Causal Functional Brain Network: An Advanced Approach to Study Brain Cognitive Variance

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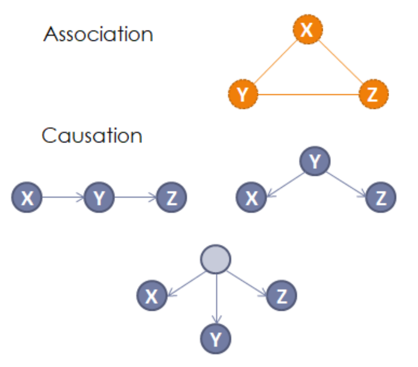
Abstract

Functional connectivity (FC) has become a primary way of understanding brain function. Popular methods of FC always apply statistical association among brain regions, which could be problematic since the associations only provide spatial connections but not causal interactions. It is necessary to switch from association to causation in FC studies. Directed acyclic graph (DAG) models have been applied in some recent FC studies. However, one often encounters problems of limited sample sizes or large scale of variables, i.e. high-dimensional situations. For this reason, it is challenging to estimate DAGs in biomedical applications due to the computational difficulty and convergence issue. To this end, we propose the ψ-learning incorporated linear non-Gaussian acyclic model (ψ-LiNGAM). Our goal is to use the proposed method to analyze the causal functional connectivity of subjects in various cognitive ability groups using resting state fMRI and further to understand the cause of the cognitive variance.

Introduction

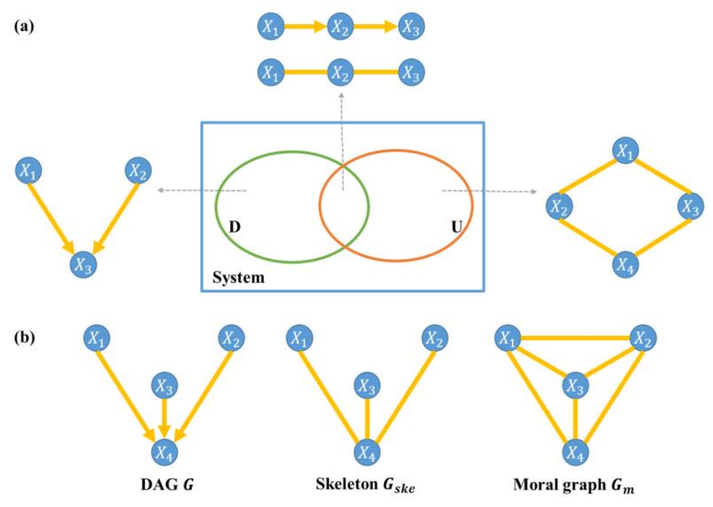
- From association to causation

- Statistical associations can be problematic to reveal the true logical relationships.
- Causal studies pinpoint the key connectivity characteristics and remove redundant features for diagnosis.



- Directed acyclic graph (DAG)

- Directed and undirected graphs: Each expresses a different independence property in a system.
- Notation: A graph G = (V,E)
V = {1, 2, ..., p}, the node set
E ⊂ V ×V, the edge set
Skeleton G_{ske}: a DAG G without the directions
Moral graph G_m: the undirected graph converted from a DAG G



Method: ψ-LiNGAM

- Linear non-Gaussian acyclic model (LiNGAM)

The observed random vector $X = (X_1, \dots, X_p) \in R_p$

$$X = B^T X + \epsilon$$

B: weight matrix that can be permuted to be strictly lower triangular

ϵ: continuous r. v.,

Independent, non-Gaussian, zero means and non-zero variances

- Ψ-LiNGAM

- Idea: incorporate the undirected graph into LiNGAM for DAG estimation
- Principle: $G_{ske} \subset G_{und}$
- Procedure:
1. Undirected graph estimations as prior using the ψ-learning method
2. Apply LiNGAM with the prior for DAG estimation
- Code: https://github.com/Aiying0512/psi-LiNGAM
- Advantages:
1. Integrate the undirected graph into the DAG model to facilitate casual inferences, and thus have faster convergence and computation speeds.
2. Capable for high-dimensional cases.

Materials

- Dataset: Philadelphia Neurodevelopmental Cohort (PNC)
- fMRI image

Resting state fMRI → Standard preprocessing through SPM[12] → 264 ROIs, 124 time slices

Preprocessing steps:
- Motion correction
- Co-registration
- Normalization
- Slice time correction
- Spatial smoothing
- Bandpass filtering: 0.01-0.1Hz

- Cognitive groups

Total subjects: 855, Age range: 8-22 → 1-hour computerized neurocognitive battery (CNB) test → Wide range achievement test (WRAT) score → Age>18, |z| > 0.5:
- z > 0.5 → High WRAT Group: 63 subjects
- z < -0.5 → Low WRAT Group: 130 subjects

Group	Mean WRAT (SD)	Age Range	Sex Ratio
High	116.36 (9.81)	18-21.75	27:36
Low	91.26 (9.74)	18-22.58	52:78

Simulation studies

- Settings:

- Simulated the random DAG G through the R package *pcalg*
- Average edge per node d =1,4
- Noise distribution: exponential
- Sample size (subject): n = 500
- Variable size (node): p = (50, 100, 200)

- Consider 5 estimation methods

- PC, GES, ICA-LiNGAM, Direct LiNGAM, ψ-LiNGAM

- Results:

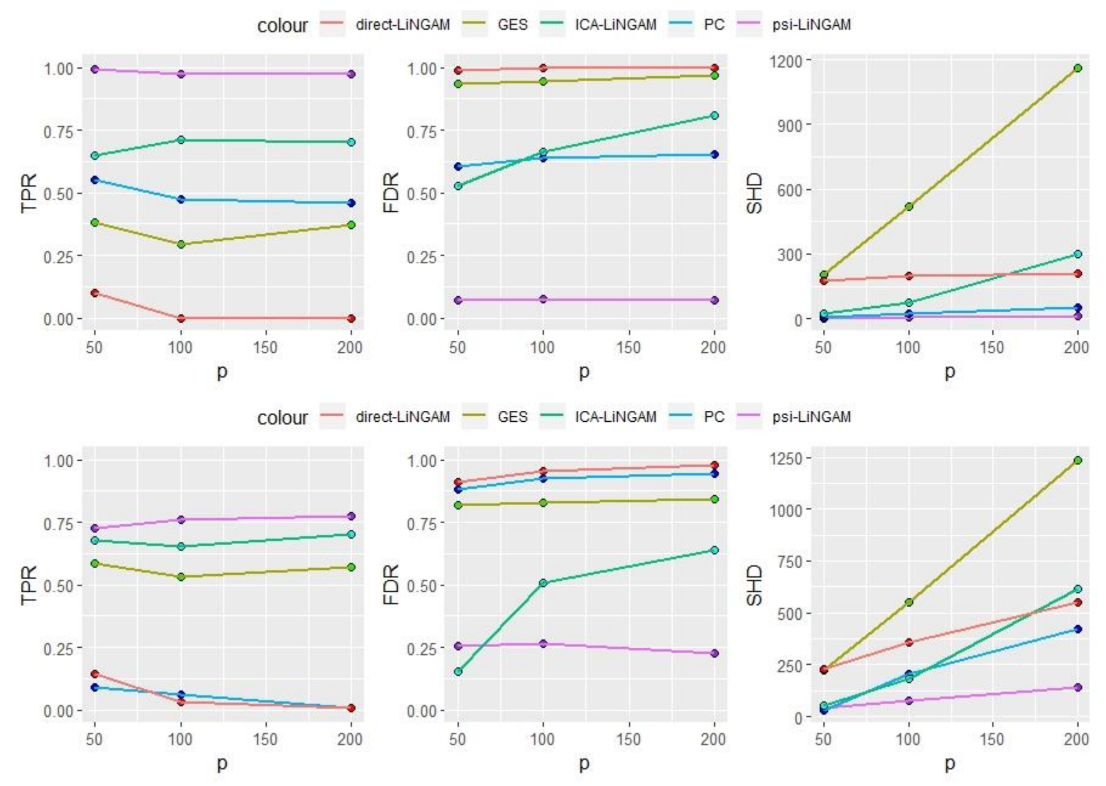


Fig 1: Simulation results with the exponential noise setting, which represent the average performance in terms of TPR, FDR and SHD under various variable (p = 50, 100, 200) and average degree (d = 1, 4) with n = 500.

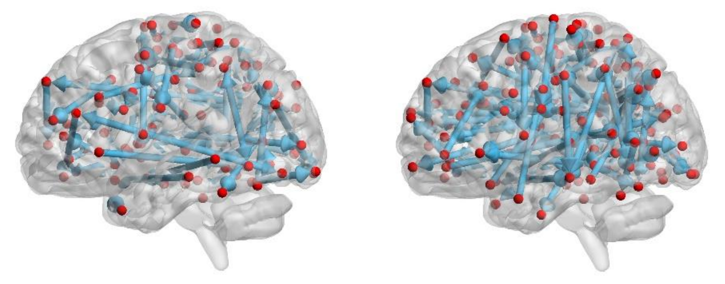
Results

- Network summary

- Group Measures

Table I: Network statistics

Group	Density	Transitivity	Global Efficiency
High	0.119	0.0033	0.0121
Low	0.233	0.0032	0.0118



(a) high WRAT (b) low WRAT

Fig. 2: Directed brain connectivity for each group, where the arrows indicate the causal flow.

- Different connectivity network

Criteria: two sample t-test ($\alpha = 0.05$)

Cohen's d effect size statistics

TABLE II. The number of edges that are significantly different for various Cohen's d thresholds.

$\lvert d \rvert >$	0.5	0.4	0.3	0.2
# of edges	2	16	141	1113

- Classification: SVM

- 8 various inputs
- 5-fold cross validation, repeat 20 times
- Results:

TABLE III: The mean accuracies by SVM with various inputs.

Input	Pearson	Partial	PC	ψ-LiNGAM
ACC	62.62%	60.77%	65.25%	67.31%
Input	$\lvert d \rvert > 0.5$	$\lvert d \rvert > 0.4$	$\lvert d \rvert > 0.3$	$\lvert d \rvert > 0.2$
ACC	70.87%	79.63%	82.37%	84.87%

Pearson correlation	|d|> 0.2
Partial correlation	|d|> 0.3
PC DAG	|d|> 0.4
Ψ-LiNGAM DAG	|d|> 0.5

The right columns are the feature selected from the previous step.

1. Generally the DAG methods (PC, ψ-LiNGAM) are better than the association methods.
2. When |d| > 0.4, the mean accuracy has increased dramatically,
3. The 16 features captured the major differences between the high and low WRAT groups.

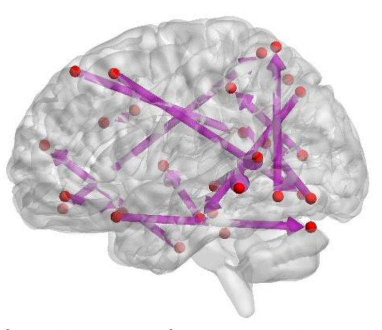


Fig. 3: The 16 causal connections selected by Cohen's d statistics with threshold $|d| > 0.4$, where the arrows indicate the causal flow.

- Intra- and inter- module connectivity

- 12 functional network modules

SSN: sensory/somatomotor network
CON: cingulo-opercular task control network
AUD: auditory network
DMN: default mode network
MRN: memory retrieval network
VN: visual network
FPN: fronto parietal task control network
SN: salience network
SCN: subcortical network
VAN: ventral attention network
DAN: dorsal attention network
CERE: cerebellum network

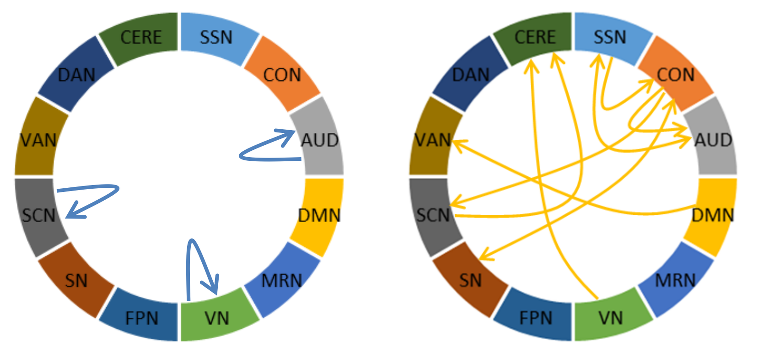


Fig.4: Identified intra- (left) and inter- (right) module causal flows.

Conclusions

- In this paper, we propose a ψ-learning incorporated linear non-Gaussian Acyclic model (ψ-LiNGAM) to study the casual interactions in human brain.
- Assumption: non-Gaussianity of the data, which we believe can help to identify the direction of the edge.
- Contribution:
1. Integrate the undirected graph as prior information into the DAG model to facilitate casual inferences.
2. Gain faster convergence and computation speeds.
3. The proposed method is stable with different settings and shows improved performance compared with 4 other methods.
4. The application to rs-fMRI data from PNC has successfully explained the cognitive variance through the directed FC.

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