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Nodal centrality of functional network in the differentiation of schizophrenia

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ABSTRACT

A disturbance in the integration of information during mental processing has been implicated in schizophrenia, possibly due to faulty communication within and between brain regions. Graph theoretic measures allow quantification of functional brain networks. Functional networks are derived from correlations between time courses of brain regions. Group differences between SZ and control groups have been reported for functional network properties, but the potential of such measures to classify individual cases has been little explored. We tested whether the network measure of betweenness centrality could classify persons with schizophrenia and normal controls. Functional networks were constructed for 19 schizophrenic patients and 29 non-psychiatric controls based on resting state functional MRI scans. The betweenness centrality of each node, or fraction of shortest-paths that pass through it, was calculated in order to characterize the centrality of the different regions. The nodes with high betweenness centrality agreed well with hub nodes reported in previous studies of structural and functional networks. Using a linear support vector machine algorithm, the schizophrenia group was differentiated from non-psychiatric controls using the ten nodes with the highest betweenness centrality. The classification accuracy was around 80%, and stable against connectivity thresholding. Better performance was achieved when using the ranks as feature space as opposed to the actual values of betweenness centrality. Overall, our findings suggest that changes in functional hubs are associated with schizophrenia, reflecting a variation of the underlying functional network and neuronal communications. In addition, a specific network property, betweenness centrality, can classify persons with SZ with a high level of accuracy.

1. Introduction

Schizophrenia (SZ) is a severe psychiatric brain disorder that affects about 1% of the population (Harrison, 1999; Insel, 2010; Ripke et al., 2013; Tandon et al., 2008). Symptoms of SZ suggest brain disturbances which affect many systems, and include hallucinations, delusions, disorganized thinking, loss of motivation, cognitive impairment and blunted emotional expression. While the etiology of schizophrenia remains poorly understood, it has been hypothesized that pathological connectivity among brain regions results in the loss of the functional integration and neural plasticity required for adaptive behavior (Andreasen et al., 1996; Friston, 1998; Stephan et al., 2006).

In the last decade, the disconnectivity hypothesis of SZ has been examined using MRI measures of functional connectivity. The majority of these studies focused on the "default mode" network (DMN) (Raichle et al., 2001; Raichle and Snyder, 2007), and found abnormalities in schizophrenia in various aspects including altered amplitude, temporal frequency, and spatial extent/location. (Garrity et al., 2007; Ongür et al., 2010; Pomarol-Clotet et al., 2008; Zhou et al., 2008a). For instance, from resting-state fMRI data, DMN spatial extent was found to be significantly greater in the dorsal anterior cingulate cortex (Ongür et al., 2010). In an auditory oddball task, aberrant "default mode" functional connectivity was reported in the frontal, anterior cingulate, and parahippocampal gyri (Garrity et al., 2007). Besides DMN, investigation of other networks also revealed altered functional connectivity between brain regions (Liang et al., 2006; Zhou et al., 2008a, 2008b). For instance, decreased functional connectivity among insula, prefrontal lobe and temporal lobe was observed along with increased connectivity from many cerebral cortical regions toward cerebellum (Liang et al., 2006).

The introduction of graph theoretical approaches applied to the brain has allowed quantitative analysis of local and global network properties derived from functional and structural brain imaging (Bullmore and Sporns, 2009; Lynall et al., 2010; Sporns, 2010; Supekar et al., 2008; van den Heuvel et al., 2013). This approach therefore is well suited for characterizing possible network alterations in schizophrenia. Methodologically, functional connectivity matrices (also referred to as a functional network) are usually derived from resting state fMRI data. In those, the strength of functional connections is

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usually characterized by the correlation of time courses between brain regions (Biswal et al., 1995). Brain network analyses have revealed a disruption of the functional and structural network structure in schizophrenia (Liu et al., 2008; Rubinov and Bullmore, 2013) including decreased clustering and small-worldness, and reduced presence of high-degree hubs. In addition, local differences of reduced degree and clustering were found in medial parietal, premotor and cingulate, and right orbitofrontal cortical nodes (Lynall et al., 2010). In another study applying independent component analysis (ICA) on resting state fMRI data, significantly lower clustering coefficient and lower small-world connectivity were also found for the network of independent components in schizophrenia patients (Anderson and Cohen, 2013). Abnormal rich club organization was also found for schizophrenia, which is potentially associated with altered functional brain dynamics.

Functional connectivity has usually been compared between groups of patients and control subjects (Lynall et al., 2010; Pettersson-Yeo et al., 2011). It is unclear whether network alterations have sufficient sensitivity and specificity to SZ to allow classification of individual subjects as affected or not. Supervised machine learning techniques may permit a much better degree of classification accuracy than convention statistical approaches, such as discriminant analysis. Previous studies have reported the potential of combining network features and machine learning for classification. For instance, a support vector machine classifier was able to differentiate older adults from younger adults based on resting state functional connectivity (Meier et al., 2012). In another study using a small set of edges showing high discriminative power, an unsupervised-learning classifier was also successful in discriminating schizophrenic patients from healthy controls with a high accuracy (Shen et al., 2010). Using a similar feature extraction approach, multiclass pattern analysis on functional connectivity also discriminated schizophrenic patients and their healthy siblings with a modest accuracy rate (Yu et al., 2013). In another study classifying schizophrenia patients based on functional network connectivity, the correlations between various ICA components were computed to be used as features and worked well for several linear and non-linear classification methods that are commonly used (Arbabshirani et al., 2013). Despite good classification performance in these previous works, the feature selection for classification was usually based on the strength of functional connectivity rather than network characteristics. There is only one study to our knowledge using network measures of clustering coefficient and small-worldness to classify schizophrenia (Anderson and Cohen, 2013), which yielded a classification accuracy of 65%.

Accuracy may be affected by the types of network measures utilized, and the criteria for quantifying connections. Functional connectivity networks have both positive and negative values as a result of pairwise correlations of time-series. The interpretation of negative connections is not yet completely understood, despite efforts to jointly analyze negative and positive connections (Deco et al., 2014; Goñi et al., 2014; Rubinov and Sporns, 2011). While thresholding the network is a plausible approach, it has been noted that most network metrics are very sensitive to doing so (Rubinov and Sporns, 2010). For instance, nodal degree or total degree decreases when a high percentage of connections are dropped. The clustering coefficient, small-worldness, global efficiency also changes accordingly. For this reason, we tested nodal betweenness centrality of the resting state functional networks, which turned out to be relatively unaffected by thresholding to compare the schizophrenic subjects (SZ) and non-psychiatric controls (NC).

Betweenness centrality (BC) is a network centrality measure that quantifies the influence of a node in connecting other nodes in a network (Freeman, 1977). It represents the fraction of all shortest paths in the network that pass through a given node (Rubinov and Sporns, 2010). The nodes with the highest BC are usually known as highly central or hubs (Buckner et al., 2009) (although other definitions of centrality exist). Previous studies have reported a reduction of betweenness centrality for frontal hubs in structural networks of schizophrenia patients (van den Heuvel et al., 2010). Because abnormal topological organizations of structural and functional brain networks have been reported for schizophrenia (van den Heuvel et al., 2013; Zhang et al., 2012), we hypothesized that there is a change of the nodal betweenness centrality in the magnitude and order (rank) that could be strongly associated with SZ and hence a key feature for our machine learning approach. Furthermore, the differences in BC are likely to be more substantial for the hubs (Rubinov and Bullmore, 2013). In order to better assess these changes, a collective analysis of an extensive set of nodes is desirable.

Based on this rationale, we employed a linear support vector machine (SVM) algorithm using nodal betweenness centrality as the feature space. The aim of this study was to test whether SVM could differentiate schizophrenia based on prior information of BC for a set of SZ and NC subjects. SVM is an unsupervised machine learning algorithm that has been widely used in classification and regression analysis. It has been successfully applied in neuroscience for multi-voxel pattern analysis and differentiating different brain states (Cox and Savoy, 2003). By selecting highly discriminative feature set from all functional connectivity between 116 brain regions, SVM was able to discriminate schizophrenia from non-psychiatric controls with a high accuracy (Shen et al., 2010).

The purpose of this study was to classify SZ from non-psychiatric controls by applying support vector machine to betweenness centrality measures of the functional network. We also compared the performance of using different features derived from betweenness centrality. Because of large variability of functional connectivity (Wang et al., 2011), we expect that the rank of BC for a subset of nodes might be the best choice to distinguish schizophrenia from normal subjects.

2. Methods

2.1. Subjects

27 SZs (8 female, mean age 36.7 ± 9.9 years) and 36 NCs (7 male, mean age 29.3 ± 6.5 years) were recruited and completed the study protocol. The subjects were provided verbal written informed consent. The study was approved by Institutional Review Board of Indiana University. Eight SZ subjects and 7 NC subjects were excluded from this study due to excessive head motion. Subjects used in the classification analysis included 19 SZs (6 female, 33.1 ± 10.9 years) and 29 NCs (15 female, mean age 28.1 ± 8.4 years). Diagnosis of schizophrenia was based on the Structured Clinical Interview for the DSM-IV Axis I Disorders (SCID-I) (First et al., 2002) and medical chart review. The SCID-I for non-psychiatric controls was used to determine that there was no history of Axis I disorders in the NCs. Current drug or alcohol abuse or dependence or a loss of consciousness lasting more than 5 min were exclusionary criteria for all participants. All subjects passed a urine screening for illicit substances at the time of the scan.

2.2. MRI data acquisition

Subjects were scanned on a Siemens TIM Trio 3 T MRI scanner using a 32-channel head coil. The high resolution (1 mm^3) anatomical scan was performed in the sagittal plane with an MP-RAGE sequence with the following parameters: matrix = 256 × 256, FOV = 256 × 256 mm, TE/TR = 2.67/1800 ms, TI = 900 ms. A total of 200 volumes of resting state fMRI data were acquired with EPI sequences for 8 min and 20 s with the following parameters: TR/TE = 2500/30 ms, FOV = 220 mm, 128 × 128 matrix, oblique plane with slice thickness = 3.6 mm, number of slices = 36, iPAT factor = 2. During the resting state fMRI scan, the subjects were at rest with eyes closed and instructed not to think of anything in particular.

2.3. Head motion characterization

All functional data were motion corrected in FSL (http://fsl.fmrib.ox.ac.uk/). We computed the mean relative translational motion