Capturing Dynamic Connectivity from Resting State fMRI using Time-Varying Graphical Lasso

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Abstract

Functional connectivity (FC) within the human brain evaluated through functional magnetic resonance imaging (fMRI) data has attracted increasing attention and has been employed to study the development of the brain or health conditions of the brain. Many different approaches have been proposed to estimate FC from fMRI data, whereas many of them rely on an implicit assumption that functional connectivity should be static throughout the fMRI scan session. Recently, the fMRI community has realized the limitation of assuming static connectivity and dynamic approaches are more prominent in the resting state fMRI (rs-fMRI) analysis. The sliding window technique has been widely used in many studies to capture network dynamics, but has a number of limitations. In this study, we apply a time-varying graphical lasso (TVGL) model, an extension from the traditional graphical lasso, to address the challenge, which can greatly improve the estimation of FC. The performance of estimating dynamic FC is evaluated with the TVGL through both simulated experiments and real rs-fMRI data from the Philadelphia Neurodevelopmental Cohort (PNC) project. Improved performance is achieved over the sliding window technique. In particular, group differences and transition behaviours between young adults and children are investigated using the estimated dynamic connectivity networks, which help us to better unveil the mechanisms underlying the evolution of the brain over time.

Keywords

Dynamic functional connectivity; Resting state fMRI; Time-varying graphical lasso; Brain development

I. INTRODUCTION

Functional connectivity (FC) within the human brain has attracted increasing attention and has been used to study both healthy and diseased brains. Multiple studies have examined the weakening or strengthening of FC with brain development. For instance, Anderson et al.

found decreased correlation between attention control and default mode networks (DMN) as age increased [1]. Hutchison et al. showed that younger people had stronger connectivity between the cognitive control system and DMN [2]. It has been reported that young adults had hyperconnectivity within the visual system compared with children [3], [4]. Moreover, prior research has shown that alcohol intoxication was associated with increases in connectivity between the brainstem and somatosensory network, as well as activities within the DMN [5], [6]. Studies have also examined abnormalities in FC for individuals with psychopathy, and investigations of schizophrenia diseases have shown abnormalities within the thalamo-cortical-cerebellar network [7], [8], [9], [10], [11], [12], [13]. Hence, FC assessment can provide critical data about the human brain.

In order to quantify brain FC, different analytical approaches have been applied to fMRI data, including seed-based analysis, graphical model, multivariate pattern analysis and data driven methods (such as independent component analysis, principle component analysis, and nonnegative matrix factorization) [14], [15], [16], [17], [18], [19], [20], [21], [22], [23]. Among them, Eavani et al. proposed a sparse connectivity extraction approach to identify FC networks [24]. Zille et al. further extended the approach by making use of a generalized fused Lasso penalty to analyze both similarities and differences in FC for different age groups [25]. However, a large number of approaches mentioned above are based on an implicit assumption that functional connectivity is stationary throughout the entire fMRI scan session [26]. Recently, the fMRI community has realized the limitation of static connectivity assumption and analysis of dynamic connectivity is more prominent in resting state fMRI analysis [27]. Dynamic FC studies have identified reoccurring patterns of the brain FC, while static techniques cannot capture [26], [28], [29]. Furthermore, they also provide a powerful tool to illuminate differences of dynamic FC in mental diseases [10], [30].

Sliding window based methods have been widely used to analyze dynamic FC. These approaches assume that functional connectivity at a given time point can be estimated from the input samples within the selected window. However, the selection of window size is a free parameter which can affect the performance of the method. Undersized windows may result in unreliable estimation and spurious variability in dynamic FC [28]. However, oversized windows cannot capture the dynamic variations in FC. To overcome the limitation, Yaesoubi et al. provided a window-less approach to catch time-varying FC in rs-fMRI data [31]. However this approach requires additional steps to evaluate dynamic transitions. Recently, Hallac et al. introduced a model named time-varying graphical lasso (TVGL), inferring dynamic networks from time series data [32]. Even when the observation interval is only one time point, the TVGL approach is able to estimate the network. Applied to rs-fMRI data, the TVGL does not require an assumption of static connectivity. Furthermore, the TVGL reveals dynamic networks of interdependencies between precision matrices. In this way, transitions in FC can be captured. Inspired by the characteristics of the TVGL, we utilize the TVGL approach to estimate time-varying functional connectivity. To validate dynamic FC analysis using the TVGL, we apply the TVGL to both simulated and real datasets and compare its performance with the sliding window technique. As a demonstration of the application of the TVGL model, FC differences between young adults and children and the transitions captured by the TVGL were assessed.

In the remainder of the paper, we first introduce the TVGL and the sliding window approaches in Section 2. We then validate the TVGL framework and compare it with the sliding window method using both simulated and real datasets in Section 3. In particular, we apply the TVGL to a large fMRI dataset (PNC) to investigate dynamic FC differences between young adults and children and their transition sequences [33]. Some discussions and concluding remarks are given in Sections 4 and 5.

II. METHODS

In this section, both the TVGL model and the sliding window approach are introduced, and the selection of key parameters involved in these two models is also described. The details are presented as follows.

A. Description of Time-Varying Graphical Lasso

Time-varying graphical lasso was defined by Hallac et al. to infer dynamic networks [32]. It was extended from the classical graphical lasso model [34], [35]. Let us assume that for each subject, we have a sequence of BOLD time series observations at $0 = t_1 < t_2 < \dots < t_T$. At each t_i , we have $I_n - 1$ different observation vectors for the whole p ROIs (Region of Interests, $t_i, I_n, p \in \mathbb{N}$). Here, the observations follow a distribution $\mathcal{N}(0, \Sigma(t))$. We aim to estimate the underlying covariance matrix $\Sigma(t)$, which changes over time. To do so, we set up a sequence of graphical lasso models to infer sparse inverse covariance matrices $\Theta = (\Theta_1, \Theta_2, \dots, \Theta_T)$ at times $t_1, t_2, \dots, t_T$, where $\Theta_i = \Sigma(t_i)^{-1}$. For these graphical lasso problems, each one is coupled with others in a chain to penalize deviations in the estimations. We would like to approximate the covariance matrices $\Sigma(t)$ by solving the following problem:

$$\min_{\Theta \in S_{++}^p} \sum_{i=1}^T -l_i(\Theta_i) + \lambda_t \|\Theta_i\|_{od,1} + \beta \sum_{i=2}^T \Psi(\Theta_i - \Theta_{i-1}) \quad (1)$$

where, $l_i(\Theta_i)$ is the log likelihood of Θ_i

$$\begin{aligned} l_i(\Theta_i) &= I_n (\log \det \Theta_i - \text{Tr}(S_i \Theta_i)) \\ \Theta_i &\text{ is subject to } S_{++}^p \text{ (symmetric positive-definite)} \end{aligned} \quad (2)$$

where λ_t and β are non-negative model parameters, and $\|\Theta\|_{od,1}$ denotes the off-diagonal L_1 norm, which enforces the element-wise sparsity for the solution of Θ . S_i is the empirical covariance matrix, and I_n is the number of observations. $\Psi(\Theta_i - \Theta_{i-1})$ is a convex penalty function, which encourages the similarity between Θ_{i-1} and Θ_i . In this way, the penalty function Ψ allows us to enforce different behaviors of the network along time. That is to say, if we have prior knowledge about how the connectivity of the network will change over time, we can achieve it through the penalty function Ψ . Because we would like to analyze

dynamic FC using rs-fMRI dataset, we assume that FC transits in a smooth way. Hence, the Laplacian penalty, $\Psi(X) = \sum_{i,j} X_{i,j}^2$ is employed, where $X_{i,j}$ refers to the i -th row, j -th column element in the matrix X . The Laplacian penalty can allow adjacent networks to differ by small amounts while large deviations are penalized [36]. An illustration of the TVGL approach can be seen in Fig. 1 (a).

B. The Proposed Algorithm for Time-varying Graphical Lasso

In order to solve the TVGL formulation defined by Eq.1, the alternating direction method of multipliers (AD-MM) is used [37]. By applying ADMM, the original problem can be divided into a series of subproblems and the globally optimal solution can be achieved. Through introducing a consensus variable $Z = \{Z_1, Z_2, Z_3\} = \{(Z_{1,0}, Z_{2,0}, \dots, Z_{t,0}), (Z_{1,1}, Z_{2,1}, \dots, Z_{t-1,1}), (Z_{2,2}, Z_{3,2}, \dots, Z_{T,2})\}$, the Eq.1 can be represented as:

$$\min \sum_{i=1}^T -l_i(\Theta_i) + \lambda_t \|\Theta_i\|_{od,1} + \beta \sum_{i=2}^T \Psi(Z_{i,2} - Z_{i-1,1}) \quad (3)$$

$$\text{subject to } Z_{i,0} = \Theta_i, \Theta_i \in S_{++}^p \text{ for } i = 1, 2, \dots, T$$

$$(Z_{i-1,1}, Z_{i,2}) = (\Theta_{i-1}, \Theta_i) \text{ for } i = 1, 2, \dots, T$$

By applying the scaled dual variable U which has the similar format to the consensus variable Z , the subproblems described in Eq.3 can be solved using Algorithm 1. The TVGL solution using ADMM can be obtained as detailed in Hallac et al.'s work [32]. Through separating the problem described in Eq.1 into two blocks, Θ and Z , converge to the global optimum solutions as guaranteed by this ADMM approach.

C. Description of Sliding Window Technique

As a classical dynamic method, the sliding window technique follows the procedures described by Allen et al. [26]. Now, let us assume that we have n subjects, T time points and p ROIs for each subject ($n, T, p \in \mathbb{N}$). We use a tapered window, which is created by convolving a rectangle with a Gaussian window and sliding in a step of 1 TR. Then, W ($W \in \mathbb{N}$) correlation matrices $\sum_i(w) \in \mathbb{R}^{p \times p}$, $w = 1, 2, \dots, W$, $i = 1, 2, \dots, n$ are extracted from windowed segments for each subject. Following Allen et al.'s work, to characterize full covariance matrices, the regularized inverse covariance matrices ($\sum_i^{-1}(w)$) are estimated using the graphical lasso with the L1 penalty [26]. The penalty parameter λ_s regulates the sparsity level of precision matrices. The estimated covariance matrices ($\sum_i^{L1}(w)$) are then assessed from precision matrices. The sliding window method is illustrated in Fig. 1(b).

Algorithm 1 TVGL algorithm using ADMM

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1: Initialize  $\Theta^0, Z^0, U^0 \in \mathbb{R}^{p \times p}$ 
2: Input regularization parameter  $\rho \in \mathbb{R}$ 
3: for  $k = 0$  to Convergence do
4:  $\Theta^{k+1} := \arg \min_{\Theta \in S_{++}^p} L_p(\Theta, Z^k, U^k)$ 
5:  $Z^{k+1} = \begin{bmatrix} Z_0^{k+1} \\ Z_1^{k+1} \\ Z_2^{k+1} \end{bmatrix} := \arg \min_{Z_0, Z_1, Z_2} L_p(\Theta^{k+1}, Z, U^k)$ 
6:  $U^{k+1} = \begin{bmatrix} U_0^k \\ U_1^k \\ U_2^k \end{bmatrix} + \begin{bmatrix} \Theta^{k+1} - Z_0^{k+1} \\ (\Theta_1^{k+1}, \dots, \Theta_{T-1}^{k+1}) - Z_1^{k+1} \\ (\Theta_2^{k+1}, \dots, \Theta_T^{k+1}) - Z_2^{k+1} \end{bmatrix}$ 
7: end for

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D. Tuning parameter selection

The parameter selection has a consequence on the performance of the approach. The TVGL model defined in Eq.1 includes three key parameters: the number of observation vectors within a segment I_n , the sparsity level of the network λ_t and the correlated level between adjacent networks β . Note that the parameter I_n controls the ability of the TVGL to estimate time-varying changes. Small values of I_n can better estimate the dynamic information. λ_t determines the sparsity level of the network. The smaller the λ_t value is, the better the network matches with the empirical data. However, it will lead to dense networks which are difficult to interpret, β affects how strongly the correlated adjacent estimations should be. As the value of β increases, the estimations of adjacent networks will become smoother over time. For the sliding window technique, two key parameters are involved: the sliding window size l and the sparsity level of the network A_s . As mentioned above, the window size l is crucial for analyzing dynamic networks. The small number of time points within the window has a greater chance to result in inaccuracy and spurious variability [28]. However, a large window may overlook dynamic changes in imaging signals. The regularization term A_s remains the same as the parameter λ_t in the TVGL model.

Since we want to analyze time-varying FC using rs-fMRI dataset, the first step of the parameter selection is to determine which terms affect the representation of the time-varying information. That is, how to select the I_n in the TVGL model and the window size l in the sliding window technique. To better describe dynamic FC using the TVGL, the parameter I_n should be as small as possible. However, by setting the I_n to be 1, functional connectivity cannot be obtained from rs-fMRI data. Thus, in this study, the I_n was set to 2. For the window size l , many previous studies have discussed its selection [10], [26], [30]. We follow their guidelines and will set l to be 30 TR in the real data analysis section.

The regularization terms λ_b , β and λ_s are optimized separately for each subject using the Akaike Information Criteria (AIC). Here, the AIC is defined by:

$$AIC(x) = -\log|\hat{\Theta}(x)| + Tr(\hat{S}\hat{\Theta}(x)) + 2k/m \quad (4)$$

where x is the parameter to be optimized (that is, λ_b , β and λ_s), and $\hat{\Theta}(x)$ is the estimated precision matrix obtained under a specific x . The component S is the empirical matrix, m is the number of observations, and k is the number of nonzero entries in the upper diagonal of $\hat{\Theta}(x)$. Since the optimizations are performed separately for each subject, these regularization terms fluctuate from subject to subject. But both λ_t and λ_s slightly change around the value of 0.01, while β fluctuates around the number of 0.1 to a small extent.

III. RESULTS

In this section, the TVGL model defined in Eq.1 is evaluated and compared with the sliding window technique using both simulated and real datasets. By analyzing dynamic connectivity through precision matrices extracted by the TVGL approach, we estimate the differences between children and young adults. In addition, the transition sequences for these two groups are analyzed.

A. Simulation

1) Simulation Setup: To evaluate the performance of the TVGL model and compare it with the sliding window technique, we first used synthetic dataset. The BOLD time series signals were simulated using the SimTB toolbox provided by Erhardt et al [38]. Signals generated included 50 ROIs for each subject. The time series contained 80 time points and a repetition time (TR) value of 2 seconds for each ROI. The number of components with connectivity patterns was set to 4. The size of each component varied from 4 to 22 ROIs. Each component was activated or inactivated at different time periods, which was represented by a binary value. An example of synthesized components is described in Fig. 2.

2) The Simulation Results: The TVGL model depicted in Eq.1 and the sliding window technique were both evaluated using the synthetic data. For the sliding window method, to illustrate the effect of the window size l , $l=20$ and $l=30$ were used respectively, leading to different results. The other key parameters were set as follows: the number of observations $I_n=2$, the sparsity level $\lambda_t=0.01$, the correlated level $\beta=0.1$ for the TVGL, and the sparsity level $\lambda_s=0.01$ for the sliding window technique. The results are shown in Fig. 3.

Fig. 3(a) displayed the ground-truth of four dynamic connectivity states for the synthetic data. These patterns showed the components varied between the activation ('1', yellow color) and inactivation ('0', blue color) situations corresponding to that illustrated in Fig. 2(b). Analysis results using the TVGL approach, shown in Fig. 3(b), indicated that the TVGL captured the dynamics connectivity within networks in spite of the existence of some small differences.

As shown in Fig. 3(c)–(d), the results demonstrated that the sliding window technique, with an appropriate window size, can also detect time-varying connectivity. However, compared with the sliding window approach, the TVGL worked better and represented the ground-truth more precisely, especially for the fourth connectivity pattern. It should be noted that the performance of the sliding window was greatly affected by the selection of window size. When the window size was unsuitable, dynamic connectivity patterns were not obtained correctly as shown in Fig. 3(d) (the fourth state was lost but one state similar to the second pattern showed up). Furthermore, we compared the error between the ground truth (Fig. 3(a)) and the results estimated by the TVGL (Fig. 3(b)) and the sliding window model (Fig. 3(c)) respectively. Here, we applied the Frobenius norm to determine the relative error, as described below.

$$error = \frac{\|\hat{C}(i) - C_g(i)\|_F}{\|C_g(i)\|_F} \quad (5)$$

where $\|\cdot\|$ is the Frobenius norm, $C_g(i)$ is the ground-truth of the state i and $\hat{C}(i)$ is the matrix estimated by the TVGL or the sliding window model for the state i . To compare the estimation performance between the sliding window and TVGL methods, we repeated the simulations 500 times. For each run, the regularization terms λ_b , β and λ_s were optimized following Equation 4. The window size l and the observations number I_n were equal to 20 and respectively. The difference of estimation error between the sliding window and TVGL based approach was used to make the comparison. By looking at the results in Fig. 3(e), we find that TVGL performs a little better than the sliding window in states 1, 2 and 3 (< 5% error lower in the TVGL than in the sliding window). Nevertheless, for state 4, the TVGL method shows obviously better performance than the sliding window based approach (> 25% error lower in the TVGL than in the sliding window). Then we perform a two-sample t-test on the estimation error calculated from these two approaches and find that in states 1, 2 and 4, the TVGL works significantly better than the sliding window based method (p-value < 0.001). This result supported the statement that the TVGL represented the ground-truth more precisely. Hence, the simulation results illustrated that the estimation using the TVGL can more accurately capture changes in the BOLD time series signal with a better performance than the sliding window based approach.

B. Real dataset analysis

1) Data acquisition and preprocessing: Data used in this work were collected through the Philadelphia Neurodevelopmental Cohort (PNC) project, which was a collaboration between the Brain Behaviour Laboratory at the University of Pennsylvania and the Children's Hospital of Philadelphia [33]. It was available via the dbGaP database including resting state fMRI (rsfMRI) for nearly 900 participants with ages ranging from 8 to 21. Functional images were preprocessed using SPM 12 (<http://www.hl.ion.ucl.ac.uk/spm/>). Preprocessing steps included motion correction, spatial normalization to standard Montreal Neurological Institute (MNI) space and spatial smoothing with a Gaussian kernel (FWHM=3mm). Regression was used to further remove the effect of head motion. A band-

pass filter ranging from 0.01Hz to 0.1Hz was applied to the BOLD time series. Finally, we reduced the dimensionality of the data by employing the standard 264 ROIs template defined by Power et al. with a sphere radius parameter of 5mm. To illustrate connectivity differences as the brain develops, the data were extracted from the full dataset based on the age in months. More precisely, participants whose ages were over 210 months belonged to the young adults group (age 18.98 ± 1.08 years, 240 total participants, 93 male and 147 female), while ages below 150 months were sorted into the children group (age 10.67 ± 1.13 years, 228 total participants, 107 male and 121 female).

2) Postprocessing and results of resting state fMRI data: Dynamic FC patterns were estimated using both the TVGL and the sliding window approaches. Specifically, time-varying FC was analyzed using the TVGL model with the number of observations $I_n = 2$, resulting in 62 precision matrices for each subject. It should be noted that these observations did not overlap between each other. On the other hand, we measured dynamic FC employing a tapered sliding window method with the length of 30 TR, leading to 94 windows based on 1 TR step. The estimated covariance matrices were then computed from windowed segments. To better compare these two approaches through functional relationships within each state, 85 ROIs out of 264 nodes were kept and divided into 5 functional networks based on Power et al's template [18]. These networks contained the sensorimotor network ("SM"), salience network ("SN"), default mode network ("DMN"), visual network ("VIS") and auditory network ("AUD"). Each of these networks are shown in Fig. 4 in terms of functional nodes considered in this work.

To compare these two models in assessing dynamic FC patterns, κ -means clustering using the LI distance function (Manhattan distance) was applied to both precision matrices and the estimated covariance matrices individually. Specifically, correlations between the 85 ROIs were used in the clustering, resulting in $(85 \times (85 - 1))/2 = 3570$ features. Prior to clustering, we estimated the optimal number of dynamic FC states (centroids) employing the elbow criterion defined as the ratio of within-cluster distance to between-cluster distance as shown in Fig. 5. The details are described as follows:

$$ratio = \frac{\sum_{n=2}^{K_1} \sum_{i=1}^N \|P_{i,n} - S_n\|_1}{\sum_{m=2}^{K_2} \sum_{n=2}^{K_1} \sum_{i=1}^N \|P_{i,n} - S_m\|_1} \quad (6)$$

where $P_{i,n}$ is the feature for the subject $i \in \{1, 2, \dots, N\}$, which belongs to the n -th group. S_n and S_m are the centroids for the n -th and m -th groups respectively. Here, $n \in \{1, 2, \dots, K_1\}$, $m \in \{1, 2, \dots, K_2\}$, $K_1 \geq K_2$. In the optimization progress, the parameters K_1 and K_2 range from 2 to 18. We observed that the optimal number of centroids for them was coincident and equal to 6. Subject exemplars were chosen as those matrices with local maxima in FC variance [26]. Initially, κ -means clustering was performed on the set of all subject exemplars. Clustering results were then determined as starting points to initialize the clustering process.

By applying the k-means clustering, 6 dynamic FC states for each method were captured, which reoccurred throughout the scan sessions and across subjects. Fig. 6(A)(a) shows the states estimated by the TVGL approach, while states captured by the sliding method are shown in Fig. 6(A)(b). In Fig. 6(B), the connection condition is used to describe the sparsity level of all the states extracted by these two approaches. There were several interesting discoveries by comparing these two sets of states. In general, dynamic FC states estimated by the TVGL model shared similar patterns to the corresponding states estimated by the sliding window. The similarity between states for each approach decreased in states 1, 3 and 6 in contrast with the others. In addition, states extracted by the TVGL method represented much hner relationships within the functional network. The TVGL results showed that the connectivity within the default mode network was weaker in states 1 and 4 (connection level was below 0.7) than others. Likewise, connectivity within the sensorimotor network was strongest in state 1 (0.53 connection level) and weakest in state 2 (0.26 connection level). Moreover, state 4 from the TVGL model showed that the salience network was positively related with other subnetworks. These patterns cannot be detected utilizing the sliding window technique. Furthermore, in states 1, 3 and 6, the sliding window states revealed that almost all of these hve functional networks were correlated with each other (average connection level was above 0.6). In state 6, calculated by the sliding window, we observed that a large portion of ROIs possessed signihcantly positive connectivity between the sensorimotor and auditory networks (0.17 connection level for the TVGL, 0.87 connection level for the sliding window), as well as the sensorimotor and visual networks (0.07 connection level for the TVGL, 0.39 connection level for the sliding window). These patterns were not detected by the TVGL.

In sum, in Fig. 6, we compared dynamic states estimated between the TVGL and sliding window approaches. Dynamic connectivity states extracted by the two methods showed similar patterns in general. It should be noted that the sliding window approach has already been applied to many related studies and obtained meaningful results [10], [26], [28]. Besides the overall similarity, fihner differences between paired states have been observed as well. By checking the results in Fig. 6, we find that some dense connectivity patterns obtained by the sliding window model disappear in the networks extracted by the TVGL (e.g., in Fig. 6(B), the connection level of many pairs estimated by the TVGL, such as the SM-VIS, SM-AUD, SN-VIS, SN-AUD, VIS-AUD, is significantly smaller compared with the links calculated by the sliding window approach). Likewise, some finer patterns described by the TVGL cannot be detected by the sliding window approach. In the TVGL, the partial correlations are calculated instead of Pearson correlations as used in the window based approach. More importantly, the prior knowledge of the brain network (e.g., sparsity, local temporal transition) is incorporated in the TVGL model, resulting in the extraction of essential characteristics of brain network dynamics. Therefore, we think that the TVGL can reveal the dynamic connectivity patterns more precisely in the brain than the sliding window technique. In addition, it demonstrates that the TVGL model can give sparser solutions relative to the sliding window, facilitating subsequent analysis.

To further validate the TVGL model, group differences in dynamic functional connectivity were considered here. As mentioned in the preprocessing section, we first divided the data into young adults and children. To determine group differences, an element-wise subject

median was computed for each state using each subject's precision matrices [10]. The visualization of medians for each state across these two groups is described in Fig. 7(A). It should be noted that not all subjects showed up in every state, thus the count of observations changed between states. Following the procedures proposed by Elena et al. [39], a univariate analysis was performed on these median matrices, which was described as follows:

$$\tilde{K} = D\beta \quad (7)$$

where $\tilde{K}$ represents the response variables, β is the linear regression coefficient, and D denotes the design matrix consisting of the age subjects. For each $i \in \{1, 2, \dots, n\}$ subject, we transform its subject median matrix $M_i^{p \times p}$ into an one dimensional vector, $K_i^{1 \times p}$ ($p = p \times p$), and concatenate them into the response variables $\tilde{K}$. Then, a two-sample t-test was applied to the regression coefficients extracted from the univariate analysis with a false discovery rate control (significant level $q = 0.001$) to investigate group differences. The results were visualized through plotting the log of p values with the sign of t statistics, $-\text{sign}(t)\log_{10}(p)$.

For the 6 states, significant group differences within functional networks between young adults and children are extracted by the TVGL and shown in Fig. 7(B). To do the comparison, we used the same procedures and then computed the FC with the sliding window approach. The comparative results are presented in Fig. 7(C). Overall, group difference of different states estimated by the TVGL also shared similar patterns with the corresponding states estimated by the sliding window method. However, the patterns are much sparser using the TVGL relative to the window based approach by checking the results in Fig. 7(B–C). The most significant parts were the connectivity between the SM, VIS and AUD subnetworks, as well as the connectivity between the DMN and other subnetworks. It should be observed that in states 1 and 3, young adults had more increased connectivity within the SN subnetworks using TVGL than using the sliding window based approach.

Based on the results from the TVGL, state 5 barely differed between these two groups. As shown in Fig. 7(B), young adults had decreased connectivity in states 2, 3 and 6 between the DMN and other subnetworks. In addition, there was stronger connectivity within the visual network in states 2, 4 and 6 for young adults. In states 2 and 6, young adults also had increased connectivity between the SM, VIS and AUD subnetworks. As age increased, stronger relationships between the VIS and AUD were detected in states 4 and 6. It should be noted that young adults had hypoconnectivity within the SN system in states 2, 4 and 6, whereas in states 1 and 3 age had a positive effect on the correlation between the SN and AUD.

In addition to identifying FC differences between two groups, we also examined state transition behaviours. Beyond clustering centroids, we can also determine which precision matrix was sorted into which state using the k-means clustering analysis. Here, the transition sequence was considered as a Markov chain (MC) system and its corresponding transition probability was estimated. Average transition matrices for the two groups are displayed in Fig. 7(D)–(E). Each square represents the transition probability from one state to another. In Fig. 7(D)–(E), the warmer color demonstrates that a specific state has a higher probability to

be entered in relative to the cooler colors. The diagonal elements reveal that each state for these two groups had a very high chance to remain unchanged. By looking at off-diagonal elements, we observed that functional connectivity within young adults was more inclined to transition from one state to another than in children. Otherwise, the average transition matrices for both groups were approximately symmetric. In other words, the transition probability from state i to state j was similar to the probability from state j to state i ($i, j \in (1, 2, 3, 4, 5, 6)$).

IV. DISCUSSION

Of particular note, fused penalty based models have been widely applied to estimate the dynamic network connectivity in the brain [40], [41], [42], [43]. However, the fused lasso regularization proposed by Wee et al. [40] and the smooth incremental graphical lasso estimation (SINGLE) algorithm introduced by Monti et al. [41] essentially used the sliding window to estimate the dynamic information. Thus, these models still have the same limitation as the window based approach. Although the sticky weighted time-varying model (SWTV) and the group-fused graphical lasso method offer better solution, they have to estimate the temporal bandwidth parameter to describe the connectivity dynamics similar to the sliding window algorithm [42], [43]. In contrast, the TVGL defined by Hallac et al. can assess the network with a “window-less approach” and it works even when the observation interval is only one time point [32]. Hence, we applied the TVGL in this work. This data-driven approach was extended from the traditional graphical lasso model. We validated the feasibility of the TVGL model and compared it with the sliding window technique using simulated experiments. We then optimized the key parameters and applied it to the analysis of rs-fMRI from the PNC data. In particular, group differences between young adults and children, and state transition behaviours were assessed, unveiling the developmental trajectory of different age groups.

Our simulated experiments illustrated that the TVGL model was able to precisely capture the time-varying connectivity patterns. By comparing with the sliding window based technique, we found that the TVGL can represent the dynamic changes in fMRI signal more accurately. The performance of the sliding window approach was clearly affected by the selection of window size. However, the TVGL model did not have such limitations, while some penalty parameters still need to be set (e.g., λ_t and β). These experiments demonstrated the robustness of the TVGL model.

To further compare the TVGL model with the sliding window technique, both were used to assess dynamic FC using rs-fMRI data from the PNC (with a relatively large sample size, $n = 468$). Dynamic FC states extracted by the TVGL model shared overall similarity to the states estimated by the sliding window method. Note that the sliding window has been utilized in many dynamic FC studies with significant findings [10], [26], [28]. These similar dynamic FC patterns remain with the use of the TVGL model. However, finer differences between paired states were observed. Specifically, under the same sparsity level, states given by the TVGL were much sparser than those provided by the sliding window approach. For example, the connection level for the connectivity pair SM-AUD in state 6 calculated by the TVGL was below 0.2, but was around 0.9 for the result from the sliding window approach.

Furthermore, the TVGL uncovered many fine relationships between different functional networks whereas these were absent from the sliding window. We think that these discrepancies relate to two inherent methodological differences. First, the TVGL estimates precision matrices in a more rigorous way that can better capture the crosstime correlation. In addition, the number of observations I_n is equal to 2 time points, which is much smaller than the sliding window size $l = 30$. Because of these characteristics, we believe that the TVGL model is more appropriate for seizing time-varying variations than the sliding window based technique.

In particular, both models were used to investigate the difference between young adults and children. We observed that group difference at different states for these two approaches also shared similar patterns as above. However, the FC networks for different states estimated by the TVGL were much sparser than those by the sliding window approach. More specifically, connectivity patterns between the SM, SN and AUD subnetworks as well as the connectivity between the DMN and other subnetworks assessed by the sliding window method were significantly denser than using the the TVGL approach. This may indicate that the TVGL model tends to give a more compact representation of brain FC networks. In addition, stronger connectivity within the SN for young adults can only be uncovered by the TVGL approach. We believe this indicates that the TVGL can better capture the change of temporal signals than the sliding window model. For the dynamic networks estimated by the TVGL, we found that there were FCs existed in almost all states for both classes. This suggests that FC networks do not change drastically, but rather gradually with brain development. This finding is in line with several previous studies [4], [44], [45]. We also observed that young adults had decreased connectivity between the DMN and other four networks. Hutchison et al. showed that age was negatively correlated with FC between the DMN and cognitive systems, which confirmed our findings [2]. We believe that these differences indicate functional networks in children are less specialized or efficient in processing information [44]. Thus, some complex cognitive or emotional processes may contain redundant links within the brain. In addition, young adults had stronger connectivity within the visual network for states 2, 4 and 6. Interestingly, many studies employing other approaches reached the same conclusion [3], [4], [25], which further support the results. In addition, our finding suggests that basic functions in the brain, such as the visual function, may have a different developmental trajectory relative to the complex cognitive or emotional processes. Young adults also showed increased FC between the SM and VIS, AUD subnetworks in states 2,4 and 6. This phenomenon is in agreement with the finding that the brain circuitry moves from segregation to integration as age increases [39], [46], [47]. Finally, hypoconnectivity within the SN and hyperconnectivity between the SN and AUD were also observed, which were in accordance with the results from several existing studies [48], [49].

By assessing the transition behaviours of states for both young adults and children, we also have some interesting discoveries. First, all functional connectivity states tended to remain unchanged across the age range. Second, young adults had a higher probability to transition from one state to another than children. This finding may suggest functional connectivity changes from segregation to integration as the brain develops with age. Several other studies have supported this point [44], [45].

Today, the most common way for extracting the connectivity dynamics in rsfMRI is the sliding window based approach. However, it is using the static connectivity assumption, and how to optimize the window size is still an open problem. Compared with the sliding window based model which investigates the connectivity from a relatively extended period (typically, 30–50 TR), the TVGL framework can analyze the dynamic patterns within a small time period (at least 1 TR). Hence, we believe that the TVGL can capture the connectivity dynamics more precisely. Furthermore, with sparsity enforcement, the analysis using the TVGL will describe the sparse connectivity networks. Both simulated and real data experiments support our points, and the results estimated by the TVGL do lead to novel findings discussed above, which are also concordant with some previous studies.

One potential limitation in our framework is the use of Laplacian penalty. While inferring the networks along time, we consider that FC changes in a smooth mode. In this way, big deviations of FC between adjacent time points are largely penalized so they rarely occur. Hence, abrupt variations within networks are suppressed. The TVGL model can utilize other penalty functions (e.g., infinite penalty, l_∞) to address this problem, but it is hard to balance the smooth transition and sudden change in model selection. In addition, we can modify the TVGL model with other regularization terms, such as generalized fused lasso, to highlight networks with significant differences between two groups.

V. CONCLUSION

We applied an approach named the time-varying graphical lasso (TVGL) to investigate dynamic brain FC using rs-fMRI data from children. Both simulated and real data were used to validate the TVGL model, and its performance relative to the sliding window technique was also compared. The results demonstrated that the TVGL model can capture dynamic FC in finer detail and can better reveal the correlation between different time series compared to the sliding window based approach. Furthermore, dynamic FC differences between young adults and children were compared between the TVGL model and the sliding window method. The results showed that the TVGL was able to give a more compact representation of connectivity patterns in the human brain, and show significant differences between two age groups. There were some interesting findings based on the results assessed by the TVGL. These findings were further supported by many existing studies. In particular, by analyzing transition behaviours, we observed that young adults had a higher probability of transition from one state to another in contrast with children. This finding demonstrates that with brain development, FC gradually moves from segregation into integration. In summary, the proposed TVGL model is a more powerful tool to evaluate dynamic FC than the sliding window method, which can find widespread applications to brain network analysis in neuroimaging [10], [50], [51].

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Fig. 1.

An illustration of the time-varying graphical lasso (TVGL) approach (a) and the sliding window technique (b). The TVGL framework in (a) is described by Eq.1. For the sliding window method in (b), dynamic $FC(\Sigma_i^{L1}(w))$ is estimated as a sequence of regularized covariance matrices within the window.

Fig. 2.

A demonstration of the synthesized data generated by the SimTB toolbox [38]. (a)

Components map for a given run (b) Activation map for components along time courses.

Note that the “1” here denotes the existence or activation and “0” means the nonexistence or inactivation.

Fig. 3.

Analysis results for the simulated data using both the TVGL and sliding window approaches, (a) Ground-truth of dynamic connectivity states for the simulated data (b) Estimated connectivity states with the TVGL model (c) Estimated connectivity states with the sliding window using an appropriate window size ($l = 20$) (d) Estimated connectivity states with the sliding window using an inappropriate window size ($l = 30$) (e) Results from the 500 simulations to analyze the difference of estimation error between the sliding window and TVGL based methods. The bar plot shows the mean and standard deviation of the difference of estimation error for all the states. Asterisks indicate $p < 0.001$ as obtained via two-sample t-test.

Fig. 4.

Five functional networks considered in this work. These networks were expressed in the 264 nodes of the template defined by Power et al.[18], SM: Sensorimotor Network, SN: Salience Network, DMN: Default Mode Network, VIS: Visual Network, AUD: Auditory Network.

Fig. 5. The selection of the number of k-means clustering centroids using the elbow criterion, (a) Optimization for the TVGL model; (b) Optimization for the sliding window technique.

Fig. 6.

A) A comparison of dynamic FC states estimated by the TVGL model (a) and the sliding window approach (b)(z-score). Connectivity states evaluated by the TVGL had sparser structure while also shared similarity to the corresponding states by the sliding window based approach. Finer differences between these states from each approach also remained. B) Sparsity level for each state evaluated by these two methods is described using the connection condition. The connection level in each region is defined as: (positive connection number + negative connection number)/whole connection number (range from 0 to 1). Here, the positive connection number or negative connection number refers to the number of positive or negative values in the specific region of the connectivity pattern (e.g. for the state 1 extracted by the sliding window, in the region of SM-SM, the positive, negative and whole connection number is 332, 48 and 400 respectively). Note that the connectivity link, for

which the absolute value of z-score is above 0.5, is considered as the effective connection. The smaller the connection level is, the sparser the region is.

Fig. 7.

A) The medians of cluster centroids for young adults (YA, top) and children groups (CH, bottom), with the count of subjects which had at least one window for each state. Note that not all subjects entered all states during the scanning time period. Thus, the number of subjects for these two groups stayed at each state was below the total number (240 for young adults group and 228 for children group). B-C) Group differences were visualized by plotting the log of p value with the sign of t statistics, $-\text{sign}(t)\log_{10}(p)$. A two-sample t-test was performed across subject median dynamic FC maps by state, with the FDR corrected ($q < 0.001$). D-E) The state transition matrix for each group was averaged over subjects. The transition probability between two states ranging from 0 to 1 was displayed on a log-scale in this map.