FUSION OF FMRI, SMRI, AND EEG DATA USING CANONICAL CORRELATION ANALYSIS

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ABSTRACT

Typically data acquired through imaging techniques such as functional magnetic resonance imaging (fMRI), structural MRI (sMRI), and electroencephalography (EEG) are analyzed separately. Each modality records brain structure and function at different scales, and fusing information from such complementary modalities promises to provide additional insight into connectivity across brain networks and changes due to disease. Recently, a number of methods have been proposed for data integration and fusion of two brain imaging modalities. We propose a new data fusion scheme based on canonical correlation analysis that enables the detection of associations across multiple modalities. Our multimodal canonical correlation analysis (mCCA) scheme works at the feature level using multi-set CCA to determine inter-subject covariations across modalities. We apply mCCA to fMRI, sMRI, and EEG data collected from patients diagnosed with schizophrenia and healthy controls. Through data collected from an auditory oddball task, we show that the fusion of multiple modalities detects more specific associations as compared to fusion of two modalities.

***Index Terms*—** biomedical fusion, fMRI, sMRI, EEG, canonical correlation analysis

1. INTRODUCTION

Brain imaging techniques such as functional magnetic resonance imaging (fMRI), structural MRI (sMRI), and electroencephalography (EEG) have made it possible to non-invasively study the brain at different spatial and temporal scales. Each of these modalities records specific facets of structure or function and provides information that may either be unique or common to other modalities. Typically, these are analyzed separately, however, the fusion of multimodal information promises to uncover new insights about the working of the brain as well as to detect changes in the brain due to diseases such as schizophrenia which has been shown to alter brain structure, networks, and function. Brain imaging data types are intrinsically dissimilar in nature, making it difficult to analyze them together without making a number of assumptions, most often unrealistic about the nature of the data. Instead of entering the entire datasets into a combined analysis, an alternate approach, which is used in data fusion techniques such as the independent component analysis (ICA) based joint-ICA (jICA) method [1], is used to reduce each modality to a feature corresponding to a particular activity or structure and then to explore associations across these feature datasets through variations across individuals [2].

A number of approaches have been proposed to integrate or fuse multi-task or multi-modal neuroimaging data. However, these have mostly been limited to two modalities or to multiple datasets from the same modality. We propose a novel data fusion method to combine information from multiple imaging modalities. Our method combines the feature-level data fusion based on inter-subject covariations, which we introduced in [3], and the multi-set canonical correlation analysis, introduced by Kettenring in [4]. In this paper, we examine the complementary information across fMRI, sMRI (gray matter), and EEG data from healthy subjects as well as subjects diagnosed with schizophrenia to detect areas of the brain that are affected by the disease.

FMRI measures brain function indirectly by recording the blood-oxygen level changes in the brain. EEG is a direct measure of the brain's electric field through the scalp. Thus, fMRI and EEG data both record brain function, however, fMRI has localized spatial resolution and low temporal resolution while EEG data has high temporal resolution but poor spatial localization of sources. SMRI images the morphology of the brain mainly the white matter, gray matter, and cerebrospinal fluid. Brain structure underlies and hence impacts brain function. Thus, these three modalities contain complementary information and their fusion promises to increase the specificity of the associations across structure and function.

Our multimodal canonical correlation analysis (mCCA) scheme is based on a linear mixing model. It seeks to decompose each dataset into a set of components and their corresponding loading parameters or modulation profiles across subjects. The components are spatial areas of activation in the case of fMRI data, temporal segments in the case of EEG

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data, and spatial localization of structure in the case of sMRI data. The associations across the modalities are based on inter-subject covariations across modalities. This is a novel application of CCA to the data fusion model since previous applications of CCA to fMRI data [5, 6] utilize spatial correlation rather than intersubject co-variances to perform data decomposition. In this paper, we extend the mCCA model to multiple datasets and we demonstrate the performance of mCCA on fMRI, sMRI, and EEG data. The results show that mCCA is a promising tool for the fusion of multiple modalities and identifies interesting associations among brain structure and function.

2. MULTIMODAL-CCA FOR DATA FUSION

In this section, we explain the generic data model and steps involved in mCCA while the specifics for the MRI and EEG data sets used in our experiments are given in Section 3.

2.1. Generative model

The mCCA method can find associations among two or more modalities and even though we describe the generative model with respect to three datasets, it can be extended to multiple datasets. We seek to decompose three datasets, $\mathbf{X}_1$, $\mathbf{X}_2$,

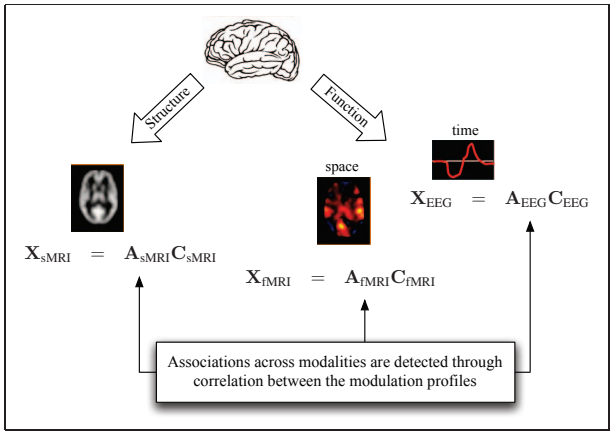

Fig. 1. Data model for fusion of brain structure and function

and $\mathbf{X}_3$ into three sets of components, $\mathbf{C}_1$, $\mathbf{C}_2$, and $\mathbf{C}_3$, and corresponding modulation profiles (inter-subject variations), $\mathbf{A}_1$, $\mathbf{A}_2$, and $\mathbf{A}_3$. The connection across the modalities can be evaluated based on correlations among modulation profiles across different modalities. Since the modulation profiles are uncorrelated within each modality, in this respect a component in one modality can be associated to only one component in another modality. This one to one correspondence aids examination of associations across modalities.

The generative model is then given by

$$\mathbf{X}_k \quad = \quad \mathbf{A}_k\mathbf{C}_k, \quad \text{for} \;\; k = 1, 2, 3$$

where $\mathbf{X}_k \in \mathbb{R}^{s\times v_k}$, $\mathbf{A}_k \in \mathbb{R}^{s\times d}$, and $\mathbf{C}_k \in \mathbb{R}^{d\times v_k}$, v_k is the number of samples in each modality (for *e.g.*, in our application the samples are the voxels for the MRI modalities and the time points for the EEG) and s is the number of subjects in $\mathbf{X}_k$ and $d \leq \min(\text{rank}(\mathbf{X}_k))$, k =1,2,3. is the number of components. As per the model, the modulation profiles given by the i^{th} column of the $\mathbf{A}$ matrices, *i.e.*, $\mathbf{a}_k^{(i)}$ $(i = 1, \ldots, d)$ satisfy the following properties:

- The modulation profiles are uncorrelated within each dataset and have zero mean and unit variance, *i.e.*,
$$\mathbf{A}_k^T\mathbf{A}_k \quad = \quad \mathbf{I}, \quad k = 1, 2, 3 \qquad (1)$$
- The modulation profiles have non-zero correlation only on their corresponding indices, and have correlation coefficients, $r_{k,l}^{(1)} \geq r_{k,l}^{(2)}, \ldots, \geq r_{k,l}^{(d)}$, where $r_{k,l}^{(i)} = {\mathbf{a}_k^{(i)}}^T\mathbf{a}_l^{(i)}$, *i.e.*,
$$\mathbf{A}_k^T\mathbf{A}_l \quad = \quad \mathbf{R}_{k,l}, \quad k \neq l, k, l = 1, 2, 3 \qquad (2)$$
where $\mathbf{R}_{k,l} = \text{diag}(r_{k,l}^{(1)}, \ldots, r_{k,l}^{(d)})$.

2.2. mCCA of two datasets

In [3], we proposed to use canonical correlation analysis to find the linear associations across two datasets. CCA is a statistical method to summarize the correlation structure between two multivariate datasets by linear transformations [7]. The method finds the first pairs of canonical coefficient vectors $\mathbf{w}_1^{(1)}$ and $\mathbf{w}_2^{(1)}$, ($\mathbf{w}_1^{(1)} \in \mathbb{R}^{v_1\times 1}$, $\mathbf{w}_2^{(1)} \in \mathbb{R}^{v_2\times 1}$) that maximize linear combinations of the two datasets given by

$$\max_{\mathbf{w}_1^{(1)}, \mathbf{w}_2^{(1)}} \text{corr}(\mathbf{X}_1\mathbf{w}_1^{(1)}, \mathbf{X}_2\mathbf{w}_2^{(1)})$$

to obtain the first pair of canonical variates given by

$$\mathbf{a}_1^{(1)} = \mathbf{X}_1\mathbf{w}_1^{(1)} \quad \text{and} \quad \mathbf{a}_2^{(1)} = \mathbf{X}_2\mathbf{w}_2^{(1)}.$$

The remaining canonical variates can be calculated similarly, with the additional constraints stated in (1) and (2). The CCA problem can be posed as a constrained optimization problem using Lagrange multipliers where d canonical covariates can be calculated by solving one eigenvalue problem [8].

Thus, mCCA models the inter-subject covariations as the canonical variates obtained by CCA and the least squares approximations of the components are given by

$$\hat{\mathbf{C}}_k = (\mathbf{A}_k^T\mathbf{A}_k)^{-1}\mathbf{A}_k^T\mathbf{X}_k = \mathbf{A}_k^T\mathbf{X}_k \text{ (from (1))}, \;\; \text{for} \;\; k = 1, 2.$$

2.3. Extension to mCCA multiple datasets

The analysis of more than two modalities collectively can help identify interesting associations across brain structure and function. We extend the mCCA model to multiple datasets using the multi-set CCA approach proposed in [4]. The canonical correlations can be obtained by optimizing a number of cost functions proposed in [4], *e.g.*, maximizing

the sum of squared correlations among the canonical variates. Consider the canonical variates $\mathbf{A}_k$, where each is a linear combination of the dataset $\mathbf{X}_k$ given as

$$\mathbf{A}_k = \mathbf{X}_k \mathbf{w}_k, \quad k = 1, 2, \ldots, K$$

and $\mathbf{w}_k$ are the canonical coefficient vectors. We can summarize the multi-set CCA procedure based on sum of squares (SSQCOR) cost as:

- Stage 1

$$\{\mathbf{w}_1^{(1)}, \mathbf{w}_2^{(1)}, ..., \mathbf{w}_K^{(1)}\} = \arg\max_{\mathbf{w}} \left\{ \sum_{k,l=1}^{K} |r_{k,l}^{(1)}|^2 \right\}$$

- Stage 2 to d

  for i = 2:d

$$\{\mathbf{w}_1^{(i)}, \mathbf{w}_2^{(i)}, ..., \mathbf{w}_K^{(i)}\} = \arg\max_{\mathbf{w}} \left\{ \sum_{k,l=1}^{K} |r_{k,l}^{(i)}|^2 \right\}$$

  s.t. $\mathbf{w}_k^{(i)} \perp \{\mathbf{w}_k^{(1)}, \mathbf{w}_k^{(2)}, \ldots, \mathbf{w}_k^{(i-1)}\}, k = 1, 2, \ldots, K$

  end

where $d \leq \min(\text{rank}(\mathbf{X}_k))$. In [4], Stage 1 is solved by first calculating the partial derivative function of the SSQCOR cost with respect to each $\mathbf{w}_k^{(1)}$ and equating it to zero to find the stationary point. Since the SSQCOR cost is a quadratic function of each $\mathbf{w}_k^{(1)}$, the partial derivative is a linear function of $\mathbf{w}_k^{(1)}$ and hence, the closed form solution can be derived. Starting from an initial point, each $\mathbf{w}_k^{(1)}$ vector is updated in sequel to guarantee an increase in the cost function and a sweep through all the $\mathbf{w}_k^{(1)}$ constitutes one step of the iterative maximization procedure. The iterations are stopped when the cost convergence criterion is met and the resulting $\mathbf{w}_k^{(1)}$ vectors are taken as the optimal solution. Stage 2 and higher stages are solved in a similar manner with the cost function replaced by a Lagrangian incorporating the orthogonality constraints on the canonical coefficient vectors.

3. EXPERIMENTS

In this section, we present an experiment on fMRI, sMRI, and EEG data to examine associations between brain structure and function. We first describe the datasets, followed by the pre-processing steps, namely, dimension reduction and feature generation and then summarize the results.

3.1. Data

The MRI and EEG data are acquired from 36 subjects (22 healthy controls and 14 schizophrenia patients). The fMRI and EEG data were collected while the subjects performed an auditory oddball (AOD) task that required them to press a button when they detect a particular infrequent sound among three kinds of auditory stimuli. Details of the task design and the participants are given in [9].

3.2. Feature generation

Lower-dimensional features of interest related to specific brain activity or structure are first extracted from the data [2]. For each subject, a feature vector is extracted from each modality and entered into the fusion analysis at the group level to detect associations across modalities.

For the fMRI data, we use the software package (SPM2) [10] to preprocess the data (slice timing correction, motion correction, spatial normalization, smoothing with a $10 \times 10 \times 10$ mm^3 Gaussian kernel) and to obtain contrast images related to task which are used as features as in [11]. ICA is used to remove ocular artifacts from the EEG data [12] and the data is low pass filtered at 20 Hz. EEG features, event-related potentials (ERPs) are calculated by averaging epochs of EEG, time-locked to the event of correct target detection from the midline central position (Cz) because it appeared to be the best single channel to detect both anterior and posterior sources for the given task. We label the ERPs based on their ordinal position following the stimulus onset (*e.g.* P3 for the third positive peak or N2 for the second negative peak). Probabilistic segmentation of gray matter images calculated from the sMRI data using SPM2 are smoothed with a $10 \times 10 \times 10$ mm^3 Gaussian kernel and used as features as in [11].

3.3. Dimension reduction

The number of variables in the feature datasets are much larger than the number of observations. Transforming each set of features to a subspace with smaller number of variables helps improve the performance by preventing overfitting. Dimension reduction is performed on each of the feature datasets using singular value decomposition (SVD) of $\mathbf{X}_1$, $\mathbf{X}_2$, and $\mathbf{X}_3$, which are given by

$$\mathbf{X}_k = \mathbf{E}_k \mathbf{D}_k \mathbf{F}_k = [\mathbf{E}_k^{'} \mathbf{E}_k^{''}] \mathbf{D}_k \mathbf{F}_k, \quad \text{for } k = 1, 2, 3.$$

where $\mathbf{E}_k^{'}$ contains the eigenvectors corresponding to the significant eigenvalues in $\mathbf{D}_k$, for k =1,2, and 3 respectively. $\mathbf{E}_k^{''}$ contains the eigenvectors that are treated as noise and hence omitted from the next steps of the analysis. We perform CCA on the dimension-reduced datasets given by

$$\mathbf{Y}_k = \mathbf{X}_k \mathbf{E}_k^{'}, \quad \text{for } k = 1, 2.$$

3.4. Results

We perform mCCA on the dimension reduced fMRI, sMRI, and ERP data to estimate 15 sets of components containing interesting associations across the modalities. Here, we highlight the key findings from our experiments. We performed t-tests on the three modulation profiles for each set of components to check for associated functional and structural differences due to schizophrenia. Among the 15 components, one set of profiles showed significantly different loadings ($\alpha \leq$

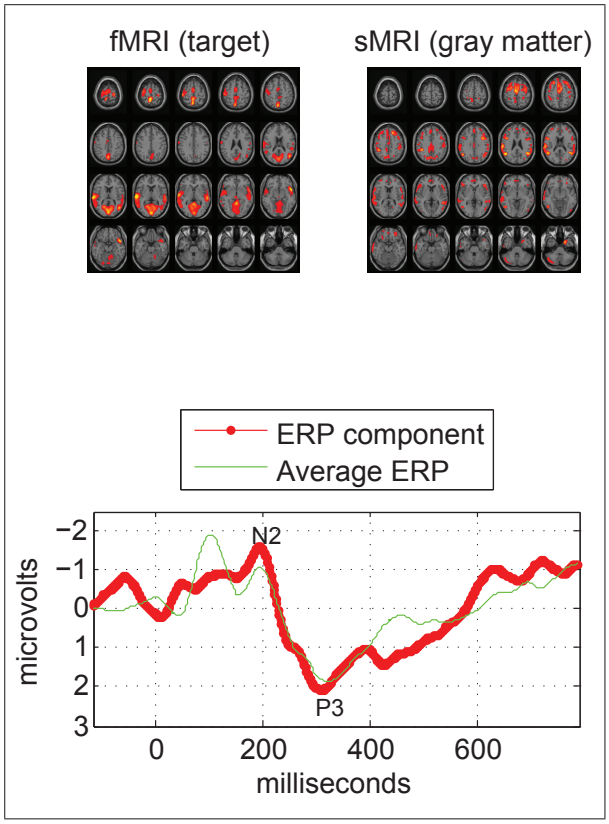

Fig. 2. Set of associated components estimated by mCCA which showed significantly different loading for patients versus controls. FMRI and sMRI activation maps are thresholded at $Z = 3$

0.05) across treatment groups for all three modalities (loading for controls was higher than that for patients). The corresponding sources for this component set is shown in Fig. 2. The fMRI and sMRI maps are thresholded based on Z-score, *i.e.*, the normalized activation levels in each map. The fMRI component shown in Fig. 2 shows activations in the motor and temporal lobes. The sMRI component shows activations in the temporal and frontal lobes as well as slight activation in the motor areas. The EEG shows a large variation across the N2/P3 complex. These results show that subjects with schizophrenia have less functional activity and less gray matter and also a large part of the ERP response appears to be affected. These findings are consistent with previous studies on schizophrenia, many of which implicate temporal lobe in fMRI and sMRI and also the P3 response in ERP. This study suggests a common linkage between the three findings.

Additionally, we perform mCCA on the fMRI and sMRI datasets while excluding the EEG data. Comparing the results of the three way analysis with those from the two way analysis, we find that for both experiments the areas detected in the fMRI and sMRI component are very similar for the component that showed significant differences between the two groups, however, the areas detected in the sMRI component are smaller in size in the three way analysis. This is an expected result since including the EEG data in the analysis would increase the specificity of the findings to areas associated with the task. Performing CCA on multiple datasets can be more restrictive since we are requiring covariation of all three modalities, however, this is also informative since we find changes that are related across the three modalities. An interesting point to note is that mCCA allows for associations in local voxels as well as remotely located voxels, thus enabling discoveries of structural changes causing compensatory functional activation in distant, but connected, regions.

4. CONCLUSION

In this paper, we have proposed a novel method for the fusion of more than two datasets. We have studied the fMRI, sMRI, and EEG data to find associations between brain structure and function that are linked to the AOD task and show changes in subjects with schizophrenia. Our results show that mCCA is a promising technique for the fusion of multiple modalities.

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