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A feature-based approach to combine functional MRI, structural MRI and EEG brain imaging data

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***Abstract*—The acquisition of multiple brain imaging types for a given study is a very common practice. However these data are typically examined in separate analyses, rather than in a combined model. We propose a novel methodology to perform joint independent component analysis across image modalities, including structural MRI data, functional MRI activation data and EEG data, and to visualize the results via a joint histogram visualization technique. Evaluation of which combination of fused data is most useful is determined by using the Kullback-Leibler divergence. We demonstrate our method on a data set composed of functional MRI data from two tasks, structural MRI data, and EEG data collected on patients with schizophrenia and healthy controls. We show that combining data types can improve our ability to distinguish differences between groups.**

I. Introduction

MANY studies are currently collecting multiple types of imaging information from the same participants. Each imaging method reports on a limited domain and likely provides some common information and some unique information. This motivates the need for a joint analysis of these data. Most commonly, each type of image is analyzed independently and then perhaps overlaid to demonstrate its relationship with other data types (*e.g.,* structural and functional images). A second approach, called *data fusion*, utilizes multiple image-types together in order to take advantage of the 'cross'-information. In the former approach, any cross-information is 'thrown' away, hence such an approach, for example, would not detect a change in functional magnetic resonance imaging (fMRI) activation maps that are associated with a change in the brain structure.

Approaches for combining or fusing data in brain imaging can be put on a spectrum with meta-analysis (highly distilled data) to examine convergent evidence at one end and large-scale computational modeling (highly detailed theoretical modeling) at the other end. In between are methods that attempt to do direct data fusion. We have recently done work showing the value of combining multi-task fMRI data [1], fMRI and structural magnetic resonance imaging (sMRI) data [2], and fMRI and event-related potential (ERP) data [3]. One important aspect of our approach is that we allow for the possibility that a change in a certain location in one modality can be associated with a change in a *different* location in another modality—in the case of ERP, one is associating time in ERP with space in fMRI [3].

Independent component analysis (ICA), a statistical and computational technique for revealing hidden factors that underlie sets of random variables, measurements, or signals [4], has demonstrated considerable promise for the analysis of fMRI [5], EEG [6], and sMRI [7] data. In this study, we present a data fusion framework via a joint ICA (jICA), and introduce a method to assess the value of data fusion by using a discrimination metric based on Kullback-Leibler (KL) divergence.

II. Brain Imaging Feature Generation

FMRI measures the hemodynamic response related to neural activity in the brain dynamically. SMRI provides information about the tissue type of the brain [gray matter (GM), white matter (WM), cerebrospinal fluid (CSF)]. Another useful measure of brain function is EEG, which measures brain electrical activity with a higher temporal resolution than fMRI (and lower spatial resolution).

The data types on which we focus in this paper are: fMRI, sMRI [including T1- and T2-weighted scans], and EEG. Processing strategies for each of these data-types have been developed over a number of years. In this study, fMRI data were preprocessed using the software package SPM2 [8]. SMRI data were segmented into GM, WM and CSF images using the same program. ICA was used to remove ocular artifacts from the EEG data [9]. The EEG data, then, were filtered with a 20Hz low pass filter. ERPs were constructed for trials in which participants correctly identified target stimuli, from the midline central position (Cz) because it appeared to be the best single channel to detect both anterior and posterior sources. Each data type, after being preprocessed as above, has been reduced into a *feature*, which contributes an input vector from each modality to jICA for each subject and each task. A feature is a sub dataset extracted from one type of data, related to a selected brain activity or structure. A summary of core features used in this study is given in Table1.

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TABLE I
CORE FEATURES FOR FMRI (STERNBERG WORKING MEMORY TASK [SB], AUDITORY ODDBALL TASK [AOD]), SMRI, AND EEG (AOD TASK)

Modality	*Core-Feature*
fMRI SB task	Recognition related activity [10]
	Encode-related activity [10]
fMRI AOD task	Target-related activity [11]
	Novel-related activity [11]
sMRI	GM concentration [12]
	WM concentration [12]
	CSF concentration [12]
EEG AOD task	Target-related ERP [13]
	Novel-related ERP [13]

III. JOINT ICA

For data fusion of multiple modalities, we assume joint spatial or temporal independence of each modality, using the following general model for the data:

$$\mathbf{X}^{(m)} = \mathbf{A} \cdot \mathbf{S}^{(m)};\ \mathbf{S}^{(m)} = \mathbf{W} \cdot \mathbf{X}^{(m)};\ \mathbf{W} = \mathbf{A}^{-1};\ m = 1:M$$

Here, m is the modality index, $\mathbf{S}^{(m)}$ and $\mathbf{X}^{(m)}$ are the $S \times V$ source and observation data matrix for modality m, respectively, and M is the total number of modalities being fused. $\mathbf{A}$ is the unknown mixing matrix. Without loss of generality, we assume each modality has V data points as one feature and each feature generated for each of the S subjects contributes to the observation matrix. For the case of two sources (two subjects), the observation matrix (mixed data) is given by

$$\mathbf{X}^{(m)} = \left[\mathbf{x}_1^{(m)} \quad \mathbf{x}_2^{(m)}\right]^T,$$

where $\mathbf{x}_i^{(m)}$ is the $V \times 1$ vector of data points for subject i and modality m. For joint ICA, we fuse multiple features (vectors) from multiple modalities into one virtual data type. The observation matrix is then formed as $\mathbf{X} = [\mathbf{X}^{(1)} \ldots \mathbf{X}^{(M)}]$ and the source matrix is defined similarly. We then have a single one shared linear mixing matrix given by $\mathbf{A}$. In the non-joint ICA case, we would instead have $\mathbf{X}^{(m)} = \mathbf{A}^{(m)} \cdot \mathbf{S}^{(m)},\ m = 1:M$, with M different mixing matrices.

We can use the independence of the sources to write the joint probability density function of observation data, given an inverse matrix $\mathbf{W}$, as

$$p\left(x_1^{(1)}, \ldots, x_1^{(M)}, x_2^{(1)}, \ldots, x_2^{(M)} \mid \mathbf{W}\right) = |\det \mathbf{W}| \cdot p\left(s_1^{(1)}, \ldots, s_1^{(M)}\right) \cdot p\left(s_2^{(1)}, \ldots, s_2^{(M)}\right),$$

where $p\left(s_j^{(1)}, \ldots, s_j^{(M)}\right)$ is the joint probability density for source j. The likelihood of observation data can be obtained as the V-dimensional density function, the product of densities evaluated at the V points in the feature

$$L(\mathbf{W}) = |\det \mathbf{W}| \cdot \prod_{v=1}^{V} p\left(\mathbf{w}_1^T \mathbf{x}_{1,v}^{(1)}, \ldots, \mathbf{w}_1^T \mathbf{x}_{1,v}^{(M)}\right) \cdot p\left(\mathbf{w}_2^T \mathbf{x}_{2,v}^{(1)}, \ldots, \mathbf{w}_2^T \mathbf{x}_{2,v}^{(M)}\right).$$

We start with the reasonable assumption that the joint sources are approximately independent conditioned upon the data. This results in a likelihood function as follows:

$$L(\mathbf{W}) = |\det \mathbf{W}| \cdot \prod_{m=1}^{M} \prod_{v=1}^{V} p_{(m)}\left(\mathbf{w}_1^T \mathbf{x}_{1,v}^{(m)}\right) \cdot p_{(m)}\left(\mathbf{w}_2^T \mathbf{x}_{2,v}^{(m)}\right).$$

If we select the same density for each modality (e.g., use the flexible sigmoid function that implies a super-Gaussian type density), then we can write

$$L(\mathbf{W}) = |\det \mathbf{W}| \cdot \prod_{m=1}^{M} \prod_{v=1}^{V} p\left(\mathbf{w}_1^T \mathbf{x}_{1,v}^{(m)}\right) \cdot p\left(\mathbf{w}_2^T \mathbf{x}_{2,v}^{(m)}\right).$$

By natural (or relative) gradient maximization of the log-likelihood (or by output entropy maximization [14]), we end up with the following update rule for M modalities:

$$\Delta \mathbf{W} = \eta \left\{ \mathbf{I} - 2 \sum_{m=1}^{M} \mathbf{y}^{(m)} \cdot \left(\mathbf{u}^{(m)}\right)^T + \sum_{m=1}^{M} \left(\mathbf{u}^{(m)}\right)^T \right\} \mathbf{W};$$

$$\mathbf{y}^{(m)} = g\left(\mathbf{u}^{(m)}\right);\ \mathbf{u}^{(m)} = \mathbf{W} \cdot \mathbf{X}^{(m)}$$

where, η is the learning rate and $g(\mathbf{u}) = 1/(1 + e^{-\mathbf{u}})$ is the nonlinearity chosen as the sigmoid function.

IV. VALIDATION AND OPTIMIZATION

Hybrid-Data: Validation of biomedical analysis methods is a difficult task since the "truth" is not generally known as it is in a simulation. We address this problem by creating a "hybrid" data set in which one or more sources are mixed and added to the actual data. This data is then unmixed through the jICA. Since the superimposed sources have a known pattern, it is straightforward to extract them from the unmixed data. Such an approach, though not perfect, enables us to evaluate the performance of the jICA algorithm under a variety of noise conditions, using partially actual data.

Selection of Optimal Features/Modalities: We also optimize among a set of features and/or feature preprocessing choices. To evaluate the performance of jICA from different features/modalities, we adopt an approach similar to our previous work in which we evaluated different ICA algorithms and processing strategies for fMRI data [15]. The performance is evaluated by comparing the unmixed sources to the ground truth using the relative entropy (KL divergence [16]) between the estimated and true distributions, as a measure of the goodness of the estimation.

V. RESULTS

In this section, we first present the generated hybrid data and discovered results from jICA, demonstrating the ability of jICA in two modalities. Then, we show two examples of the jICA applications to real data from multiple tasks/modalities using: 1) multi-task fMRI data, 2) ERP/fMRI data. Furthermore, we select the best input features for the jICA data fusion to achieve the optimal performance, in terms of classifying subjects. At last, we extend our test to analyze the impact of preprocessing steps, by evaluating the performance of jICA on features derived from different preprocessing steps.

Hybrid Data: An example of a hybrid data fusion analysis is shown in Fig. 1. A known source was added to gray matter segmentation images and fMRI activation images from 30 subjects to different degrees. The data were then analyzed by the jICA and 10 components were estimated. The component whose loading parameter

correlated most highly with the known coupling parameter (correlation=0.97) is also displayed. The jICA algorithm extracted the coupled source into a separate component and enables us to visualize where in each data set the coupling occurs, as well as the loading parameters.

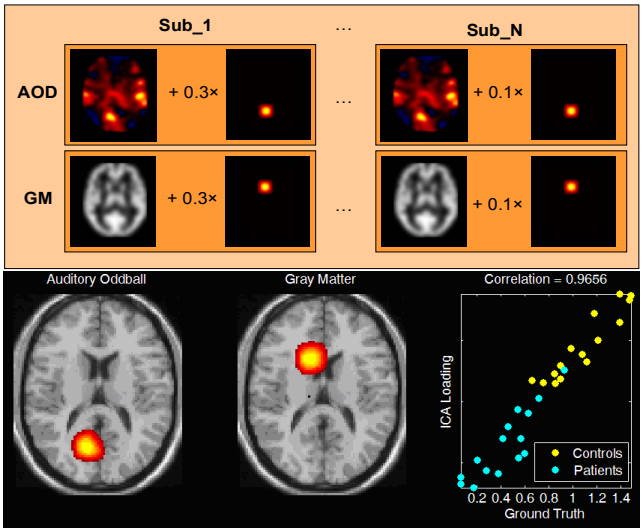

Fig. 1 Generation (top) of hybrid data and results (bottom) involving gray matter segmentation and auditory oddball fMRI data.

Multi-task fMRI Data: We performed a joint analysis of fMRI data collected from a Sternberg (SB) task and an auditory oddball (AOD) task. Data in each task were collected from 15 controls and 15 patients with schizophrenia. Additional details of the tasks and subjects are provided in [1]. A single joint component was found to discriminate schizophrenia patients and healthy controls. A joint histogram was computed by ranking voxels surviving the threshold for the AOD and SB parts of the joint source in descending order and pairing these two voxel sets. Single subject and group-averaged joint histograms are presented in Fig. 2 (a) and (b) and the marginal histograms for the AOD and SB tasks are presented in Fig. 2 (c) and (d).

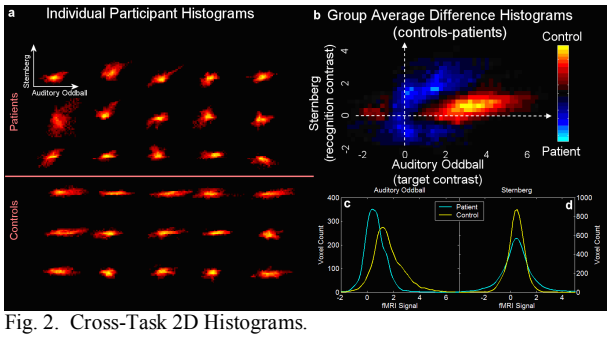

Fig. 2. Cross-Task 2D Histograms.

In general, more AOD task voxels were active in the controls and the SB task showed a slight increase standard deviation for the patients. Results also revealed significantly more correlation between the two tasks in the patients ($p<0.000085$). A possible synthesis of the findings is that patients are activating less, but also activating with a less unique set of regions for these very different tasks, consistent with a generalized cognitive deficit.

ERP/fMRI Data: We now show results combining ERP and fMRI data collected from 23 healthy controls and 18 chronic schizophrenia patients, during the performance of the AOD task. Fifteen joint components were estimated from the target-related ERP time courses and fMRI activation maps via the jICA. One joint component was found to distinguish patients and controls using a two-sample t-test ($p<0.0001$) on patient and control loading parameters. This identified component shows a clear difference in fMRI at bilateral frontotemporal regions implicated in schizophrenia (Fig. 3 right) and in ERP at times during the N2/P3 complex (Fig. 3 left) which have been previously implicated in patients.

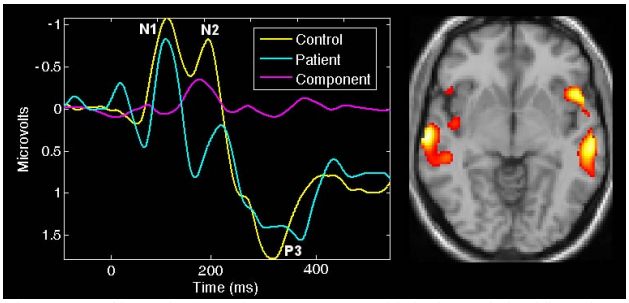

Fig. 3. ERP/fMRI jICA: Joint component which showed significantly different loading parameters ($p<0.0001$) for patients versus controls. Left: control (yellow) and patient (blue) average ERP plots along with the ERP part of the identified joint component (pink). Right: Thresholded fMRI part of the joint component showing bilateral temporal and frontal lobe regions.

Selection of Feature Combinations: In this section we discuss a unified approach for selecting which combinations of features are important. We compute features for 1) AOD target-related fMRI activity (AOD_T), 2) AOD novel-related fMRI activity (AOD_N), 3) SB recognition fMRI activity (SB), and 4) sMRI GM values (GM). All four of these features were collected on each of 15 controls and 15 patients with schizophrenia. We then perform a 2-way jICA for all combination of features and select the components which show the greatest difference in their ICA loading parameter. The estimated distributions for these components are computed separately for each group and the KL divergence is computed between the patient (sz) and control (hc) distributions (i.e., $\mathbf{D}(p_{sz}(\mathbf{f}) \| p_{hc}(\mathbf{f}))$, where $\mathbf{f}$ is a multi-dimensional feature/modality vector). The results shown in Fig. 4 are ranked according to this measure in order to determine which combination of features provides better separation. For example, it shows that combining the SB feature with the AOD_N or AOD_T features provides increased separation beyond SB or AOD_T alone. It also suggests that the incorporation of GM tends to decrease the separation. Note that though we have demonstrated above a comparison of patients and controls, this method is useful for addressing questions for healthy controls as well. We could have examined, instead, e.g., age-related activity only in healthy controls.

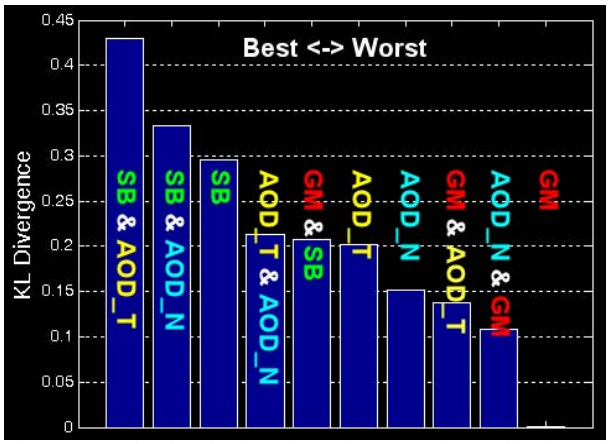

Fig. 4. Example of evaluation of KL Divergence for combinations of features comparing 2-way fusion with non-fusion. Larger KL Divergence values represent better patient versus control separation.

Impact of Preprocessing: We can also use this method to evaluate the impact of preprocessing steps upon the results [15]. For example, shown in Fig. 5 is a comparison of the AOD_T and GM features computed with and without inter-modality co-registration procedures. Specifically, GM_1 used the standard spatial normalization procedure to match the T1 images to an MNI template (but no direct inter-modality co-registration was performed). The GM_2 feature was computed by adding an additional co-registration step to match the T1 and the EPI scans directly. In this case, we see that the results are improved and that the GM data becomes more effective. Additionally, when GM_2 and AOD are fused, the performance increases beyond either AOD or GM_2 alone. Without co-registration, the fusion of GM_1 and AOD_T decreases performance.

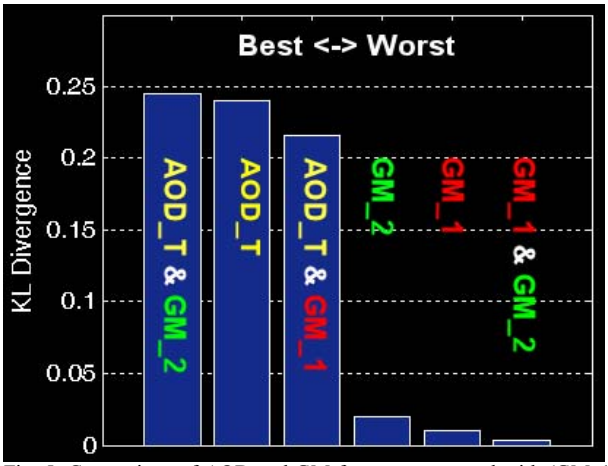

Fig. 5. Comparison of AOD and GM features computed with (GM_1) and without (GM_2) inter-feature co-registration.

VI. CONCLUSION

We present a general framework for combining different types of brain imaging data at the group level via features computed from each data type. This approach enables us to take advantages of the strengths and limitations of various modalities in a unified analytic framework and demonstrates that data fusion techniques can be successfully applied to joint brain imaging data to reveal information that cannot be evaluated in any one modality. The main purpose of our jICA approach is to discover unique components from multiple modalities, which share similar correspondences between subjects. The approach we outline additionally enables the identification of which discovered components (and which modalities) best differentiate patient and control groups.

REFERENCES

[1] V. D. Calhoun, T. Adali, K. A. Kiehl, R. S. Astur, J. J. Pekar, and G. D. Pearlson, "A Method for Multi-Task FMRI Data Fusion Applied to Schizophrenia," *Hum. Brain Map.*, 2005.

[2] V. D. Calhoun, T. Adali, N. Giuliani, J. J. Pekar, G. D. Pearlson, and K. A. Kiehl, "A Method for Multimodal Analysis of Independent Source Differences in Schizophrenia: Combining Gray Matter Structural and Auditory Oddball Functional Data," *Hum. Brain Mapp.*, 27(1):47-62, 2006.

[3] V. D. Calhoun, G. D. Pearlson, and K. A. Kiehl, "Neuronal Chronometry of Target Detection: Fusion of Hemodynamic and Event-Related Potential Data," *NeuroImage*, 2005.

[4] A. Hyvarinen, J. Karhunen, and E. Oja, *Independent Component Analysis*, New York, NY: Johns Wiley & Sons, 2001.

[5] M. J. McKeown, S. Makeig, G. G. Brown, T. P. Jung, S. S. Kindermann, A. J. Bell, and T. J. Sejnowski, "Analysis of FMRI Data by Blind Separation Into Independent Spatial Components," *Hum. Brain Map.*, vol. 6, pp. 160-188, 1998.

[6] S. Makeig, T. P. Jung, A. J. Bell, D. Ghahremani, and T. J. Sejnowski, "Blind Separation of Auditory Event-Related Brain Responses into Independent Components," *Proc. Natl. Acad. Sci.*, vol. 94, pp. 10979-10984, 1997.

[7] T. Nakai, S. Muraki, E. Bagarinao, D. J. Mikulis, Y. Takehara, K. Matsuo, C. Kato, H. Sakahara, and H. Isoda, "Application of Independent Component Analysis to Magnetic Resonance Imaging for Enhancing the Contrast of Gray and White Matter," *NeuroImage*, vol. 12, pp. 251-260, 2004.

[8] Statistical parametric mapping. http://www.fil.ion.ucl.ac.uk/spm/.

[9] T. P. Jung, S. Makeig, C. Humphries, T. W. Lee, M. J. McKeown, V. Iragui, and T. J. Sejnowski, "Removing Electroencephalographic Artifacts by Blind Source Separation," *Psychophysiology*, vol. 37, pp. 163-178, 2000.

[10] M. R. Johnson, N. Morris, R. S. Astur, V. D. Calhoun, K. A. Kiehl, and G. D. Pearlson, "Schizophrenia and Working Memory: A Closer Look at FMRI of the Dorsolateral Prefrontal Cortex During a Working Memory Task," in *Proc. CNS*, New York, NY, 2005.

[11] K. A. Kiehl, M. Stevens, K. R. Laurens, G. D. Pearlson, V. D. Calhoun, and P. F. Liddle, "An Adaptive Reflexive Processing Model of Neurocognitive Function: Supporting Evidence From a Large Scale (n=100) FMRI Study of an Auditory Oddball Task," *NeuroImage*, vol. 25, pp. 899-915, 2005.

[12] N. Giuliani, V. D. Calhoun, G. D. Pearlson, A. Francis, and R. W. Buchanan, "Voxel-Based Morphometry Versus Regions of Interest: A Comparison of Two Methods for Analyzing Gray Matter Disturbances in Schizophrenia," *Schizophr. Res.*, vol. 74, pp. 135-147, 2005.

[13] K. A. Kiehl, A. M. Smith, R. D. Hare, and P. F. Liddle, "An Event-Related Potential Investigation of Response Inhibition in Schizophrenia and Psychopathy," *Biol. Psychiatry*, vol. 48, pp. 210-221, 2000.

[14] J. F. Cardoso, "Infomax and Maximum Likelihood for Source Separation," *IEEE Letters on Signal Processing*, vol. 4, pp. 112-114, 1997.

[15] V. D. Calhoun, T. Adali, and G. D. Pearlson, "Independent Component Analysis Applied to FMRI Data: A Generative Model for Validating Results," *Journal of VLSI Signal Proc. Systems*, vol. 37, pp. 281-291, 2004.

[16] T. Sawa, "Information Criteria for Discriminating Among Alternative Regression Models," *Econometrica*, vol. 46, pp. 379-423, 1978.