Detecting abnormal connectivity in schizophrenia via a joint directed acyclic graph estimation model

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Abstract

Functional connectivity (FC) between brain region has been widely studied and linked with cognition and behavior of an individual. FC is usually defined as the correlation or partial correlation of fMRI blood oxygen level-dependent (BOLD) signals between two brain regions. Although FC has been effective to understand brain organization, it cannot reveal the direction of interactions. Many directed acyclic graph (DAG) based methods have been applied to study the directed interactions but their performance was limited by the small sample size while high dimensionality of the available data. By enforcing group regularization and utilizing samples from

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Supplementary material

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both case and control groups, we propose a joint DAG model to estimate the directed FC. We first demonstrate that the proposed model is efficient and accurate through a series of simulation studies. We then apply it to the case-control study of schizophrenia (SZ) with data collected from the MIND Clinical Imaging Consortium (MCIC). We have successfully identified decreased functional integration, disrupted hub structures and characteristic edges (CtEs) in SZ patients. Those findings have been confirmed by previous studies with some identified to be potential markers for SZ patients. A comparison of the results between the directed FC and undirected FC showed substantial differences in the selected features. In addition, we used the identified features based on directed FC for the classification of SZ patients and achieved better accuracy than using undirected FC or raw features, demonstrating the advantage of using directed FC for brain network analysis.

**Keywords**

Functional imaging; Brain; fMRI analysis; Connectivity analysis; Probabilistic and statistical methods

1. **Introduction**

Over the past decades, research on brain functional connectivity (FC) has been widely conducted in the field of brain imaging (Jafri et al., 2008). Specifically, studies using functional MRI (fMRI) have shown that there are significant connectivity changes in mental disorder patients compared to a normal cohort (Calhoun et al., 2009; Cerliani et al., 2015). As a serious mental illness, schizophrenia has been conceived as a psychiatric disorder with FC changes in large-scale brain networks (Lynall et al., 2010). Previous meta-analytic reviews of MRI studies on schizophrenia also suggest underlying abnormalities in gray matter density (Ellison-Wright et al., 2008; Glahn et al., 2008), as well as in the interregional FCs derived from fMRI time series (Liang et al., 2006; Ma et al., 2019; Salvador et al., 2010).

As a popular tool for assessing functional organization of brain and an important biomarker for neurological disorders, functional connectivity (FC) is often defined as the Pearson correlation to reflect the association between different regions of interest (ROIs). Although follow-up studies used either partial correlation to remove the indirect correlation between brain regions (Marrelec et al., 2006; Ryali et al., 2012), they still cannot truly determine the direction of interactions between ROIs. A precise understanding of this directed information flow is necessary to better understand brain functional integration. The Bayesian network based probabilistic graphical model has been used for this purpose, which represents a set of variables and their conditional dependencies via a directed acyclic graph (DAG). Several directed FC estimation methods have been independently proposed to characterize the mental disorders in terms of the DAG. For example, the greedy equivalent search (GES) method (Chickering, 2002; Meek, 1997), as an efficient estimate of the DAG, has been applied to investigate differences in brain integration between patients with autism spectrum disorders (Hanson et al., 2013) and individuals with traumatic brain injury (Dobryakova et al., 2015). By modeling the non-Gaussianity of fMRI data, researchers have also employed
the linear non-Gaussian acyclic models (LiNGAM) (Shimizu et al., 2006) to reveal the key differences in the default-mode network between patients with bipolar disorders and those with major depression (Liu et al., 2015).

Recently, a score-based approach for structure learning of DAG (Zheng et al., 2018) has been proposed. Different from other GES approaches, it incorporates the DAG constraints by introducing an algebraic characterization on the adjacency matrix of DAG, which gives more flexibility in modeling the structure of Bayesian network. However, high dimensionality and moderate individual variation prevent the score-based method from fitting well to the fMRI data, since most score criteria are defined as the likelihood of a Bayesian network. To mitigate this limitation, we formulate a joint structure learning framework, namely joint DAG estimation model, by incorporating information from other observations or groups in fMRI studies. Although the joint DAG estimation model is not a convex optimization problem, we found that using the augmented Lagrangian (Nemirovsky, 1999) and proximal quasi-Newton method (Zhong et al., 2014) can solve the problem and deliver significantly improved results. The performance of the model is first validated through a series of simulations with various settings for random graphs, in comparison with four widely-used DAG estimation methods. Finally, we apply the proposed model to the fMRI data from MCIC study to detect abnormal directed connectivity in schizophrenia (SZ) patients. We identified the decreased network integration, altered organization of hub nodes and characteristic edges (CtEs) in SZ patients compared to healthy controls. In addition, we found that using the selected features based on directed networks can improve the accuracy of SZ diagnosis.

The rest of this paper is organized as follows. In Section 2, we give a brief introduction on Bayesian networks, formulate our joint DAGs estimation model and describe the optimization strategy. In Section 3, we show the results from both the simulation and real fMRI studies. We discuss the findings and limitations of the proposed method in Section 4 and conclude this paper in Section 5.

2. Methods

2.1. Preliminary

A Bayesian network is a probabilistic graphical model that encodes the random variables as its nodes and their conditional dependencies as the directed edges. The node set $V$ and the edge set $E = V \times V$ make up with a DAG $G = (V, E)$, in which each edge $(i, j)$ represents a directed edge from variable $i$ to $j$. In this case $i$ is called the parent node of $j$ and $j$ is the child node of $i$ accordingly. Given one variable $j$, and the set of its parent nodes $Pa_j$, we can write the conditional probability distribution of $j$ as $P(j \mid Pa_j)$. Without loss of generality, the joint distribution of random variables $Y = \{y_1, y_2, \ldots, y_d\}$ can be factorized as $P(y) = \prod_{i=1}^{d} P(y_i \mid Pa_i)$.

Given the data matrix $X \in \mathbb{R}^{n \times d}$ as the $n$ observations of random variables $y \in \mathbb{R}^{d}$, learning the underlying structure of the Bayesian network or DAG is to find a proper distribution $P(y)$ defined on the graph $G = (V, E)$. More specifically, we want to determine all the
conditional dependencies via the observation $X$. We model these conditional dependencies via a structural equation model (SEM) defined by $X = XW + z$, where $W \in \mathbb{R}^{d \times d}$ is the weighted adjacency matrix and $z$ is the noise term. Without any further assumption on the noise distribution, we follow the approach in (Zheng et al., 2018) and use the least square loss function to measure the fitting of the linear SEM. It should be noted that the loss can be changed to any other smooth functions over $\mathbb{R}^{d \times d}$. Several previous studies have shown that minimizing the least square loss can guarantee the identification of true DAG with high probability in finite-samples and even in high dimensional setting ($d \gg n$). This result is consistent for both Gaussian SEM (Aragam et al., 2015), (Van de Geer et al., 2013) and non-Gaussian SEM (Loh and Bühlmann, 2014).

In (Zheng et al., 2018), the authors first characterized the adjacency matrix of a DAG algebraically and turned the fussy searching problem in traditional GES methods into a continuous optimization. The characterization of DAG is formulated an equation using the adjacency matrix. A matrix $W \in \mathbb{R}^{d \times d}$ is an adjacency matrix of a DAG if and only if

$$h(W) = \text{Tr}(e^{W \ast W}) - d = 0,$$

where $\ast$ is the Hadamard product and $e^\cdot$ is the matrix exponential operator. Besides, $h(W)$ is differentiable and its gradient is

$$\nabla h(W) = 2(e^{W \ast W})^T \ast W.$$

With this algebraic equation, they developed a simple approach and formulated a continuous optimization for structural learning: Non-combinatorial Optimization via Trace Exponential and Augmented lagRangian for Structure learning (Notears).

$$\min_W \quad F(W) = \frac{1}{2n} \left\| X - XW \right\|_F^2$$
subject to $h(W) = 0,$

(1)

Alternatively, the Notears method replaced the DAG searching with a smooth equality constraint. However, for heterogeneous data with limited sample size, this method cannot give a satisfactory answer and additional modelling is needed to bridge the gap in application.

### 2.1.1. Joint DAG estimation model

To overcome the sample size limitation and take advantage of data from multiple groups, we propose a joint DAG estimation model to incorporate the similarity prior. The primal problem can be formulated as

$$\min_W \quad F(W) = l(W; X) + P(W)$$

subject to $h(W(k)) = 0$, $\forall k \in [K]$
where \( l(W; X) \) is the loss function used to derive SEM, i.e. \( l(W; X) = \sum_{k=1}^{K} \frac{1}{2n_k} \left\| X^{(k)} - X^{(k)}W^{(k)} \right\|^2 \), \( K \) is the number of groups, \( X^{(k)} \in \mathbb{R}^{n_k \times d} \) and \( W^{(k)} \in \mathbb{R}^{d \times d} \) are the data matrix and the adjacency matrix of group \( k \) and \( \{ K \} = \{ 1, 2, \ldots, K \} \). \( P(W) \) is the penalty term on the weighted adjacency matrices, which is usually chosen to encourage \( W^{(1)}, W^{(2)}, \ldots, W^{(K)} \) to share similar characteristics like the same number of nonzero elements. In addition, the sparsity on those matrices is usually enforced as prior knowledge which benefits both model training and result interpretation. Considering the similar causal structure underlying different observations, we add group regularization preference in the undirected graphical model to encourage the shared DAG structures, which has been proven successful in gene expression network studies (Danaher et al., 2014; Wu et al., 2019). The group regularization term is often formulated as:

\[
P(W) = \lambda_1 \sum_{k=1}^{K} \sum_{i \neq j} |W_{ij}^{(k)}| + \lambda_2 \sum_{i \neq j} \left( \sum_{k=1}^{K} (W_{ij}^{(k)})^2 \right)^{1/2}
\]

where \( \lambda_1 \) and \( \lambda_2 \) are nonnegative parameters. \( \lambda_1 \) controls the sparsity of \( W^{(k)} \)s. The larger \( \lambda_1 \) is, the sparser the solution of (2) will be. On the other side, \( \lambda_2 \) restrains the patterns of the nonzeros in \( W^{(k)} \)s. The larger \( \lambda_2 \) is, the more identical \( W^{(k)} \)s will be. If \( \lambda_1 \) and \( \lambda_2 \) are set to 0, the model is degraded to the original Notears model.

2.2. Optimization

By applying the augmented Lagrangian, the primal problem is written as

\[
\begin{align*}
\min_W & \quad l(W; X) + P(W) + \rho \sum_{k=1}^{K} |h(W^{(k)})|^2 \\
\text{s.t.} & \quad h(W^{(k)}) = 0, \ \forall k \in [K]
\end{align*}
\]

We use the dual ascent algorithm to solve problem (4) and the Lagrange multiplier is derived as

\[
L(W, a_1, a_2, \ldots, a_K) = l(W; X) + P(W) + \rho \sum_{k=1}^{K} |h(W^{(k)})|^2 + \sum_{k=1}^{K} a_k h(W^{(k)})
\]

Hence, the corresponding dual function is

\[
g(a_1, a_2, \ldots, a_K) = \min_W L(W, a_1, a_2, \ldots, a_K)
\]
The dual problem is then
\[
\max_{a_1, a_2, \ldots, a_k} g(a_1, a_2, \ldots, a_k)
\]
(7)

We denote \( W_\alpha \) as the local minimizer of problem (6), i.e., \( g(a_1, a_2, \ldots, a_k) = L(W_\alpha, a_1, a_2, \ldots, a_k) \). Noting that \( g(a_1, a_2, \ldots, a_k) \) is a linear function of \( a_k \), the partial derivatives are given by
\[
\frac{\partial g(a_1, a_2, \ldots, a_k)}{\partial a_k} = h\left(W^{(k)}_\alpha\right).
\]
Hence we can perform the dual ascent by updating \( a_k \) with
\[
a_k \rightarrow a_k + \rho h\left(W^{(k)}_\alpha\right)
\]
(8)

The rest of the concern will be the unconstrained optimization of the subproblem (6). Due to its high dimensionality and non-convexity, we follow the similar idea in (Zheng et al., 2018) to solve it with the L-BFGS algorithm (Byrd et al., 1995) when \( \lambda_1 = \lambda_2 = 0 \). When \( \lambda_1, \lambda_2 > 0 \), the problem can be solved with the proximal quasi-Newton (PQN) method (Zhong et al., 2014). As an iteration algorithm, at the \( k \)-th step, the descent direction is searched through a quadratic approximation of the smooth term:
\[
d_k = \arg \min_{d \in \mathbb{R}^p} g_k^T d + \frac{1}{2} d^T B_k d + \lambda_1 \| w_k + d \|
\]
(9)

where \( g_k \) is the gradient of \( f(w) \) and \( B_k \) is the L-BFGS approximation to the Hessian matrix of \( f(w) \). In addition, for each coordinate \( j \), the solution of problem (9) has a closed form update \( d \leftarrow d + z^* e_j \) in which \( e_j \) is the unit vector in standard basis and
\[
z^* = \arg \min_a \frac{1}{2} B_j z^2 + (g_j + (B d)_j) z + \lambda_1 \| w_j + d \|
\]
\[
= -\frac{c}{a} + \frac{S_c - \lambda_1 \approx a}{c}
\]
(10)

It should be noted that the low-rank structure of \( B_k \) makes it sparse and fast to compute during the coordinate update. The sparse regularization in the model further enables us to speed up the computation. Instead of updating for all the coordinates, an active set of coordinates can be chosen based on the subgradients and we only need to update coordinates in the active set. More details of the subproblem optimization can be found in Appendix A.

2.3. Parameter tuning

In the joint estimation model, two parameters, i.e., \( \lambda_1 \) and \( \lambda_2 \) need to be specified for structure learning. Different settings of these parameters will lead to different DAG structures. Training the model with a larger \( \lambda_1 \) will lead to a sparser \( W \) but may cause underfitting.

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issue. On the other hand, the model with a smaller $\lambda_i$ gives rise to a denser $W$ but may also cause overfitting. That is, an improper choice of the parameter will give inaccurate results: a sparser DAG tends to have more false negatives while a denser graph usually has more false positives. Hence, we need to balance between the simplicity and the goodness of fit. Similarly, the parameter $\lambda_i$ reflects how similar the DAG structures will be between groups. A larger $\lambda_i$ implies more similar structures between groups and vice versa. When $\lambda_i$ is trivially set to 0, the joint estimation model is degraded to $K$ separate Notears models for $K$ groups with the same sparsity regularization. As $\lambda_i$ goes to $\infty$, group variations will be wiped out gradually and the resulting $K$ DAGs will be identical to each other. To find a proper combination of $(\lambda_1, \lambda_2)$, we performed a grid search using the least square loss $l(W)$ as the performance measure via crossvalidation.

2.4. Simulation data generation

To validate the performance of our joint DAG estimation method, we first evaluated it with the simulation data sets under different circumstances. Our proposed method was compared with the score-based GES (Chickering, 2002), the PC algorithm (Spirtes et al., 2000), the LiNGAM (Shimizu et al., 2006), and the Notears method (Zheng et al., 2018). Regarding the synthetic data, a random graph $G_0$ was firstly generated from three different random graph models: Erdős-Rényi (ER) graph, scale-free (SF) graph and small-world (SW) graph. Then we randomly added extra edges to $G_0$ and got $G_1$ and $G_2$ to simulate the case-control study. In this way, we can build the association between the two graphs: shared edges are the ones in $G_0$ and the varied edges are those independently added. Once graphs were generated, we equipped edges with the weights according to an uniform distribution and obtained weight matrix $W_i$ for each graph. The generation and alternation of random graphs were realized through the Python package NetworkX. Given $W_i$, the observation sequences were then sampled on the basis of $X_i = X_i W_i + \epsilon_i$ for various distributions of $\epsilon_i$. In this paper, we tested three types of noise distributions: Gaussian, exponential, and Gumbel. We repeated the above procedure to generate $X_i \in \mathbb{R}^{n \times d}$ in two simulation settings. For ER and SF graphs, we generated the first group of simulation data with $n = 300$ and $d = \{10, 20, 50, 100\}$; for the high dimensional case, we generated the second group of simulation data with $n = 50$ and $d = \{20, 40, 60, 100\}$. For SW graphs, we generated the simulation data with $n = \{50, 300\}$ and $d = \{16, 32, 64, 128\}$. It has been confirmed in many literatures that scale-free structure is ubiquitous in the real-world networks including genetic networks, social networks, and the brain functional networks (Eguiñuz et al., 2005; van den Heuvel et al., 2008). Small-world properties are also proven to exist in human brain networks from several independent studies (Bassett and Bullmore, 2006; Liao et al., 2017).

2.4.1. Parameter settings in simulation—For each data set, we ran GES, PC, LiNGAM, Notears and our proposed method, and compared their performances in terms of the consistence with the ground truth DAGs for two groups. Detailed information of software implementation is listed in 2.6. Here are further remarks on the compared methods: both PC and GES methods output a graph instead of the weight matrix $W$; the graph by these two methods is a completed partially DAG (CPDAG) rather than a DAG, that is, part of edges are undirected. During the evaluation, we treated PC and GES methods...
favorably by regarding undirected edges as the true positives if there exist directed edges between the same nodes. For parameter tuning, we followed the same setting according to the suggestions in (Zheng et al., 2018).

2.4.2. Metrics used for comparison—To evaluate the estimated DAGs (for LiNGAM, Notears and our method) or CPDAGs (for PC and GES method), we used three common metrics: 1) false discovery rate (FDR), 2) true positive rate (TPR), and 3) structural Hamming distance (SHD). The first two measures are derived from the confusion matrix, which can be found in Appendix B.

The SHD is defined as the number of operations needed to convert the estimated graph to the ground truth graph. These operations include edge additions, deletions and direction reversals. Since we consider directed graphs, a distinction between true positives (TP) and reversed edges (R) is needed: the former is estimated with correct direction while the latter is not. Likewise, a false positive (FP) is an edge that is not in the undirected skeleton of the true graph. In addition, positive (P) is the set of estimated edges, true (T) is the set of true edges, and false (F) is the set of non-edges in the ground truth graph. Finally, let E be the extra edges from the skeleton and M be the missing edges from the skeleton. The three metrics are respectively defined by:

- \( \text{FDR} = \frac{R + FP}{P} \)
- \( \text{TPR} = \frac{TP}{T} \)
- \( \text{SHD} = E + M + R \)

2.5. Data acquisition and preprocessing

The fMRI data were acquired from the MIND Clinical Imaging Consortium (MCIC) collected by Mind Research Network (MRN). The data include 208 subjects (92 SZ patients (age: 34 ± 11, 22 females) and 116 healthy controls (age: 32 ± 11, 44 females)) during a sensory motor task, a block design motor response to auditory stimulation. All subjects provided informed consent to participate in the study that was approved by the human research committees at each of the sites (UNM HRRC #03-429; UMinn IRB #0004M59124; MGH IRB #2004P001360; UIowa IRB #1998010017) and were recruited for this study between July 2004 and July 2006. The demographic information of the involved subjects can be found in Appendix C.1. Specifically, the images were acquired on a Siemens3T Trio Scanner and 1.5 T Sonata with echo-planar imaging (EPI) sequences taking parameters TR = 2000 ms, TE = 30 ms(3.0T)/40ms(1.5T), field of view = 22 cm, slice thickness = 4 mm, 1 mm skip, 27 slices, acquisition matrix = 64 × 64, flip angle = 90°). Then the data were pre-processed with SPM5 (http://www.fil.ion.ucl.ac.uk/spm) and were realigned, spatially normalized and resliced to 3 × 3 × 3 mm, smoothed with a 10 × 10 × 10 mm³ Gaussian kernel, and analyzed by multiple regression considering the stimulus and their temporal derivatives plus an intercept term as regressors. Finally the stimulus-on versus stimulus-off contrast images were extracted with 53 × 63 × 46 voxels and all the voxels with missing measurements were excluded resulting in 41,236 voxels. In order to filter irrelevant information, we further implemented a multiple t-test between case and control groups at the voxel level. Finally, 9816 voxels were left for analysis. The brain regions were
parcellated into 116 ROIs based on the automated anatomical labeling (AAL) brain atlas (Tzourio-Mazoyer et al., 2002) and 264 ROIs based on Power atlas (Power et al., 2011). For each ROI, we averaged the beta values of the voxels within that ROI and denoted as beta map. The preprocessed data were then normalized using z-score. For the 116 ROIs, we divide them into 9 lobes including prefrontal, motorstrip, insula, parietal, temporal, occipital, limbic, cerebellum, and subcortical region. For the 264 ROIs, we divide them into 12 functional network (FN) modules, including sensory/somatomotor network (SSN), cingulo-opercular task control network (CON), auditory network (AUD), default mode network (DMN), memory retrieval network (MRN), visual network (VIS), frontoparietal task control network (FPN), salience network (SAL), subcortical network (SCN), ventral attention network (VAN), dorsal attention network (DAN) and cerebellum network (CERE).

In two parcellation schemes for defining brain regions, we used the 5 -fold cross-validation to do model selection independently. For AAL 116 atlas, the optimal combination of parameters is $\lambda_1, \lambda_2 = (0.001, 0.01)$; for Power 264 atlas, the optimal combination of parameters is $\lambda_1, \lambda_2 = (0.01, 0.01)$. The details of cross-validation results can be found in Appendix C.3. After splitting the data into two groups, we fed them into the joint estimation model, and obtained the corresponding DAGs and the weighted adjacency matrices $W^{(1)}, W^{(2)}$ for SZ patients and healthy controls respectively. The analysis pipeline is summarized in Fig. 2.

2.6. Data and code availability statements

Specifically, GES, PC and LiNGAM were implemented using the widely used R package pcalg, which is available at https://cran.r-project.org/web/packages/pcalg/. Notears method was implemented using Python available at https://github.com/xunzheng/notears. The proposed joint DAG method was implemented with Python and the code is available at https://github.com/gmeng92/joint-notears.

The cohort data is accessible through the website (https://coins.trendscenter.org/) of COINS (COllaborative Informatics Neuroimaging Suite) database (Scott et al., 2011). Further information can also be found in (Gollub et al., 2013).

3. Results

3.1. On simulation data

In Fig. 1, we give a demonstration of the joint estimation method on a synthetic data set for two groups and with limited sample size $(n = d = 20)$. Both Notears and the proposed joint DAG estimation model were used to estimate the DAG structure. By comparing the estimation results with the ground truth DAG, we can clearly see that the Notears method delivers many false positives (marked with blue squares in the third column) while the joint DAG model gives more accurate estimation (the fifth column) under the same condition. This demonstrates that structure learning benefits from the use of group regularization when group structure exists and the number of observations is limited.
Moreover, we show results for ER graphs in Fig. 3 with Gaussian noise when average degree is 4, and sample size is $n = 300$ and $n = 50$ respectively. Both Notears method and the proposed joint method give the highest TPR and the lowest FDR and SHD, demonstrating the superiority of the structure learning framework. It is noticeable when the sample size decreases and the number of variables grows, the FDR and the SHD increase significantly. However, both the FDR and SHD are kept at a low level for the joint DAG estimation model; the estimation accuracy is sustained even in the high dimensional scenario. For synthetic data sets with different noise types, graph densities and random graph types, the joint DAG model also outperforms other methods. The detailed results on simulation data can be found in Appendix B.

3.2. On real fMRI data

3.2.1. Summary of graph measures—The resulting DAGs in AAL atlas were visualized in Fig. 4 with 207 directed edges for SZ group and 187 directed edges for healthy controls. In the first step, we compared the two DAGs using graph metrics with the purpose of finding structural differences between the two groups. Since the effect size of the weight cannot be well estimated yet, the structures that have a high power and the edge weights are ignored in the computations. Those measures were computed using the brain connectivity toolbox (Rubinov and Sporns, 2010) and their definitions can be found in Appendix C.2. Table 1 shows the summary of the measures used in the graph analysis and the $p$-values of the permutation test were listed in the last column. We also compared those graph measures from raw functional connectivity matrices defined by Pearson correlation matrices. The results were listed in Appendix C.2.

3.2.2. Hub nodes identification—To gain a better understanding of the key local structure of estimated directed brain networks, we further identified the hub nodes to be of significantly higher degrees than average for two groups. More specifically, we defined the node to be the one whose degree is higher than mean degree by three standard deviations. Since we have three types of degrees here: in-degree, out-degree and sum-degree, we can similarly define three types of hub nodes for the directed networks: in-hub, out-hub and sum-hub. For some nodes identified as sum-hubs, because they had high in-degrees or out-degrees, we only keep the sum-hubs if they are not in-hubs or out-hubs.

For the healthy control group, we were able to identify two in-hubs located in gyrus rectus (REC.L) and cerebellum (CRBL10.R), one out-hub in superior occipital lobe (SOG.R) and one sum-hub in cerebellum (CRBL45.L). For the SZ patient group, we identified three in-hubs located in right temporal pole (TPOmid.R), cerebellum (CRBL10.R) and vermis (Vermis10), and two out-hubs in inferior frontal gyrus (IFGtriang.L) and cerebellum (CRBL3.R). Those results are summarized in Table 2.

3.2.3. Variations of edges between groups—The graph measures only give a brief summary of differences between the two groups. In this study, we are more interested in a subset of edges or nodes shared between the two groups or specific to a group. Hence, we further did a permutation test for the comparison. 100 permutation tests were performed and the subjects were randomly shuffled into two groups - one with 92 subjects and the
other with 116 subjects. Then we extracted the significantly different edges \( p < 0.01 \) with FDR corrected value at \( q = 0.05 \) in case and control groups. For each group, the edges that exclusively exist within one group were marked as the characteristic edges (CtEs). Finally, 19 and 15 edges were identified as CtEs in SZ patients and healthy controls respectively, which are illustrated in Fig. 5.

### 3.2.4. Comparison with undirected graphs

An interesting question one may ask is the added value of the directed graphs over the undirected ones measured with Pearson correlation or partial correlation, namely functional connectivity (FC). Since edges from both graphical models represent conditional dependency, there are considerable overlaps between the two graphs. Recent progress also suggests that the FC can be utilized as a prior to benefit the causal inference (Reid et al., 2019). Specially, we used the \( \psi \)-learning method to estimate the undirected brain networks for SZ patients and healthy controls separately. \( \psi \)-learning is a novel method for high-dimensional Gaussian Graphical Model (GGM) (Liang et al., 2015). Compared to other partial correlation based methods, it can help ease computational burden and provide more accurate inference for the underlying networks. This method has also been proven to be an equivalent measure of the partial correlation coefficient and thus is flexible for network comparison via statistical testing. In this paper, we used the same implementation as in our previous work (Zhang et al., 2018) with R package “equSA”. The parameters were set as \( \alpha_1 = 0.1 \) and \( \alpha_2 = 0.01 \) as suggested in (Liang et al., 2015; Zhang et al., 2018). For the group comparison, we set the significance level at 0.01 and further corrected the FDR with \( q = 0.05 \). Finally, we obtained 148 edges and 104 edges in SZ patients and healthy controls using \( \psi \)-learning method respectively. To compare the undirected networks with the directed ones, we mainly checked the following three aspects: the hub nodes in undirected networks, the overlapped edges, and the detected group variances between undirected networks and directed networks. The identified hub nodes are listed in Table 3. Opercular region of inferior frontal gyrus (IFGoperc.R) at the right lobe was identified as hub nodes in both groups. In SZ patients, parahippocampus in both lobes (PHG.L and PHG.R) were identified as hub nodes. In healthy controls, a region in vermis (VERMIS45) was also identified as hub node. It should be noted that there are no overlapped hub nodes between directed networks and undirected networks. The overlapped edges between directed networks and undirected networks for both groups are visualized in Fig. 6. There are no CtEs showing in either group. For the pairwise comparison, significantly different edges between two groups are visualized in Fig. 7. As a comparison, we also highlight the overlapped edges from both directed networks and undirected networks with blue color in the figure. There are 12.96% and 15.57% overlapping edges among the SZ patients and healthy controls respectively.

### 3.2.5. Classification analysis

We have investigated the connectivity difference at the group-level between SZ patients and healthy controls. However, it is unclear whether the identified connectivity abnormalities are useful for distinguishing patients from healthy controls. To this end, we performed an individual-level classification to further validate our findings. We used the linear support vector machine based classifier (SVC) implemented by scikit-learn with default parameter setting. Five different inputs were compared. First group
of features are the beta values of fMRI signals or beta maps for all 116 ROIs, which is the baseline in this study. Second and third groups of features are the beta maps, corresponding to the CtEs of estimated directed (43 ROIs) and undirected (83 ROIs) networks respectively. We also randomly sampled the same number of ROIs since their appearance in directed or undirected CtEs may have influence on the classification result. The data was split into training (80%) and testing (20%) sets and the testing accuracy was reported as the average of the repeated 100 times of experiments. Results of classification are shown in Fig. 8. The baseline model reached an accuracy of 56.21%, while models using features from the estimated networks have the accuracy at 60.51% (directed network) and 57.85% (undirected network), respectively. When we randomly choose the same number of ROIs, they give the accuracy of 53.90% (directed network) and 56.07% (undirected network) respectively.

3.2.6. **Functional network-level analysis**—Besides the ROI-level connectivity analysis, we further investigated the connection abnormalities at the functional network level. Among the 261 edges, we counted the number of edges for module pairs and conducted a hypergeometric test \((\alpha = 0.05)\) with FDR correction to illustrate the within/between modular connections, which are different between SZ patients and healthy controls. The significant connections are summarized in Fig. 9 while the detailed functional network-level connections can be found in Appendix C.4. The directed connections within CON, AUD and MRN are found to be significantly different between the two groups. 9 pairs of between-modular connections are shown to have between-group variances. Among them, the bidirectional connection (FPN↔VIS) is considered as two different connections. Other directed connections include AUD→CON, AUD→SSN, CON→SSN, VAN→SCN, VAN→FPN, SAL→VAN, SAL→FPN.

4. **Discussion**

The analysis of functional connectivity provides a powerful way to detect aberrant connectivities associated with SZ. However, the directed functional connectivity is rarely used as a feature for the SZ study so far. From the comparison between the SZ and control groups, we found that the directed brain network is significantly denser in SZ patients than in controls. Moreover, the mean clustering coefficient of SZ patients is larger than that of the controls. With a denser network, we observed that both the global and local efficiency of SZ patients are significantly smaller than those of healthy controls. Since functional integration represents the capability of the brain to combine information from distributed brain regions, our results indicate that for SZ patients their brain regions communicate less effectively as a directed network either globally or locally in the auditory task. It can be noted that the comparison results are consistent with the two brain atlases.

Among the hub nodes identified in two groups, we also observed disruptions of the hub structures in SZ patients. The gyrus rectus (REC.L), as an in-hub in the left hemisphere, is missing in SZ patients. A previous study (Zhao et al., 2018) demonstrated that the pronounced gray matter volume decline at gyrus rectus was observed in SZ patients, which supported our findings. Another study (Li et al., 2019) also showed that reduced functional connectivity was observed between gyrus rectus and other regions within the self-referential processing network. Inferior frontal gyrus, triangular at left hemisphere (IFGtriang.L), has
been shown to have increased activity during auditory hallucinations (McGuire et al., 1993), and supported with the theory of mind (ToM) deficits (Das et al., 2012) in schizophrenia patients. Our result further implies that the hyperconnectivity related to this region is potentially an important marker of schizophrenia. The behavior of temporal pole on the right hemisphere (TPOmid.R) is abnormal in SZ group, which agrees with the findings (Chen et al., 2020; Gao et al., 2020). Interestingly, we also found that the ROI named as Vermis10 has 0 in-degree in healthy controls, which plays an important role as in-hub in SZ patients. We believe that this altered structure is related to the responsive movements in the motor tasks of the fMRI scanning as shown in (Andreasen and Pierson, 2008; Lošák et al., 2016).

From Table 3, parahippocampus on both sides are identified as hub nodes in undirected functional connectivity for SZ patients. The parahippocampus plays an important role in the encoding and recognition of environmental scenes. A previous study discovered the abnormal connections between parahippocampus and temporal pole in early stage SZ patients (Du et al., 2018). Several related studies also revealed the aberrant increased connectivity between parahippocampus and other limbic areas (Hua et al., 2020), including hippocampus (Kraguljac et al., 2016).

In addition to the abnormal hub structures in SZ patients, we also have several findings consistent with previous studies by comparing the CtEs extracted from both groups. For example, previous research (Kiparizoska and Ikuta, 2017) revealed that olfactory bulbs disconnectivity of olfactory regions in schizophrenia may account for olfactory dysfunction and disrupted integration with other sensory modalities in SZ patients. The missing connections to the olfactory cortex in CtEs of SZ patients also confirm this finding. In the subcortical regions, pallidum, putamen and caudate work together to communicate with the subthalamic nucleus (Alexander and Crutcher, 1990). Our result illustrated the missing communications within and between putamen and pallidum, which is in line with the findings in (Cui et al., 2016; Wang et al., 2017).

In the classification analysis, we demonstrated that using the beta maps within ROIs selected from directed networks outperformed other features in classifying SZ patients. Based on the classification result, we also analyzed the parameter sensitivity (See Appendix C.5) following the similar pipeline in (Zhou et al., 2020). Our results demonstrate that the classification appears to be accurate and stable when $\lambda_1 \times \lambda_2 \in [0.001, 0.01] \times [0.01, 0.1]$. Based on current results, it might be promising to explore the association between the estimated FC and clinical variables, which will offer direct evidence to differentiate the patients using features from directed network. The distinct directed connections within and between functional modules also imply the altered auditory, cingulo-opercular task control network, control and downstream sensorimotor (AUD $\rightarrow$ CON $\rightarrow$ SSN) in the auditory stimulated motor task session, and reflect abnormal organization in motor function (Marek and Dosenbach, 2018).

When we compared the findings between directed graphical model and undirected graphical model, we found that the features from undirected networks and directed networks cannot carry the same information in depicting the interactions between brain regions (See Appendix C. 7 for details). Since we do not know the ground truth and each method can
only provide one aspect of the description, we reported the pairwise comparison results of both methods.

4.1. Limitations

Currently, both the Notears and the proposed method are optimized with the second order approximation with a global searching over the feasible space. It is time-consuming if we want to extend the methods to applications with hundreds of variables, a typical case in brain imaging. For example, it is computationally intractable to directly apply the method to network analysis at the voxel-level. It will be desirable if we can find a way to reduce the search space in the model optimization. In fact, we can incorporate the prior information into the model, which can significantly alleviate the computational burden. The prior information includes known connections/disconnections and the directions of connections. The computational inconvenience also reminds us that we need to reconduct the joint estimation when we deal with unseen samples. One potential approach might be incorporating sparsity and group structure as the prior knowledge and maximizing the posterior distribution. With such a Bayesian approach, one can update the posterior accordingly for newly added data (Opper and Winther, 1998). Another limitation lies in the variances of the results that we found between the directed network and the undirected network. Most FC studies are based on either directed or undirected network analysis. It will be meaningful to cross-validate the findings with other modalities such as electroencephalogram (EEG) or magnetoencephalography (MEG) with higher temporal resolution.

5. Conclusion

In this paper, we propose a joint DAG estimation model for structural learning via a continuous optimization framework. By incorporating both the shared and group-specific information between groups into the DAG structure, the model can learn the DAGs for multiple groups simultaneously. The efficiency of the proposed model was tested and validated with the simulation data with a wide range of variations on density levels, noise types, etc. By comparing with other structural learning methods, the proposed model delivered higher TPR and lower FDR, especially in high dimensional cases. Finally, the proposed model was applied to detect abnormal brain networks in schizophrenia patients collected from MCIC. The lower global and local efficiency of the brain network indicated the deficiency of functional integration in SZ patients versus healthy subjects.

In addition, we identified disrupted hub structures and characteristic edges in SZ patients. Based on these results, we found that the selected features from directed networks can significantly improve the diagnosis accuracy. Further functional network analysis illustrated the abnormal connections from task-control region to downstream sensorimotor region in the auditory stimulated motor task session. Some of the findings have been in line with those reported in previous schizophrenia studies. Moreover, we compared the results between using directed networks and undirected networks. Although both network modelling methods can detect the key alterations between schizophrenia patients and healthy controls,
directed networks carry more informative or significant features, which enable us to gain a better understanding of neurological mechanisms underlying mental disorders.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.
A demonstration of the joint estimation method compared to the Notears method. The top and bottom row show the weighted DAGs from group 1 and group 2, respectively. From left to right: the ground truth graphs, DAGs estimated by Notears, the variation of Notears estimation compared to ground truth, DAGs estimated by joint estimation, the variation of joint estimation compared to ground truth. In the 3rd and 5th column, the less the colored squares are, the better the performance the respective method has.
Fig. 2.
An illustration of the analysis pipeline with the proposed joint DAG estimation model. After the preprocessing step, the beta maps of SZ patients and healthy controls were fed into the joint DAG estimation model. The resulting DAGs were analyzed based on graph metrics to extract shared network and exclusive networks, which were compared with undirected FC networks.
Fig. 3.
Results for the simulated networks. We reported the TPR, FDR and SHD for two simulation data sets with sample size: (a) $n = 300$ and (b) $n = 50$. 
Fig. 4. The jointly estimated directed brain networks of SZ patients (left) and healthy controls (right).
Fig. 5.
The Characteristic edges in directed networks of SZ patients and healthy controls. Arrows represent the direction of edges and numbers represent the ROI indexes which can be found in Appendix C. 7 Table 4.
Fig. 6.
The overlapped edges between directed and undirected networks of SZ patients and healthy controls.
Fig. 7.
The group-variant edges between SZ patients and healthy controls in undirected networks. The lines colored with blue indicate their appearance in respective directed networks. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
Fig. 8.
The classification results using different features. Random_D: classifier using beta maps of randomly selected 43 ROIs as the input; Directed: classifier using beta maps of 43 ROIs in CtEs of directed network as the input; All: classifier using beta maps of 116 ROIs as the input; Undirected: classifier using beta maps of 83 ROIs in CtEs of undirected network as the input; Random_UD: classifier using beta maps of randomly selected 83 ROIs as the input.
Fig. 9.
The identified within-(blue arrows, left) and between-(green arrows, right) modular directed connections. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
| Measures / groups | AAL     | SZ     | Power | HC     | p-value | SZ     | Power | HC     | p-value |
|-------------------|---------|--------|-------|--------|---------|--------|-------|--------|---------|
| Density           | 0.0155  | 0.0139 | 0.0137| 0.001  | <0.001  |
| Transitivity      | 0.0275  | 0.025  | 0.0134| 0.014  | <0.001  |
| Mean_Cluster      | 0.0308  | 0.029  | 0.0328| 0.014  | <0.001  |
| Maximum_RC       | 0.929   | 0.9274 | 0.001 | 1      | 0.99    |
| Efficiency(G)     | 0.0314  | 0.0251 | 0.018 | 0.001  |
| Efficiency(L)     | 0.0419  | 0.0351 | 0.031 | 0.99    |
| Assortativity     | -0.0138 | -0.0688| 0.27  | -0.4313| -0.4872| 0.14  |

Mean_Cluster = Mean clustering coefficient; Maximum_RC = Maximum rich club coefficient; Efficiency(G) = Global efficiency; Efficiency(L) = Mean local efficiency; Assortativity = Assortativity coefficient.
Table 2
The identified hub nodes for case and control group.

|       | Index | ROI      | MNI coordinate     | Degree |
|-------|-------|----------|--------------------|--------|
| **SZ Patients** |       |          |                    |        |
| In-hub | 88    | TPOmid.R | (44.22, 14.55, −32.23) | 8      |
|        | 108   | CRBL10.R | (25.99, −33.84, −41.35) | 7      |
|        | 116   | Vermis10 | (0.36, −45.8, −31.68)  | 6      |
| Out-hub| 13    | IFGriang.L| (−45.58, 29.91, 13.99)  | 5      |
|        | 96    | CRBL3.R  | (12.32, −34.47, −19.39) | 5      |
| **Healthy control** |       |          |                    |        |
| In-hub | 27    | RECL     | (−5.08, 37.07, −18.14)  | 6      |
|        | 108   | CRBL10.R | (25.99, −33.84, −41.35) | 5      |
| Out-hub| 50    | SOG.R    | (24.29, −80.85, 30.59)  | 5      |
| **Sum-Hub** | 97    | CRBL45.L | (−15, −43.49, −16.93)  | 6      |
Table 3
The identified hub nodes for SZ patients and healthy control using undirected networks estimation.

| Index | ROI       | MNI coordinate       | Degree |
|-------|-----------|----------------------|--------|
|       | SZ Patients |                      |        |
| 12    | IFGoperc.R | (−50.2, 14.98, 21.41) | 19     |
| 39    | PHG.L     | (−21.17, −15.95, −20.7) | 15     |
| 40    | PHG.R     | (25.38, −15.15, −20.47) | 21     |
|       | Healthy control |                |        |
| 12    | IFGoperc.R | (−50.2, 14.98, 21.41) | 21     |
| 111   | Vermis45  | (1.22, −52.36, −6.11)  | 7      |