1 Hz to 0.5 Hz and cardiac, 0.6 Hz to 1.2 Hz) noise contributed only 10% of the functional connectivity maps. We believe that investigation the spectral behavior of FNC can also be useful in understanding the complex interactions in the brain and their impact on the neurological disorders. Our approach in this paper is novel in the sense that the GCT approach we use enables us to determine causal information as a function of frequency. Hence we can identify which frequencies are driving the identified relationships between the time courses.

A particularly useful application of FNC would be to examine abnormal relationships among brain networks in psychiatric patients to better understand the neurobiological basis of the disorders. Schizophrenia is a chronic mental illness whose symptoms are thought to have a strong neurobiological basis. Functional segregation (i.e. the brain is an ensemble of functionally segregated areas) and functional integration (i.e. functionally specialized areas are integrated and psychological function are caused by distributed interactions) are two main views on brain functioning and they both find support today with the recent developments in functional neuroimaging (Friston, 1994). Localized pathophysiology of cortical areas in the brain might be sufficient to explain some aspects of schizophrenia, but does not appear sufficient to fully account for all possible symptoms, clinical course, or treatment considerations, which instead may be more related to the (dys)function of distributed networks (Friston and Frith, 1995). Indeed, one hypothesis is that schizophrenia is related to disruption of proper functional integration within key neural circuits in the brain (Friston and Frith, 1995; Friston, 1998).

Based on popular 'disconnection' theories in schizophrenia (Friston and Frith, 1995; Friston, 1998; Benes, 2000), we broadly hypothesized that patients with schizophrenia would show disrupted patterns of causal influence among networks. Previous functional neuroimaging literature has identified specific abnormalities in lateral and medial prefrontal cortex regions, along with evidence for disturbance in the integration of activity across a number of brain regions that include auditory cortex (Fletcher et al., 1999; Friston, 1999).

We previously examined FNC differences between schizophrenic and healthy adult control participants (Jafri et al., 2008) using the lag between time courses of independent components obtained via ICA. This approach defined the temporal relationships among ICA component time courses as a measure of functional network connectivity and applied it on the data for patients with schizophrenia and healthy controls. Using fMRI data obtained during an alert, passive "resting state", it was found that patients with schizophrenia showed higher correlation than healthy controls.

In this study, we present a novel approach to analyze the causal relationships between functional brain networks without being dependent on any brain region to analyze the difference between patients with schizophrenia and healthy controls. There are several key differences between previous work and what we are proposing in this paper. First is the examination of FNC during two active tasks instead of passive rest. Our methodological approach also differs in that after application of ICA to decompose the fMRI data into maximally independent spatial components and corresponding time courses, the time courses are used as input to Granger causality test and spectral responses are presented for different directions, as described in the seminal paper (Granger, 1969). We are presenting the same equations in the Granger causality test in spectral domain section for the sake of completeness and the background information on signal processing and statistics can be obtained from various sources (Oppenheim et al., 1996; Stark and Woods, 2001). The causal relationships between functional networks are presented as a spectrum and not just as a scalar to differentiate the low/high-frequency responses and to investigate the differing behavior in various frequency bands.

In the Data and methods section, we give detailed information on the data we used and the methods followed. Then, we present example simulations to demonstrate the validity of the technique and results that we obtained using fMRI data of a neurological task in the Results and discussion section. Next, we apply to two tasks collected from 155 patients with schizophrenia and healthy controls. In this case, we can identify the best distinguishing causal relationships between the groups by applying a two-sample presents the concluding remarks and discusses the applicability of the technique.

Data and methods

Data

We obtained the fMRI data used in this study through the Mind Research Network, which is a research consortium founded to help diagnose mental illnesses and other brain disorders, and to understand the course and neural mechanisms of schizophrenia. The data whose results were presented here were 155 subjects; 57 schizophrenia patients and 98 healthy controls, from two different sites (New Mexico and Iowa).

The data from the New Mexico site included 70 subjects; 34 patients with schizophrenia and 36 healthy controls. Patients with schizophrenia were receiving stable treatment with atypical antipsychotic medications (aripiprazole(7), olanzapine(2), risperidone (1), ziprasidone(1), clozapine(1)). Twenty eight subjects in each class were males. There were no significant between-group differences in age. The healthy controls ranged in age from 18 to 54 years (mean = 28.9, SD = 12.3). The patients ranged in age from 18 to 60 years (mean = 31.4, SD = 11.6).

The data from the Iowa site included 85 subjects: 23 patients with schizophrenia and 62 healthy controls. Patients with schizophrenia were receiving stable treatment with atypical antipsychotic medications (aripiprazole(13), olanzapine(7), risperidone(12), ziprasidone (4), clozapine(1), quetiapine(5)). 32 of the healthy controls and 10 of the patients were males. Healthy participants ranged in age from 18 to 57 years (mean = 30.2, SD = 10.6). Patients ranged in age from 18 to 60 years (mean = 32.4, SD = 12.3). In the second data set, there was no significant difference in the average ages of the two groups.