Discovery of Aberrant Brain Connectivity in Schizophrenia using Gaussian Graphical Models

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Abstract

Schizophrenia (SZ) has long been considered as a disorder of brain connectivity. With the development of functional Magnetic Resonance Imaging (fMRI) technology and graph theory, we can further explore the brain connectivity. We constructed voxel-based networks which can give more and precise information about the connectivity within each brain region. However, it is still a challenge to construct and interpret the networks due to the high dimensions of data. In this paper, we adopted a novel high-dimensional Gaussian Graphical Model (GGM) -- ψ-learning method, which can help solve the computational burden while can keep at least the same accuracy. Using real fMRI data from SZ study with 92 SZ patients (case) and 116 healthy people (control), the ψ-learning method reveals sets of distinct aberrant interaction hubs for the schizophrenia patients, which are verified to be both statistically and biologically significant.

Introduction

Schizophrenia (SZ) is a chronic and severe mental disorder that affects how a person thinks, feels, and behaves. In the past it was believed that this disorder is related to disrupted brain connectivity. The development of functional Magnetic Resonance Imaging (fMRI) technology helps the hypothesis to be verified and allows further exploration of brain connectivity. By incorporating the graph theory into connectivity analysis, we gain a new understanding of the characteristics of human brain, from a micro-scale connectivity between single neurons to a macro-scale connectivity between regions of interests (ROIs) or voxels in brain images. Region-based networks fail to illustrate the connectivity within the ROIs and can't give more precise location information. Voxel-based networks can overcome the shortfalls, but remains a challenge to be constructed efficiently and accurately due to computational burden and the small sample size. In this paper, we adopted a novel high-dimensional Gaussian Graphical Model (GGM)-- ψ-learning method, which can solve these issues by providing more accurate inference for underlying graphs with less CPU cost. The computational complexity is only $O(p^2)$ for $p > n$, whereas other methods have usually higher than $O(p^3)$, where p represents the variable size and n is the sample size .

Methods

Gaussian graphical model (GGM) is a popular method to study association networks for a large number of variables. The key idea is to use partial correlation coefficient as a measure of dependency. Since the construction of brain network is a high dimensional low sample size problem, traditional GGM is not working. Thus we adopted the ψ-learning method, which works based on an equivalent measure of the partial correlation calculated with reduced conditional sets. The definition of the ψ-correlation is given by

$$\psi_{ij} = \rho_{ij|S_{ij}}$$

where S_{ij} represents the reduced conditional set of nodes X_i, X_j, called the separator set. Here we use a correlation screening with a threshold parameter α_1 to choose the separator sets S_{ij}'s and apply a so-called ψ-screening with a threshold parameter α_2 to control the density of the constructed network.
It has proven that the ψ-partial correlation coefficient is equivalent to the true partial correlation coefficient in the sense that

$$\psi_{ij} = 0 \Leftrightarrow \rho_{ij|V\backslash ij} = 0$$

if $\rho_{ij|V\backslash ij} \neq 0$ then $corr(X_i, X_j) \neq 0$ is guaranteed. This method is also proved to be consistent under mild conditions, i.e. the network will converge to the true one as the sample size goes to infinity.

Materials

We applied the method to fMRI data collected by The Mind Clinical Imaging Consortium (MCIC). The data were from 208 subjects, among them 92 schizophrenia patients (age: 34 ± 11, 22 females) and 116 healthy controls (age: 32 ± 11, 44 females). They were collected during a sensor motor task, a block design motor response to auditory stimulation. We followed the same pre-processing procedures as outlined in [4] that 116 ROIs were extracted based on the AAL brain atlas and 41236 voxels were left for analysis. To reduce data dimension, we further implemented a multiple t-test between case and control groups on the voxel level and got $p = 9816$ voxels in 111 ROIs left for analysis.

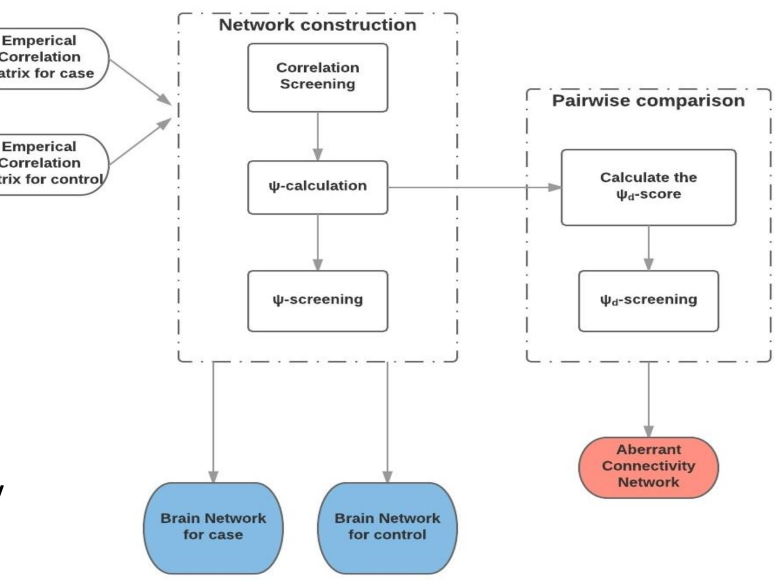

Fig.1. The flowchart for the study procedure

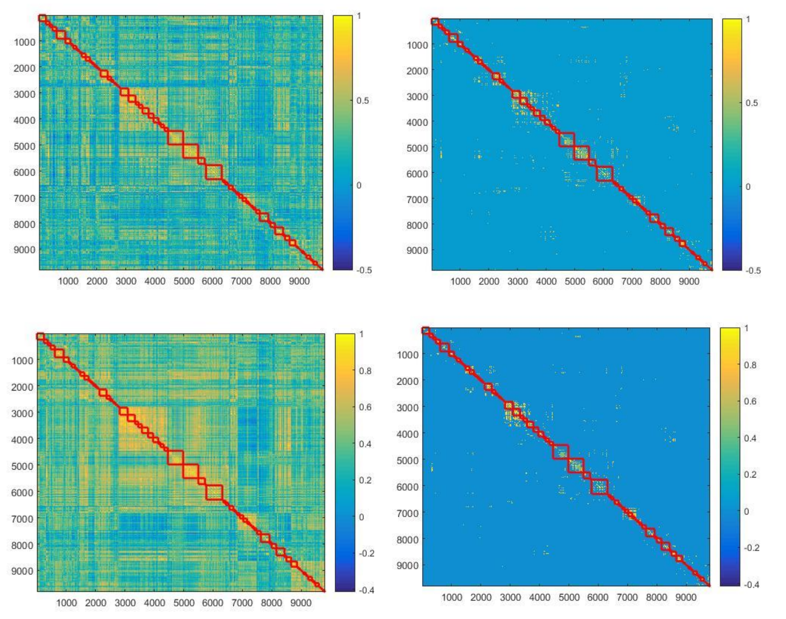

Fig.2. Visualizations of correlation matrices before (left) and after (right) correlation screening with the significance level $\alpha_1 = 0.1$ the case (top) and healthy controls (bottom) separately.

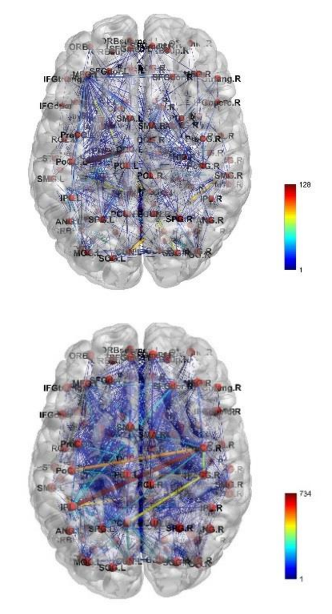

Fig.3. Axial view of the brain connectivity's on ROI level for case (top) and control (bottom).

Table 1. Basic measures of the networks

Measures	Case group	Control group
Mean clustering coefficient	0.0800	0.4886
transitivity	0.0073	0.0029
Global efficiency	0.0374	0.4568
Characteristic path length	0.00015	0.0012

Results

The whole process is shown in Fig.1. We set $\alpha_1 = 0.1$ and $\alpha_2 = 0.01$ through the recommendation of Liang [1] and got 7353 edges in the case group and 57388 edges in the control group. The screening effect is shown in Fig.2. Table 1 gives some basic measures of the networks. As we can see, the mean clustering coefficient of the case is far larger than that of the control, which shows, on average, it is more clustered around individual nodes in the case group. Both the global efficiency and characteristic path length of the case group are smaller than that of the control group. This may suggest the functional integration of the SZ brain is not as good as that of healthy individuals, which means the SZ patients may not be able to rapidly combine specialized information from distributed brain regions compared to healthy people.
The visualizations of the brain connectivity for each group have been shown in Fig.3. We that found the most reduced connectivity centers appear in the left inferior temporal gyrus (T3G), right precentral gyrus (FAD), right inferior temporal gyrus (T3D), left anterior cingulate gyrus (CIAG), left lingual gyrus (LINNG) and right anterior cingulate gyrus (CIAD). We also observed several newly generated hub centers in right inferior temporal gyrus (T3D), right precentral gyrus (FAD) and right caudate nucleus (NCD). The most abnormal connectivity between ROIs, the region T3G and FAD appear multiple times, with the most serious differences including FAD, PAD and T3G. Furthermore, we also discovered that the abnormal connectivity is not happening region-wide, instead there exist sub-areas in each ROI where the changes occur (see Fig.4.).

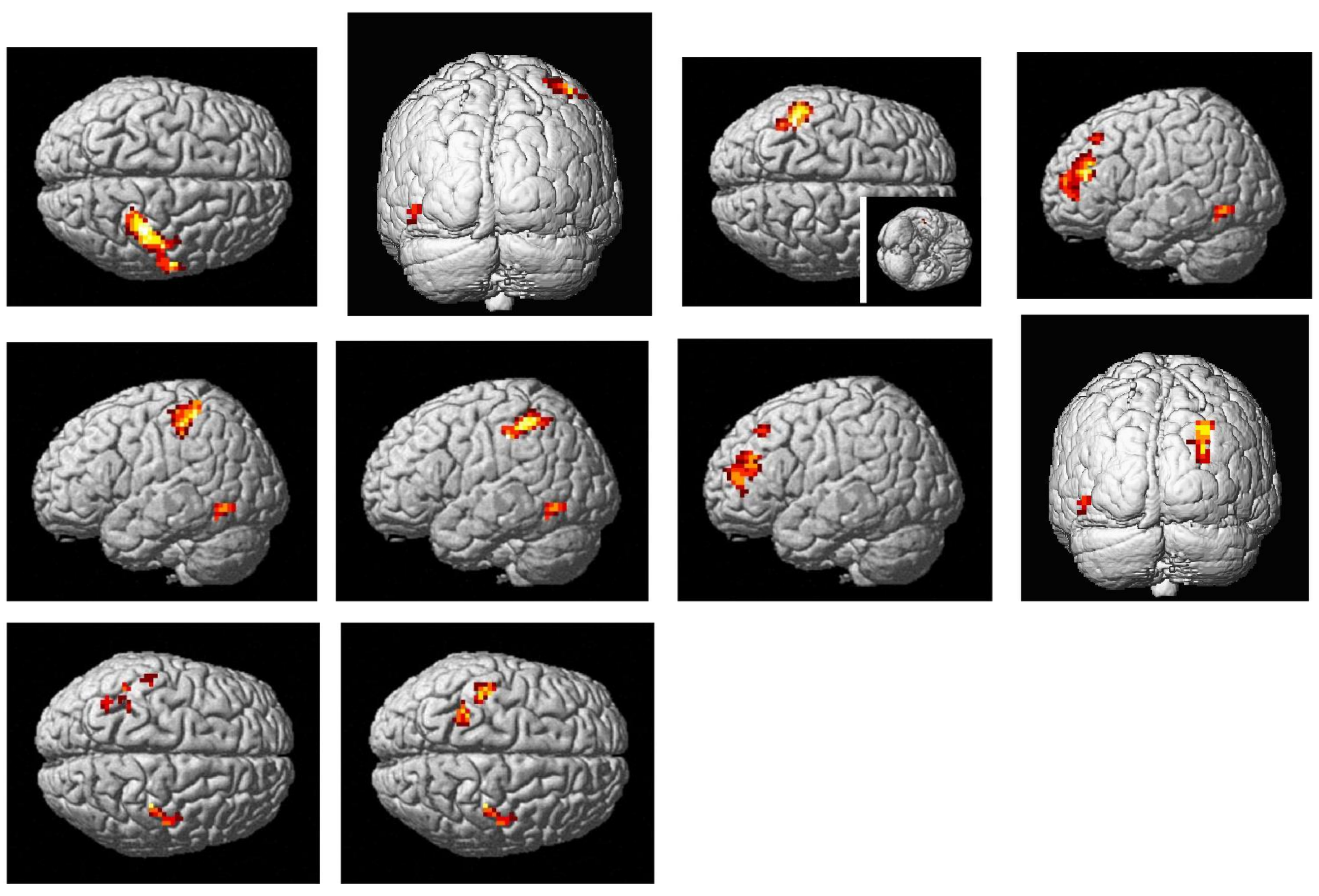

Fig.4. The affected sub-areas of identified aberrant ROI-ROI connectivity

Conclusions

- During the auditory stimulation task, schizophrenia patients exhibited significantly reduced brain connectivity.
- The network measurements showed that SZ patient's brain network pattern is less clustered and its functional integration ability is not as extensive as healthy people.
- From our results, right precentral gyrus (FAD) and right inferior temporal gyrus (T3D) are the two brain regions that are most affected by the disease. Thus, the sub-aberrant areas we have displayed may be worth further study.
- The computational speed of ψ-learning method outperforms other algorithms. On a 2.8 GHz computer, -learning takes 2hrs 15mins, while gLasso takes more than 7 days.

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