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GROUP SPARSE DICTIONARY LEARNING AND INFERENCE FOR RESTING-STATE FMRI ANALYSIS OF ALZHEIMER'S DISEASE

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ABSTRACT

A novel group analysis tool for data-driven resting state fMRI analysis using group sparse dictionary learning and mixed model is presented along with the promising indications of Alzheimer's disease progression. Instead of using independency assumption as in popular ICA approaches, the proposed approach is based on the sparse graph assumption such that a temporal dynamics at each voxel position is a sparse combination of global brain dynamics. In estimating the unknown global dynamics and local network structures, we perform sparse dictionary learning for the concatenated temporal data across the subjects by constraining that the network structures within a group are similar. Under the homoscedasticity variance assumption across subjects and groups, we show that the mixed model group inference can be easily performed using second level GLM with summary statistics. Using extensive resting fMRI data set obtained from normal, Mild Cognitive Impairment (MCI), Clinical Dementia Rating scale (CDR) 0.5, CDR 1.0, and CDR 2.0 of Alzheimer's disease patients groups, we demonstrated that the changes of default mode network extracted by the proposed method is more closely correlated with the progression of Alzheimer's disease.

Index Terms— Resting state fMRI, sparse dictionary learning, inference, mixed model, Alzheimer's disease

1. INTRODUCTION

Data driven analysis methods including independent component analysis (ICA) [1] are well suited for studying resting state fMRI data [2], since there is no pre-defined paradigm for resting state brain. It is now well-known that these methods can extract default mode network (DMN) from resting state brain. In humans, the default network has been considered to generate spontaneous thoughts at rest and has been hypothesized that weakening DMN may be related to certain disorders including Alzheimer's disease, autism, and schizophrenia [3]. However, as the concept of brain functional connectivity can only be reasonable based upon certain level of dependence between signals in the brain, algorithms such as ICA based on the independence of signals may have fundamental limitations in analyzing brain connectivity. More interestingly, it has been demonstrated that the success of ICA for resting state data analysis is due to their ability to handle sparse components rather than independent components [4]. Inspired by these findings, our group has developed a data driven fMRI analysis method called *sparse SPM* using sparse dictionary learning that extract data-dependent regressors, and have demonstrated excellent activation detection in individual analysis in fMRI experiments [5].

However, one of the technical difficulties in data-driven approach like sparse SPM is that the extracted temporal dynamics corresponding to each DMN highly depends on each individual. Moreover, the individual dependent regressors should be estimated at the same time while the group level statistical inferences should be performed using the subject specific regressors. This makes the group sparse learning and statistical inference complicated. Similar difficulties have been observed in other data driven approaches such as ICA. In group ICA, the problem has been addressed using concatenating the data or using tensor factorization. However, while group wise activation maps can be detected using these type of approaches, more advanced group analysis like two-sample t-test, or analysis of variance (ANOVA) are often difficult to explain in a unified framework.

In this paper, to overcome such limitation in group analysis, we propose a unified mixed model framework where a group level sparse dictionary learning and group inference can be performed in a unified linear mixed model framework. More specifically, under the homoscedasticity variance assumption across subjects and groups, which are often used in SPM, we show that group sparse dictionary learning can be performed using K-SVD [6] for concatenated data and the group inference is equivalent to the inference using summary statistics. To validate the proposed method, we compared DMN changes among normal, MCI, CDR 0.5, CDR 1.0 and CDR 2.0 of patients with Alzheimer's disease groups. Through this, we expect our proposed method would show the disease progression signatures, which clearly indicates that the results using the proposed method are closely correlated with clinical progression.

2. THEORY

2.1. Group Sparse Dictionary Learning

In Sparse SPM [5], the interactions of neural signal between brain's functional systems are modeled by a set of nodes (voxels) linked by connections as shown in Fig. 1. Each circle denotes voxel or node where a temporal dynamics of BOLD signal is measured continuously. A set of nodes in functional brain network form a community sharing same information flows in addition to long-range connections from different communities. For example, in Fig. 1, time series at the node 1 and 2, denoted by $\mathbf{y}_1 \in \mathbb{R}^m$ and $\mathbf{y}_2 \in \mathbb{R}^m$, is given by

$$\mathbf{y}_1 = 3\mathbf{d}_1 + \mathbf{d}_3 + \mathbf{d}_4, \quad \mathbf{y}_2 = 4\mathbf{d}_2 + \mathbf{d}_4 + \mathbf{d}_5 \, .$$

If we define a global dictionary D by collecting all local or long-range information flows as

$$D = [\mathbf{d}_1, \mathbf{d}_2, \cdots, \mathbf{d}_5] \, ,$$

then we can easily see that the temporal dynamics at the nodes 1 and 2 are described as a *sparse* linear combination of the atoms in the global design matrix. In general, we have

$$\mathbf{y}_n \quad = \quad D_{I_n}\mathbf{x}_{I_n} + \boldsymbol{\varepsilon}_n, \; n = 1, \cdots, N \qquad (1)$$

where $\boldsymbol{\epsilon}$ denotes noise, $D_{I_n} \in \mathbb{R}^{m \times k}$ is a submatrix of D composed of elements in the index set I_n, and $\mathbf{x}_{I_n} \in \mathbb{R}^k$ denotes the corresponding weight vectors. Note that a local subset index I_n represents a local network structure at the n-th voxel, and a regressor is a representative dynamics in a network module or community that shares the same information flow.

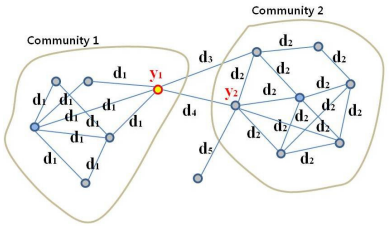


Fig. 1. A graph theoretical model for Sparse SPM.

For sparse dictionary learning from L subjects within a group, we perform sparse dictionary learning using the concatenated times series from multiple subjects. More specifically, suppose $Y^{(l)} = [\mathbf{y}_1^{(l)}, \cdots, \mathbf{y}_N^{(l)}]$ denotes a collection of time trace across all N voxels, then we construct a concatenated temporal time trace from L subjects across all voxels $Y = [Y^{(1)T}, \cdots, Y^{(L)T}]^T$. Then, K-SVD algorithm [6] decomposes the concatenated data Y as following:

$$Y \equiv \begin{bmatrix} Y^{(1)} \\ \vdots \\ Y^{(L)} \end{bmatrix} = DX = \begin{bmatrix} D^{(1)} \\ \vdots \\ D^{(L)} \end{bmatrix} [\mathbf{x}_1, \cdots, \mathbf{x}_N] \qquad (2)$$

where D denotes the concatenated global sparse dictionary and $D^{(l)}$ denotes the corresponding l-th subject individual sparse dictionary, and X is the corresponding coefficients. Once the dictionary D is obtained, the individual dictionary $D^{(l)}$ is normalized such that each column has unit norm.

Recall that in K-SVD, the i-th column of D represents the first principle component of the set of temporal dynamics at the voxel locations that have non-zero coefficients in the i-th row of X. Hence, the i-th column of resulting individual dictionary $\{D^{(l)}\}_{l=1}^L$ share the same geometric connectivity. Hence, if we assume that the local design matrix index I_n is same across all subjects, it implies that our sparse learning rule is imposing the constraint that local network structure within a group is same. This learning rule is very advantageous to identify the group differences since the network connectivity changes between groups are one of the main biomarkers in resting-state fMRI analysis.

2.2. Group Analysis using Mixed Model

Suppose we are interested in comparing a different groups. Once the group sparse dictionary learning is performed, the temporal dynamics at the n voxel of the subject l in the i-th group model is modeled as

$$\mathbf{y}_n^{(il)} = D^{(il)}_{I_n^{(i)}}\mathbf{x}^{(il)}_{I_n^{(i)}} + \boldsymbol{\epsilon}_n^{(il)}, \quad \boldsymbol{\epsilon}_n^{(il)} \sim \mathcal{N}(\mathbf{0}, R_n^{(il)}) \qquad (3)$$

where $i = 1, \cdots, a, \; l = 1, \cdots, L_i$ denote the indices for group and the subject index for each group, respectively, and L_i is the number of subjects for the group i. Now, the subject differences within a group can be modeled as random effects:

$$\mathbf{x}^{(il)}_{I_n} = \boldsymbol{\alpha}_n^{(i)} + \boldsymbol{\beta}_n^{(il)}, \quad \boldsymbol{\beta}_n^{(il)} \sim \mathcal{N}(\mathbf{0}, G_n), \qquad (4)$$

where $\boldsymbol{\alpha}_n^{(i)}$ denote a group mean. Hence, if we stack the data together, (after ignoring the voxel dependent index n), we have the following mixed model

$$\mathbf{y} = X\boldsymbol{\alpha} + Z\boldsymbol{\beta} + \boldsymbol{\epsilon} \, , \qquad (5)$$

where

$$\begin{aligned} \mathbf{y} &= [\mathbf{y}_n^{(11)T}, \mathbf{y}_n^{(12)T}, \cdots, \mathbf{y}_n^{(1L_1)T}, \cdots, \mathbf{y}_n^{(2L_2)T}]^T \in \mathbb{R}^M \\ \boldsymbol{\alpha} &= [\boldsymbol{\alpha}^{(1)T}, \boldsymbol{\alpha}^{(2)T}]^T \in \mathbb{R}^p \\ \boldsymbol{\beta} &= [\boldsymbol{\beta}_n^{(11)T}, \boldsymbol{\beta}_n^{(12)T}, \cdots, \boldsymbol{\beta}_n^{(1L_1)T}, \cdots, \boldsymbol{\beta}_n^{(2L_2)T}]^T \in \mathbb{R}^q \end{aligned}$$

and the random effect matrix Z is given by

$$Z = \begin{bmatrix} D^{(11)}_{I_n^{(1)}} & 0 & \cdots & 0 \\ 0 & D^{(12)}_{I_n^{(1)}} & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & D^{(2L_2)}_{I_n^{(2)}} \end{bmatrix} ,$$

and the fixed effect matrix is

$$X = ZX_G, \quad X_G = \begin{bmatrix} \mathbf{1}_{L_1} \otimes I & 0 \\ 0 & \mathbf{1}_{L2} \otimes I \end{bmatrix} .$$

Then, using the standard results for the solution of mixed model, the fixed effect parameter estimate $\hat{\boldsymbol{\alpha}}$ from the mixed

model is equivalent to the second level GLM using the summary statistics

$$\hat{\boldsymbol{\chi}} = X_G\boldsymbol{\alpha} + \boldsymbol{\eta}, \quad \boldsymbol{\eta} \sim \mathcal{N}(\mathbf{0}, V_G). \tag{6}$$

where $\hat{\boldsymbol{\chi}} = [\hat{\mathbf{x}}_{I_n^{(1)}}^{(11)T}, \hat{\mathbf{x}}_{I_n^{(1)}}^{(12)T}, \cdots, \hat{\mathbf{x}}_{I_n^{(1)}}^{(1L_1)T}, \cdots, \hat{\mathbf{x}}_{I_n^{(2)}}^{(2L_2)T}]^T$ and

$$\hat{\mathbf{x}}_{I_n^{(i)}}^{(il)} = \left(D_{I_n^{(i)}}^{(il)T} R^{-(il)} D_{I_n^{(i)}}^{(il)}\right)^{-1} D_{I_n^{(i)}}^{(il)T} R^{-(il)} \mathbf{y}_n^{(il)} \tag{7}$$

Under the assumption that $G_n = g_n^2 I$, V_G is a block diagonal matrix whose (il)-th block is composed of

$$\left(D_{I_n^{(i)}}^{(il)T} R^{-(il)} D_{I_n^{(i)}}^{(il)}\right)^{-1} + g_n^2 I. \tag{8}$$

2.3. Group Inference

In practice, the covariance component $R^{(il)}$ and $G_n = g_n^2 I$ need to be estimated. A rigorous way of doing covariance estimation is using restricted maximum likelihood (ReML) method. However, ReML is usually computationally expensive. Moreover, transferring the individual design matrix $D_{I_n^{(i)}}^{(il)}$ to the second level analysis is computationally demanding and memory intensive, since the design matrix is spatially and individually varying. To simplify the covariance estimation and the resulting inference, we first approximate that $D_{I_n^{(i)}}^{(il)T} D_{I_n^{(i)}}^{(il)} \simeq I$. Since each individual dictionary is normalized to have unit norm, this implies that each regressors are nearly orthogonal. If the assumption does not hold, the contrast can be correlated, but we can still obtain meaningful inferences as discussed in existing SPM. Next, we assume that the noise in individual temporal dynamics is white, i.e. $R_n^{(il)} = \sigma_n^{(il)2} I$. This can be easily satisfied using prewhitening procedure. Finally, we employ the homoscedasticity variance assumption across subjects and groups, i.e. $\sigma_n^{(ij)2} = \sigma_n^2$, which has been also often used in SPM.

Another important advantages of these approximation is that the proposed group sparse dictionary learning can be shown as maximum likelihood estimation framework with the unified mixed model. Moreover, as described in the following, the group level inference can be significantly simplified. More specifically, in group inference, we are interested in testing the following null hypothesis:

$$H_0 : C\boldsymbol{\alpha} = \mathbf{0},$$

where $C \in \mathbb{R}^{p_1 \times p}$ denotes the contrast matrix. Since $(X^T V^{-1} X)^- = (X_G^T V_G^{-1} X_G)^-$, the test statistics for the mixed model is equivalent to the second level inference statistics:

$$\mathcal{S} \;=\; \hat{\boldsymbol{\alpha}}^T C^T \left(C(X_G^T \hat{V}_G^{-1} X_G)^- C^T\right)^{-1} C\hat{\boldsymbol{\alpha}}/p_1 \,.$$

Now, under the aforementioned assumptions, we can show that $\hat{V}_G$ is diagonal matrix, hence using simple matrix manipulations, we can show that

$$\mathcal{S} \;=\; \frac{\hat{\boldsymbol{\chi}}^T (P_{X_{G,0}}^{\perp} - P_{X_G}^{\perp})\hat{\boldsymbol{\chi}}}{\hat{\boldsymbol{\chi}}^T P_{X_G}^{\perp} \hat{\boldsymbol{\chi}}} \frac{M-p}{p_1} \sim F_{p_1,u}$$

where $X_{G,0}$ denotes the reduced model by excluding the effect estimated by contrast C and $u = m\sum_{il} L_{il} - p$ and $\hat{\boldsymbol{\chi}}$ is summary statistics. Since this F-statistics are standard statistics for ANOVA analysis, the result indicates that we can perform classical ANOVA analysis using the summary statistics, and such analysis is equivalent to the inference in mixed model as long as our assumption holds. Moreover, we do not need to perform computationally expensive ReML covariance estimation since the ReML variance estimation parts are already built-in within the resulting F-statistics.

3. METHOD

3.1. Data Acquisition

We collected five groups of resting-state fMRI data: 1) normal of 22 subjects (8 male, mean age 70 years), 2) MCI of 37 subjects (21 male, mean age 72 years), 3) CDR 0.5 of 20 subjects (5 male, mean age 72 years), 4) CDR 1.0 of 27 subjects (6 male, mean age 73.5 years), and 5) CDR 2.0 of 13 subjects (6 male, mean age 73.6 years). During the task period, subjects were instructed to awake and alert, but not actively involved in a task with eye closed. A 3.0T fMRI system (Philips, Netherland) was used to measure the BOLD response. The echo planar imaging (EPI) sequence was used with TR/TE = $3000/35\ ms$, flip angle = 90°. Each acquisition consisted of 35 continuous slices, and FOV (RL, AP, FH) = 220 mm x 140 mm x 220 mm; voxel size (RL, AP) = 2.875 mm x 2.875 mm. In the subsequent anatomical scanning session, T1-weighted structural images were acquired. A total of 100 acquisitions are obtained for each subject thus the total recording time was 300 sec. The experiments have been approved by the Institutional Review Board of the Samsung Medical Center in South Korea.

3.2. Data Analysis using Conventional Methods

We used two conventional methods for resting state fMRI analysis and compared with the proposed method. First, Multi-session temporal concatenation of Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC v3.0) within FMRIB's Software Library (FSL) was used as an ICA methods. The following parameters were applied in MELODIC analysis: 128 sec for the high pass filter cutoff, motion correction, smoothing using a Gaussian kernel of FWHM 8 mm, normalization into MNI coordinates with resampling resolution 2 mm, variance-normalise timecourses, and 20 independent components for the dictionary regressor to make the analysis condition as same as the one of our proposed method. Second, we used

Functional connectivity toolbox (conn) based on Statistical Parametric Mapping (SPM) for seed based analysis. The region posterior cingulate cortex (PCC) was used for ROI of this analysis and following procedures were also applied: realignment, segmentation, normalization, smoothing using a Gaussian kernel of FWHM 8 mm, band pass filter with cutoff frequency of $0.008 - 0.09$ Hz, and threshold p-value 0.001.

4. RESULTS

Comparative analyses of seed based analysis, ICA, and the proposed method, were conducted among normal, MCI, CDR 0.5, CDR 1.0, and CDR 2.0. As in Fig. 2, the DMN patterns can be extracted by any method, however the noticeable diminishing of DMN pattern along with AD progression can be clearly seen by the proposed method while hardly distinguishable changes were acquired with other methods. After performing omnibus F- test to find statistically significant group effect on DMN (results not shown), we performed 1×2 ANOVA to find the differences between adjacent groups. Fig. 3 illustrates two representative slices. As shown in the figure, drastic changes in DMN and additional superior temporal and inferior frontal gyri are observed between normal and MCI groups. From MCI groups along with disease progression, the statistically significant different changes are observed mostly in PCC with noticeable change in lateral parietal area at the CDR 2.0.

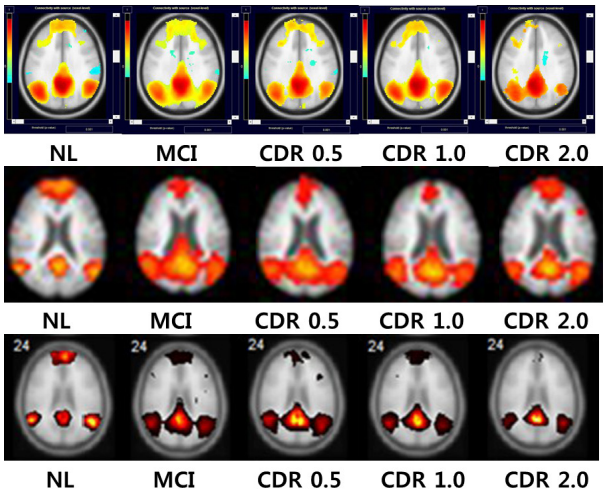
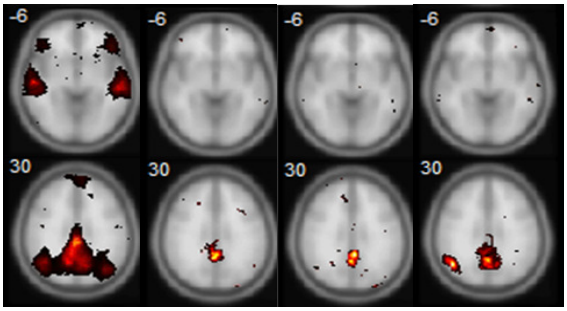


Fig. 2. The results of extracted DMN map using seed based analysis (first row), ICA (second row), and the proposed method (third row).

5. CONCLUSION

In this paper, we developed a unified mixed-model for group sparse dictionary learning and inference for resting state fMRI analysis. We compared our tools with the existing seed-based and ICA approaches for normal, MCI and Alzheimer's disease with different disease stage. The results indicated that DMN network extracted using our method is closely correlated with the progression of disease, indicating that the tool has great potential for resting state fMRI analysis.



(a) (b) (c) (d)

Fig. 3. 1×2 ANOVA maps with $p < 0.05$ (uncorrected): (a) normal vs. MCI (b) MCI vs. CDR 0.5, (c) CDR 0.5 vs. CDR 1.0, (d) CDR 1.0 vs. CDR 2.0. The top rows represents slice -6, and bottom one is slice 30.

6. ACKNOWLEDGEMENT

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