Causal brain network in schizophrenia by a two-step Bayesian network analysis

Aiying Zhang[1], Gemeng Zhang[1], Vince D. Calhoun[2], Yu-Ping Wang[1]
[1] Department of Biomedical Engineering, Tulane University
[2] Tri-institutional Center for Translational Research in Neuroimaging and Data Science (TReNDS) Georgia State University, Georgia Institute of Technology, Emory University, Atlanta, GA 30030

Abstract

- Functional connectivity (FC) has become a primary way of understanding brain functions. Popular methods for FC analysis always apply statistical association among brain regions, which is a good starting point for estimating brain network interactions. With in-depth study, the causal interactions in brain need to be revealed.
- In this work, we study the causal networks to understand the mechanisms underlying Schizophrenia (SZ). We analyze the fMRI images of healthy and SZ subjects from the Mind Clinical Imaging Consortium (MCIC) and design a two-step Bayesian network analysis for this case-control study.
- We reveal that compared to healthy people, SZ patients have a diminished ability to combine specialized information from distributed brain regions.

Introduction

- Schizophrenia (SZ) is a chronic mental disorder characterized by hallucinations, derealization, delusions, loss of initiative, and cognitive dysfunction, which has long been believed to be associated with dysfunctional brain connectivity.
- Current association analysis methods to estimate the functional brain networks include Pearson's correlation, partial correlation analysis, independent component analysis (ICA).
- Approaches that characterize statistical associations are likely a good starting point for estimating brain network interactions. However, it could be problematic since the associations only provide spatial connections but rather causal interactions.
- It is natural to shift the focus to causal interactions, which can pinpoint the key connectivity characteristics and remove some redundant features for diagnosis.
- Directed acyclic graph (DAG) models, also known as Bayesian networks, are designed to model causal relationships in complex systems.
- Classic methods for DAG identification can be divided into three categories: constraint-based, score-based and hybrids of these two methods.
  - Constraint-based methods: the PC algorithm
  - Score-based methods: the greedy equivalence search (GES) algorithm
- Existing methods have focused on estimating a single directed graphical model. However, in many biomedical applications such as the SZ study, we have data from multiple classes.
- Therefore, we propose a two-step Bayesian network analysis to fit the case-control study, which considers both the similarity and the difference between the two groups.

Methods

In this paper, we propose a two-step framework to estimate multiple graphs that are distinct but related.

Step 1. Greedy equivalence search (GES) for the union graph

- GES is a score-based method, which posits a scoring criterion for each possible circumstance, then searches for the graph with the highest score given the observations.
- The score criterion: the Bayesian Information Criterion (BIC)

$$BIC = -2ln(ML) + kln(n)$$

ML: the maximum likelihood estimate,
k: the dimension of the model,
n: the sample size.

- Assumption: the case and control groups share a common graphical structure, but the strength of the connections may vary.
- Implementation:
  - Apply the GES to each group separately,
  - Use the union of the directed graphs $\hat{G}_{union}$ as the common structure

Step 2. Lasso regression for the exact causal influence

- Goal: estimate the directed graphs $\hat{G}_{case}$ and $\hat{G}_{control}$ by searching over the subset of $\hat{G}_{union}$.
- Implementation:

For each node j in $\hat{G}_k$, $k = case\ or\ control$, we estimate its parents by regressing X_j^k on $X^k_{pa_j(\hat{G}_{union})}$using LASSO penalty, then the weighted adjacency matrix $B_k = \left(\beta_j^k\right)_{j=1,2,\ldots,n}$ for each group can be estimated through

$$\hat{\beta}_j^k = \underset{supp\left(\beta_j^k\right)\subset pa_j(\hat{G}_{union})}{\operatorname{argmin}} \frac{1}{n_k}\left||X_j^k - X^k\beta_j^k|\right| + \lambda^2\left||\beta_j^k|\right|_1$$

X_j^k: the observation in the k-th group for the j-th node (variable),
$pa_j(\hat{G}_{union})$: the parents of j in $\hat{G}_{union}$,
n_k: the sample size for the k-th group.

Materials

The fMRI data description:

- Source: the Mind Clinical Imaging Consortium (MCIC)
- Number of subjects: 183
  - 79 SZ patients (age: 34 ± 11, 22 females)
  - 104 healthy controls (age: 32 ± 11, 44 females)
- Design: sensory motor task, a block design motor response to auditory stimulation

The fMRI preprocessing steps:

- Standard steps using SPM 12
  - Motion correction,
  - Spatial normalization to standard MNI space (adult template),
  - Spatial smoothing with an 3mm FWHM Gaussian kernel.
- Multiple regression step:
  - Considering the influence of motion was performed
  - The stimulus on-off contrast maps for each subject were collected.
- 264 region of interests (ROIs) were extracted
  - Power parcellation method
  - The signal of all voxels with a sphere radius parameter of 5 mm of each node is averaged.

Schizophrenia Study

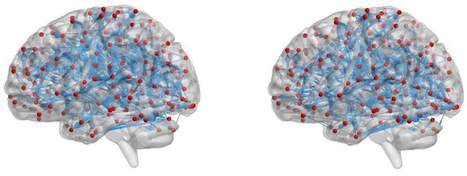
Data Implementation: through R packages

- GES: ***pcalg***
- LASSO regression: ***glmnet***

Parameter setting: $\lambda = 0.25$

Results:

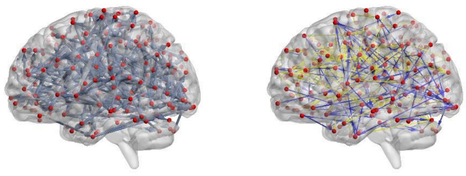
- Causal networks



(a) SZ patients (b) Health Controls

Figure 1. The sagittal views of the brain connectivity patterns for the case (a) and the control (b) groups. The arrows represent the directions of the connectivity.

- Network comparison



(a) Shared connectivity (b) Different connectivity

Figure 2. The shared and different brain connections between the case and control groups. The arrows represent the directions of the connectivity. In (b), the purple edges are the disappearing connections of SZ patients, while the yellow edges represent the unique patterns of SZ.

- Network statistics:

Table 1. Global network measures for the case and control groups

	Density	MCC	Transitivity	GE
SZ patients	0.0073	0.0657	0.0716	0.162
Healthy control	0.0074	0.0758	0.0924	0.168

MCC: mean clustering coefficient; GE: global efficiency

- Hub ROIs:

Table 2. The identified hub ROIs from different connectivity patterns

Index	MNI Space	Anatomical location	Functional Networks
55	(-45 ,0, 9)	Rolandic operculum, left	Cingulo-opercular task control
73	(-30,-27,12)	Insula, left	Auditory
138	(-10, 11, 67)	Supplementary motor area, left	Ventral attention
177	(-53, -49, 43)	Inferior parietal gyrus, left	Fronto-parietal Task Control
178	(-23, 11, 64)	Middle frontal gyrus, left	Fronto-parietal Task Control
227	(-22, 7, -5)	Putamen, left	Subcortical

Conclusions

Network statistics

- The MCC and the transitivity show significant differences between the case's and control's.
- The ability of combining specialized information from distributed brain regions for SZ patients may be reduced.

Hub ROIs

- Six ROIs were identified from the different connectivity network.
- Anatomically: they are located at the left hemisphere of the brain, which indicate asymmetric abnormality.
- Functionally: they are closely related to auditory processing and task control, which give a reasonable explanation for the poor performance of the SZ patients during the auditory motor task.

Acknowledge

The work is partially funded by NIH (R01GM109068, R01MH104680, R01MH107354), and NSF (#1539067).

Contact

Aiying Zhang
Tulane University
Email: azhang4@tulane.edu
Phone:(352)281-9166
Wechat:

Major References

1. R.L., Gollub, et al. "The MCIC collection: a shared repository of multi-modal, multi-site brain image data from a clinical investigation of schizophrenia." Neuroinformatics, vol. 11, pp. 367–388 (2013).
2. A. T. Reid, et al., "Advancing functional connectivity research from association to causation," Nature neuroscience, vol. 1(10), 2019.
3. D. M., Chickering. "Optimal structure identification with greedy search". Journal of machine learning research, vol. 3, pp. 507-554 (2002).
4. M. Rubinov and O. Sporns, "Complex network measures of brain connectivity: uses and interpretations," Neuroimage, vol. 52, pp. 1059–1069 (2010).
5. J. Power, D. Fair, B. Schlaggar, and S. Petersen, "The development of human functional brain networks," Neuron, vol. 67, pp. 735–748 (2010).