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IDENTIFYING PATTERNS IN TEMPORAL VARIATION OF FUNCTIONAL CONNECTIVITY USING RESTING STATE FMRI

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Abstract

Estimating functional brain networks from fMRI data has been the focus of much research in recent years. Low sample sizes (time-points) and high dimensionality of fMRI has restricted estimation to a temporally averaged connectivity matrix per subject, due to which the dynamics of functional connectivity is largely unknown. In this paper, we propose a novel method based on constrained matrix factorization that addresses two major issues. Firstly, it finds a set of basis networks that are the semantic parts of the time-varying whole-brain functional networks. The whole-brain network at any point in time, for any subject, is a non-negative combination of these basis networks. Secondly, significant dimensionality reduction is achieved by projecting the data onto this basis, facilitating subsequent analysis of temporal dynamics. Results on simulated fMRI data show that our method can effectively recover underlying basis networks. We apply this method on a normative dataset of resting state fMRI scans. Results indicate that the functional connectivity of a subject at any point during the scan is composed of combinations of overlapping task-positive/negative pairs of sub-networks.

Index Terms

resting state fMRI; functional connectivity; temporal network dynamics

1. INTRODUCTION

The human brain is known to be a dynamic network of functionally connected regions, continually relaying and processing information, even at rest. Given that a typical resting state fMRI scan is several minutes long and lacks any stimulus, it is reasonable to expect that functional connectivity undergoes substantial changes due to underlying cognitive processes. Averaging inter-regional correlation across the entire span of the scan discards important information about the organization of sub-networks and the interactions between them. Recent work in [1][2] have demonstrated that the correlations are highly dynamic. However, the nature of this variation remains unknown.

High dimensionality of the data and low sample sizes prevent robust estimation of a temporal sequence of correlation matrices per subject. However, it is reasonable to assume that there is some amount of redundancy within these matrices, and this can be exploited to perform dimensionality reduction. While standard matrix factorization methods like PCA and ICA are able to achieve dimensionality reduction, the resulting bases are not generally meaningful. In this paper we present a novel data-driven method which is able to separate correlation matrices into clinically interpretable basis networks. Our approach uses constrained matrix factorization, which is increasingly being used in data analysis, as the

right assumptions about underlying structure of the data can yield a basis with a reasonable interpretation.

2. APPROACH

The input to our method is a set of (noisy) correlation matrices from each subject. In order to understand temporal variations in the correlation, these matrices are sampled at various time-scales, by embedding our method in a hierarchical window framework. If T is the total number of time-points per subject, we compute one correlation matrix from all the T time-points, two from $T/2$, four from $T/4$, and so on. Thus, every *parent* window is split into two *child* windows. Let $\mathbf{x}_i$ denote the vectorized, upper triangular part of the correlation matrix obtained from window i . Then the data matrix is $\mathbf{X} = [\mathbf{x}_1, \mathbf{x}_2, \dots, \mathbf{x}_{NW}] \in \mathbb{R}^{R^2/2 \times NW}$, where R is the number of ROIs, N is the number of subjects and W is the total number of windows per subject.

The goal is to find a set of K basis vectors, denoted by matrix $\mathbf{B} = [\mathbf{b}_1, \mathbf{b}_2, \dots, \mathbf{b}_K] \in \mathbb{R}^{R^2/2 \times K}$, and corresponding coefficients, represented by matrix

$\mathbf{C} = [\mathbf{c}_1, \mathbf{c}_2, \dots, \mathbf{c}_{NW}] \in \mathbb{R}_+^{K \times NW}$, such that $\mathbf{X} \approx \mathbf{BC}$. We also note that each time the window size halves, the correlation estimate gets noisier, i.e, its variance increases. If we assume the approximation error follows a Gaussian distribution, then we allow

$p(\mathbf{x}_i | \mathbf{B}, \mathbf{c}_i) \sim \mathcal{N}(\mathbf{Bc}_i, \frac{1}{|w_i|^2} \mathbf{I})$, where $|w_i|$ is the length of window i and $\mathbf{I}$ is the identity matrix. We would like to find the values of the parameters $\mathbf{B}$ and $\mathbf{C}$ that maximize the

likelihood of the data, which amounts to minimizing $\sum_{i=1}^{NW} |w_i|^2 (\mathbf{x}_i - \mathbf{Bc}_i)^T (\mathbf{x}_i - \mathbf{Bc}_i)$. This is the same as $\text{trace}((\mathbf{X} - \mathbf{BC})^T \mathbf{W}(\mathbf{X} - \mathbf{BC}))$ where $\mathbf{W}$ is a diagonal matrix of weights $|w_i|^2$ and $\text{trace}(\cdot)$ denotes matrix trace.

In order to make the resulting factorization clinically interpretable, we constrain the matrices $\mathbf{B}$ and $\mathbf{C}$ as follows:

Constraints on the basis vectors

For the elements of the basis vectors $\mathbf{b}_j$ to be valid correlations, they must lie in the interval $[-1, 1]$. In addition, we would like each basis to consist of relatively small network configurations, that form the “parts” of the whole-brain network, and are repeatedly used in time and across subjects. This requires that the basis be sparse, and can be achieved by constraining the l_1 norm of each basis vector to be small.

Constraints on the coefficients

As described above we would like to represent each “network” $\mathbf{x}_i$ by a linear combination $\mathbf{c}_i$ of basis networks $\mathbf{B}$. For ease of clinical interpretability, we will enforce two constraints on $\mathbf{c}_i$; (1) non-negativity, i.e, $\mathbf{c}_i \geq 0$ and (2) summation to one, i.e, $\sum_j \mathbf{c}_{ij} = 1$. Thus every element of vector $\mathbf{c}_i$ denotes the relative *proportion* that the corresponding basis vector contributes to $\mathbf{x}_i$.

An additional constraint we would like to impose on $\mathbf{C}$ at the single subject level is that of *temporal consistency*. The dependence in the observations between a parent window p and

its child windows q and r is enforced in their corresponding coefficients, i.e, $\mathbf{c}_p \approx \frac{1}{2}\mathbf{c}_q + \frac{1}{2}\mathbf{c}_r$. This is a linear constraint in the coefficients, and there are as many constraints per subject as there are parent windows. Collecting the coefficients across all these linear constraints into a large matrix $\mathbf{A}$, this constraint amounts to minimizing $\|\mathbf{CA}\|_{F^*}^2$.

Bringing all the constraints together, we are faced with the optimization problem:

$$\underset{\mathbf{B}, \mathbf{C}}{\text{minimize}} \text{trace}((\mathbf{X} - \mathbf{BC}))^T \mathbf{W}(\mathbf{X} - \mathbf{BC}) + \lambda_1 \|\mathbf{CA}\|_F^2 \text{ subject to } \begin{aligned} & -1 \leq \mathbf{b}_k \leq 1, \quad \|\mathbf{b}_k\|_1 \leq \lambda_2, \quad k=1, \dots, K \\ & \mathbf{c}_i \geq 0, \quad \sum_{j=1}^K \mathbf{c}_{ij} = 1, \quad i=1, \dots, NW \end{aligned}$$

The objective function of the above problem is jointly non-convex in $\mathbf{B}$ and $\mathbf{C}$. However, if one of the two matrices is already specified, the problem becomes convex. This suggests an iterative optimization strategy that repeatedly solves for one variable (e.g. $\mathbf{B}$) while holding the other fixed (e.g. $\mathbf{C}$) until a local optimum is reached. We will use the spectral projected gradient (SPG) solver with an efficient projection method, similar to the algorithm proposed in [4].

Choice of parameters

The free parameters of the proposed method are the number of basis vectors K , the sparsity level on the basis vectors λ_2 and the temporal consistency parameter λ_1 . We will now briefly discuss the significance of the parameters.

- 1) λ_1 : The temporal consistency constraint ensures that coefficient estimates from the longer windows (which are more robust) contribute towards better estimates for smaller windows. This parameter can be tuned with respect to subsequent analysis of temporal dynamics (for e.g., using Hidden Markov Models to analyze the $\mathbf{C}$ matrix). For the experiments we performed for this paper, we found that using $\lambda_1 = 1$ gave us fairly reliable results.
- 2) λ_2 : This parameter controls the amount of sparsity in the basis network and can be set based on known clinical information, for e.g., the average size of a sub-network, like the default mode network (DMN) or the fronto-parietal network.
- 3) K : If the number of basis vectors is too large, the model *over-fits* the data. To avoid overfitting, and to assess how the results generalize, we will resort to repeated split-sample validation. For every value of K , and at every iteration, the dataset is split into two halves. The model is trained on one half, and using the $\mathbf{B}$ from this half, the optimal value of $\mathbf{C}$ is computed for the second half. The average split-sample error for each K is then averaged across iterations. The optimal number of basis vectors K is chosen to be the smallest value at which the error does not significantly drop.

3. SIMULATION STUDY

We used NetSim[3] to generate time-series data in order to evaluate our method. This software takes as input the underlying network configuration(s) and returns realistic BOLD time series while incorporating neural lag (50 ms), variability in Haemodynamic Response Function (0.5 s) and thermal noise (1% of signal power).

Our simulation consists of 15 nodes arranged in three subnetworks, which are positively correlated within each other. The connections between these three sub-networks vary with time - they are either zero, or negative. The ground truth basis networks are shown in Fig 1 (Values in red indicate positive correlation and blue indicate negative correlation). At any point in time and in any subject, the simulated network is a sparse, non-negative combination of these three basis networks. The basis networks and 50 randomly generated temporal sequences was input to NetSim. This resulted in BOLD time series data for 50 “subjects”, with TR=3 s and 120 time-points each. This was input to our method.

We performed split-sample validation for varying values of $K \in \{1, 2, \dots, 10\}$. For each value of K , the experiment was repeated ten times. λ_1 was fixed at 1 and the sparsity level was set to 20%. Figure 2 shows the split-sample error as K varies. The vertical bars reflect the standard deviation of the error. Observe that there is a significant drop in split-sample error up to $K = 4$ beyond which the error saturates. This suggests that the subsequent bases do not provide the model with new information.

The results of our algorithm for $K \in \{1, 2, 3, 4, 5\}$ are shown in Fig 3. It is evident that our algorithm effectively recovers the network basis. These networks are also interpretable, since these network configurations repeatedly occur in the data across time and across subjects. Observe that for $K = 3$, each time K is increased by one, the method incrementally adds to the previous set of basis networks. It is also interesting to note that for $K > 3$, the same basis networks tend to repeat, albeit with slightly different values. This behavior is highly desirable; no matter which value of K is being used, we are assured of getting valid network configurations.

For comparison, we also ran ICA on the data matrix $\mathbf{X}$. The bottom row in Fig 3 shows the basis output by ICA. Clearly, ICA is unable to find the basis we are looking for; none of these network configurations occur in the data, and are hard to interpret.

4. APPLICATION TO FMRI

4.1. Data and preprocessing

BOLD fMRI was acquired (TR/TE = 3000/32 ms, voxel resolution = $3 \times 3 \times 3$ mm and number of timepoints = 120) on 100 normal participants, aged 8–21 years old (mean 15.9 years, stdev 3.3 years). Functional images were slice-time corrected, motion corrected, spatially smoothed (6mm FWHM, isotropic) and temporally altered to retain frequencies 0.01–0.1 Hz. Several sources of confounding variance, including six motion parameters, mean white matter time-course, mean CSF timecourse, and mean whole-brain time-course were regressed out. The residual time courses for each subject was co-registered with the anatomical image and transformed to standard MNI anatomical space.

We used 160 regions of interest (ROIs) recently described by Dosenbach et al. [5], which were derived from a meta-analysis of a large sample of task-based fMRI studies. Each ROI was a non-overlapping 10mm diameter sphere, and was categorized as belonging to one of six sub-networks: defaultmode, cingulo-opercular, fronto-parietal, sensorimotor, occipital, or cerebellar. The mean time-series at each ROI were extracted from the registered fMRI image. This was input to our method.

The variation of split-sample validation error with respect to parameter K is shown in Fig. 5. We fixed the sparsity level of the basis networks at 20%, and λ_1 was set to unity, as before. Observe that drop in error is fairly rapid up to $K = 10$, but far more gradual after that. The basis networks found using $K = 10$ were ranked in descending order with respect to how often they occurred (mean of the rows of $\mathbf{C}$ matrix). Fig. 4 shows the top three basis networks.

The most frequently occurring network configuration is revealed by the first basis network in Fig. 4. This basis shows that two sub-networks - the occipital and cerebellar sub-networks are 'on' at the same time, and are both anticorrelated with a small part of the default mode network (bi-lateral anterior, medial, ventro-medial and ventro-lateral pre-frontal cortex). Similarly, observe that the second basis is mainly the anti-correlation between the sensorimotor network with the DMN. The third basis shows anti-correlation between cingulo-opercular/sensorimotor networks and the DMN.

We also report that the resulting c_i coefficient vectors corresponding to individual time-points are sparse (not shown). The average sparsity level is around 50%, suggesting that only few of the basis networks are active in the brain at any given point in time.

5. CONCLUSION

Our basis learning formulation allows us to obtain sparse and overlapping components without having to use strong constraints like orthogonality or independence of the basis [6]. The basis networks show that the functional brain is a dynamic system consisting of pairs of anti-correlated task-positive/negative sub-networks that repeatedly occur in time and across subjects. Temporal dynamics of connectivity is encoded in the coefficient vectors in matrix **C**. These vectors are of a much lower dimension, and therefore are more amenable for working with complex models.

We hope to further our research in this direction by analyzing the basis networks in much greater detail. We will also model the temporal variations in matrix **C** using Hidden Markov Modeling. This will allow us to obtain subject-specific measures which can be used for analysis in population studies. This will pave the way towards creating resting state fMRI biomarkers that can predict disease-related phenotypes.

REFERENCES

1. Handwerker DA, Roopchansingh V, Gonzalez-Castillo J, Bandettini PA. Periodic changes in fmri connectivity. *NeuroImage*. 2012; vol. 63(no. 3):1712–1719. [PubMed: 22796990]
2. Chang C, Glover GH. Time-frequency dynamics of resting-state brain connectivity measured with fmri. *Neuroimage*. 2010; vol. 50(no. 1):81–98. [PubMed: 20006716]
3. Smith SM, Miller KL, et al. Network modelling methods for fmri. *Neuroimage*. 2011; vol. 54(no. 2):875–891. [PubMed: 20817103]
4. Batmanghelich NK, Taskar B, Davatzikos C. Generative-discriminative basis learning for medical imaging. *Medical Imaging, IEEE Transactions on*. 2012; vol. 31(no. 1):51–69.
5. Dosenbach NUF, Fair DA, Miezin FM, Cohen AL, et al. Distinct brain networks for adaptive and stable task control in humans. *Proceedings of the National Academy of Sciences*. 2007; vol. 104(26):11073.
6. Smith SM, Miller KL, et al. Temporally-independent functional modes of spontaneous brain activity. *Proceedings of the National Academy of Sciences*. 2012; vol. 109(no. 8):3131–3136.

Fig. 1.

Simulated data: Ground truth correlation matrices (left) was input to NetSim[3]. The resulting time-series form the input to our method.

Fig. 2.
Split-sample validation error for simulated data

Fig. 3.
 (Top) Basis networks output by our method for $K \in \{1, 2, 3, 4, 5\}$. (Bottom) ICA components for $K=5$

Fig. 4. Top three basis networks found using resting state fMRI data. The ROIs are sorted according to their Dosenbach[5] network labels.

Fig. 5.
Split-sample validation error for resting state fMRI data