LOCAL LINEAR DISCRIMINANT ANALYSIS (LLDA) FOR INFERENCE OF MULTISUBJECT FMRI DATA

Martin J. McKeown[1], Junning Li[2], Xuemei Huang[3], Z. Jane Wang[2]
[1]Pacific Parkinson's Research Centre, Brain Research Centre, University of British Columbia
[2]Department of Electrical and Computer Engineering, University of British Columbia, Canada
[3]Department of Neurology, University of North Carolina, Chapel Hill, NC, USA

ABSTRACT

Large intersubject variability is a well-described feature of fMRI studies, making inter-group inference, of critical importance for biological interpretation, difficult. Therefore, traditional approaches involve spatially transforming the data of each subject and heavily spatially smoothing the data. Here we propose an alternate method: after first defining individually-specific Regions of Interest (ROIs) of each subject, we utilize Local Linear Discriminant Analysis (LLDA) to jointly optimize the individually-specific and group linear combinations of ROIs that maximally discriminates between groups characterized by either disease status or task. The proposed method was applied to fMRI data recorded from eight normal subjects performing a motor task, and it was shown to successfully detect activation in multiple cortical and subcortical structures that were not present when the data were traditionally analyzed by warping the data to a common space. We suggest that the proposed method for group fMRI data analysis may be more suitable when examining co-activation in small subcortical regions susceptible to mis-registration, or examining older or neurological patient populations.

Index Terms**—** Discriminant Analysis, FMRI, Group Analysis, Regions of Interest

1. INTRODUCTION

Functional magnetic resonance imaging (fMRI) has been widely applied for studying brain activity, as it a non-invasive method that does not require the injection of intravenous contrast. Although the analysis of single-subject fMRI studies has been well investigated, the modeling and inference of fMRI data from groups of subjects remains a challenge due to individual differences in brain shape and differences in the magnitude and spatial distributions of activation patterns. Nevertheless, group analysis of fMRI is of critical importance for proper biological interpretation of the results.

Group fMRI analyses are usually done using a Summary Statistics method, a two-staged approach: first individual models are fit to each subject, and then a second level is applied to make group inferences [2] by using a multivariate regression analysis. For the voxel-based analysis, the multi-subject fMRI data need to be voxel-aligned first, where data are spatially transformed to a common space, e.g. the atlas by Talaraich [1], to minimize inter-subject differences. Different implementations were proposed to implement the above analysis in a practical way, such as the popular SPM2 package [3, 4]. However, there are a number of shortcomings with the voxel-based approaches, including the possibilities of mis-registration and the lack of explicit modeling interactions between brain regions. Therefore, we are interested in the regions-of-interest (ROI)-based analysis, which does not require rigid spatial transformation.

Our goal is to find which combination of brain regions is maximally different between tasks. Thus, in contrast to the above two-stage approach, it is desirable to jointly optimize the individual statistical model and the overall models simultaneously, and there is a need for a multivariate, discriminant analysis approach that works at the ROI level, as indicated in our previous work [5].

In some cases the magnitude of inter-subject differences in fMRI activation can exceed the task-specific differences within individuals. To deal with this situation, yet still maintaining the benefits of linear discriminant analysis, we propose using a recently developed Local Linear Discriminant Analysis (LLDA), initially designed to solve a somewhat different, but still related, problem [6]: finding a classifier that was sensitive to static images from different subjects, yet insensitive to different poses from the same subject. We therefore propose using LLDA to sensitively discriminate between task-dependent ROI patterns of activity, while being relatively robust to the differences between subjects.

In the paper, we apply the proposed method to fMRI data derived from a motor paradigm that would be expected to activate cortical and subcortical structures. We show that the proposed method, consistent with prior neuroscience knowledge derived from animal models, detects significant group activation in subcortical structures that was not present when the same group of data were analyzed using standard methods utilizing spatial normalization.

2. METHODS

2.1. FMRI Data Pre-processing

The fMRI data were preprocessed for each individual independently for motion correction, and slice time realignment using standard fMRI software (SPM 2). The data were not spatially smoothed and were not spatially transformed to a common space. Eight ROIs were defined bilaterally (total = 16 ROIs) and manually traced on the T1-weighted structural images for each subject based on anatomical sulcal landmarks and with the guidance of a brain atlas [7]: anterior cingulate cortex (ACC), supplementary motor areas (SMA), primary motor cortex (PMC), dorsal lateral prefrontal cortex (DLPFC), caudate (Caud), globus pallidus/putamen (GP/PUT), thalamus, and lateral cerebellum hemisphere.

The proposed method is a post-processing method that utilizes pre-computed statistical parametric maps. To ensure that any benefits from the proposed method were not due to the methods of obtaining the statistical parametric maps themselves, we utilized simple t-tests based on the BOLD signal changes in all runs between a task and rest (e.g., right hand IG vs. rest). The voxels in the statistical maps were then labeled by the appropriate ROIs drawn on the anatomical image. The labeled statistic parametric maps for different conditions (e.g. Right Hand IG vs. rest contrasted to Right EG vs rest) were then contrasted with LLDA.

Then similar to [5], using the notation $t(s,r,v)$ = $t(subject, region, voxel)$, for each subject, we randomly select a voxel from within each of P ROIs, and assemble the result into a column feature vector., e.g. for subject #1:

$$t(1,\mathbf{v}) = \left(t(1,1,v_1), t(1,2,v_2), t(1,P,v_P)\right), \tag{1}$$

where v_i is the v_i-th voxel in the ith ROI, and i = 1,2,…. P. This random selection process will be repeated a number of times, say B times, and then the mean of the feature vectors, $\bar{\mathbf{t}}_k(1)$, is taken to ensure the data can be modeled as multivariate Gaussian. The above process is repeated (k = 1,2,…M) to perform bootstrap resampling. All feature vectors from the first subject are then collected:

$$\overline{F_1} = \left[\bar{\mathbf{t}}_1(1), \bar{\mathbf{t}}_2(1), ..., \bar{\mathbf{t}}_M(1)\right], \tag{2}$$

where $\overline{F}_1$ is P by M. This process is then repeated for all S subjects in the group, and the P-variate vectors are assembled into a P by S x M matrix, $\boldsymbol{X}$,

$$X = \left[\overline{F_1}, \overline{F_2}, ..., \overline{F_S}\right]. \tag{3}$$

This whole process is repeated for either another group of subjects doing the same task or the same subjects doing a different task, (e.g., group '2') to provide another P by S x M matrix. Now p-variate linear analyses can now be performed on $\boldsymbol{X}$ [5].

2.2. Modified LLDA

The underlying idea of LLDA is to solve multi-class nonlinear classification problems by using a set of locally linear transformations. The overarching assumption of LLDA is that global nonlinear data structures are, in many cases, locally linear and these local structures can then be linearly aligned. The LLDA linearly transforms each local structure (called a "cluster") to a common vector space with a transformation matrix and optimizes the discriminant between different classes globally in the common space.

Consider the resampled t-statistic matrices $\boldsymbol{X_1}$ and $\boldsymbol{X_2}$ in a study involving K subjects and two tasks. We regard the data of each subject as a local linear structure /cluster and try to find a transformation matrix for it such that the transformed data of all the subjects are globally optimally discriminated between the tasks/classes. Let $\boldsymbol{x}$ be a column of either $\boldsymbol{X_1}$ or $\boldsymbol{X_2}$ and it belongs to a subject $\boldsymbol{k} \in \{\mathbf{1,2,...,}\boldsymbol{K}\}$ and a task $c \in \{1,2\}$. Notations $\boldsymbol{x} \in \boldsymbol{k}$ and $\boldsymbol{x} \in \boldsymbol{c}$ will respectively mean that $\boldsymbol{x}$ belongs to subject k and task c. Next, $\boldsymbol{x}$ is transformed to $\boldsymbol{y}$ in the common vector space with Eq. (12)

$$\boldsymbol{y} = \mathbf{U}_{\boldsymbol{k}}^{\mathbf{T}} (\boldsymbol{x} - \boldsymbol{m}_{\bullet \boldsymbol{k}}) \tag{4}$$

$$\boldsymbol{m}_{\bullet \boldsymbol{k}} = \frac{\mathbf{1}}{\boldsymbol{N}_{\bullet \boldsymbol{k}}} \sum_{\boldsymbol{x} \in \boldsymbol{k}} \boldsymbol{x} \tag{5}$$

where N is the dimension of the transformed space. $\mathbf{U}_{\boldsymbol{k}} = [\mathbf{u}_{\boldsymbol{k}1}, ..., \mathbf{u}_{\boldsymbol{kn}}, \ldots, \mathbf{u}_{\boldsymbol{kN}}]$ is the N × N orthogonal transformation matrix of cluster k with $\mathbf{u}_{\boldsymbol{kn}}$ being its nth base, $\boldsymbol{m}_{\bullet \boldsymbol{k}}$ is the mean vector of cluster k, and $\boldsymbol{N}_{\bullet \boldsymbol{k}}$ is number of $\boldsymbol{x}$'s belonging to cluster k. The mean of each cluster is removed in the transformation.

The discriminant after transformation is scored with Eq. (6):

$$J = \log\left(\frac{|\widetilde{B}|}{|\widetilde{W}|}\right) \tag{6}$$

where $\widetilde{\boldsymbol{B}}$ and $\widetilde{\boldsymbol{W}}$ are the between-class and within-class scatter matrices in the common space. The transformed scatter matrices are given as:

$$\begin{aligned}\widetilde{\boldsymbol{B}} &= \sum_{\boldsymbol{c}=\mathbf{1}}^{\boldsymbol{C}} \boldsymbol{N}_{\boldsymbol{c}\bullet} (\widetilde{\boldsymbol{m}}_{\boldsymbol{c}\bullet} - \widetilde{\boldsymbol{m}})(\widetilde{\boldsymbol{m}}_{\boldsymbol{c}\bullet} - \widetilde{\boldsymbol{m}})^{\mathbf{T}} \\ &= \sum_{\boldsymbol{c}=\mathbf{1}}^{\boldsymbol{C}} \boldsymbol{N}_{\boldsymbol{c}\bullet} \widetilde{\boldsymbol{m}}_{\boldsymbol{c}\bullet} \widetilde{\boldsymbol{m}}_{\boldsymbol{c}\bullet}^{\boldsymbol{T}}\end{aligned} \tag{7}$$

$$\widetilde{\boldsymbol{W}} = \sum_{\boldsymbol{c}=\mathbf{1}}^{\boldsymbol{C}} \sum_{\boldsymbol{x} \in \boldsymbol{c}} (\mathbf{y} - \widetilde{\boldsymbol{m}}_{\boldsymbol{c}\bullet})(\mathbf{y} - \widetilde{\boldsymbol{m}}_{\boldsymbol{c}\bullet})^{\mathbf{T}} \tag{8}$$

where $\widetilde{\boldsymbol{m}} = \frac{\mathbf{1}}{\boldsymbol{N}} \sum_{\boldsymbol{x}} \boldsymbol{y} = \mathbf{0}$ and $\widetilde{\boldsymbol{m}}_{\boldsymbol{c}\bullet} = \frac{\mathbf{1}}{\boldsymbol{N}_{\boldsymbol{c}\bullet}} \sum_{\boldsymbol{x} \in \boldsymbol{c}} \boldsymbol{y}$ are the global mean and the mean of class $\boldsymbol{c}$, respectively, after the transformation, and $\boldsymbol{N}_{\boldsymbol{c}\bullet}$ is the number of $\boldsymbol{x}$'s belonging to class $\boldsymbol{c}$. Because the mean of a cluster is removed in the transformation, in our case $\widetilde{\boldsymbol{m}}$ equals 0. $\widetilde{\boldsymbol{B}}$ and $\widetilde{\boldsymbol{W}}$ can also be written in matrix form for analysis.

LLDA attempts to maximize J in (6) under the orthogonality normal constraint, $\mathbf{U}_{\boldsymbol{k}} \mathbf{U}_{\boldsymbol{k}}^{\boldsymbol{T}} = \mathbf{U}_{\boldsymbol{k}}^{\boldsymbol{T}} \mathbf{U} = \boldsymbol{I}$. The constrained nonlinear programming is solved by successively calculating the bases of $\mathbf{U}_{\boldsymbol{k}}$ from the subspace orthogonal to the already calculated bases. Unlike the original LLDA description in [6], we propose using an overall optimization procedure using two routines, a "subspace" routine, and a "one-base" LLDA routine, which we found more robust and reliable for fMRI data. The "subspace" routine creates subspaces orthogonal to the already calculated bases $\mathbf{u}_{\boldsymbol{k}\mathbf{1}} \cdots \mathbf{u}_{\boldsymbol{k}(\boldsymbol{n}-\mathbf{1})}$ and calculates $\mathbf{u}_{\boldsymbol{kn}}$ in the subspace by calling the "one-base" which solves a one-base LLDA problem. The "subspace" routine repeats iteratively until all the bases are calculated. The "one-base" routine solves a one-base LLDA problem that is similar to LLDA but with a different constraint $\mathbf{U}_k^T \mathbf{U}_k = 1$ where $\mathbf{U}_k$ is just a column vector and only subject to the normal constraint. The procedure proposed here has several advantages over the original one, in terms of computational cost and stable convergence. Detail derivations are omitted here due to limited space limit.

In contrast to the original classification problem proposed for LLDA, our goal is to further determine the linear combination of ROIs that maximally discriminate between groups. A straightforward way is to use the average of $\mathbf{U}_k$'s. However, as pointed out by Kherif et al [8], averaging of fMRI data across individuals is only prudent when the mean is a good representation of the group. They suggested a way to look for selecting subjects with "similar" activation patterns. In the current situation, since the activation statistics from each individual have been transformed to a common vector space (defined by the $\boldsymbol{y}_i$'s), we can now selectively weight each subject so that the transformed $\boldsymbol{y}_i$'s are maximally discriminable in the transformed vector space. Specifically, we can weight each subject, k, by a small positive factor α_i,

$$\boldsymbol{y}_i = \alpha_k \mathbf{U}_k^{\mathrm{T}} (\boldsymbol{x}_i - \boldsymbol{m}_{\bullet k}), \quad \text{subject to:}$$

$$\sum_{i=1}^{K} \alpha_i = 1, \alpha_i \in [0,1] \tag{9}$$

where k is the subject and there are K total subjects and the means of the y's are maximally discriminable by, e.g., a standard t-test. The α_i's can then be estimated by constrained non-linear optimization methods.

Thus, the overall transformation describing the linear combination of ROIs that maximally discriminate between groups is then estimated by:

$$\overline{\mathbf{U}} = \sum_{k=1}^{K} \alpha_k \mathbf{U}_k \tag{10}$$

To determine the significance of the elements of $\overline{\mathbf{U}}$, we can estimate one element at a time via the Kolomogorov-Smirnov (KS) test to determine whether the distribution of transformed data $\boldsymbol{y}$ is altered by elimination of that element [9]. This nonparametric test is more general than parametric tests such as the t-test.

3. RESULTS

3.1. fMRI Experiment

To demonstrate the proposed method, we utilized fMRI data that would be expected, based on prior knowledge, to activate subcortical structures. The paradigm consisted of externally guided (EG) or internally guided (IG) movements based on three different finger sequencing movements (FSMs) performed alternatively by either the right or left hand. For FSM #1, subjects had to (a) make finger-to-thumb opposition movements in the specific order of the index, middle, ring and little finger; (b) open and clench the fist twice; (c) complete finger-to-thumb oppositions in the opposite order (i.e., little, ring, middle and index finger); (d) open and clench the fist twice again; and then (e) repeat the same series of movements. The FSM #2 was the same as above except the sequence for (a) changed to index, ring, middle and little fingers and (c) changed to the reversed order of the revised (a) (i.e., little finger, middle, ring, and index finger). The FSM #3 was the same as above except the sequence for (a) changed to middle, little, index, and ring fingers and (c) changed to the reverse of above the revised (a) (i.e., ring, index, little, middle fingers). The above three sequences (instead only one sequence) were chosen to insure the continuous engagements of the subjects' attention.

The above FSM were performed in two test conditions (see Figure 1): *following* (Externally guided movements-EG) and *continuation* (Internally guided movements-IG). The two consecutive conditions were preceded and followed by a rest (R) period (30 s). The EG, IG, and R periods were designated using the visual cues, "FOLLOW," "CONTINUE," and "REST", respectively. The FOLLOW-CONTINUE-REST cycle was repeated four times during each run (total duration of 6 minutes). There were total of 4-6 runs performed on each subject. (Details are in this paper's submitted journal version.)

3.1. Performance and Discussions

To illustrate the performance of the proposed LLDA-based approach, we also performed Standard SPM analysis on our data. The first level comparisons were made between right hand and left hand finger sequential movements, and the individual activation map (right > left; and left > right) for each subject was first generated by a fixed-effect model with the voxels that exceeded a probability threshold of p = 0.05 (FDR (False Discovery Rate) corrected). The second level analysis was made based on the results of the individual activation maps generated in the first level comparison. That is, the contrast images, one from each of 10 subjects from the first level comparison (for example, right>left) were assessed using one sample t test by a random-effect model. The regions that have clusters with at least 5 contiguous voxels exceeded a probability threshold of p = 0.001 (uncorrected) were identified as activated regions.

Using standard SPM, we found activation in the left primary motor cortex during right hand movement, and similarly left primary motor cortex activation during right hand movement. Activation in the left cerebellar hemisphere was detected using left hand movement only (Figure 1a).

In contrast, with LLDA significant activation was detected with in the left primary cortex, left anterior cingulate cortex, the left putamen/globus pallidus, the left thalamus, and right cerebellar hemisphere during right hand movement. With left hand movement LLDA detected significant activity in the right primary motor cortex, the right supplementary area, the left caudate, the right putamen/globus pallidus, the right thalamus and the left cerebellar hemisphere, as in Figure 1(b). In all cases the separation across each subject using $\overline{\mathbf{U}}$ was statistically significantly.

Compared with SPM, in addition to finding activations similar to the SPM approach, the proposed approach also found a number of subcortical regions that were significantly active, including the contralateral thalamus, putamen/GP. We also found differences between the use of the right and left hand, such that the right SMA was activated only during left hand performance. This result most likely reflects differences due to hand dominance.

4. CONCLUSION

In this paper, we developed a modification of the local linear discriminant (LLDA) algorithm to perform ROI-based groupwise analysis on activation maps using fMRI data. Based on analysis with real fMRI data, the proposed approach provides more expected activation than that of standard SPM. This suggests that the vector space of ROI-based activation statistics is relatively robust to individual subjects, but differs by task activation.

There is growing recognition that warping of individual subjects' brains to a common space may cause particular registration problems, especially with small subcortical structures [20, 21]. Despite widespread evidence that subcortical structures such as the thalamus are an integral part of the network used for motor control, only the proposed LLDA-based approach, when applied to unwarped data, was able to detect significant activation differences between right and left handed task performance.

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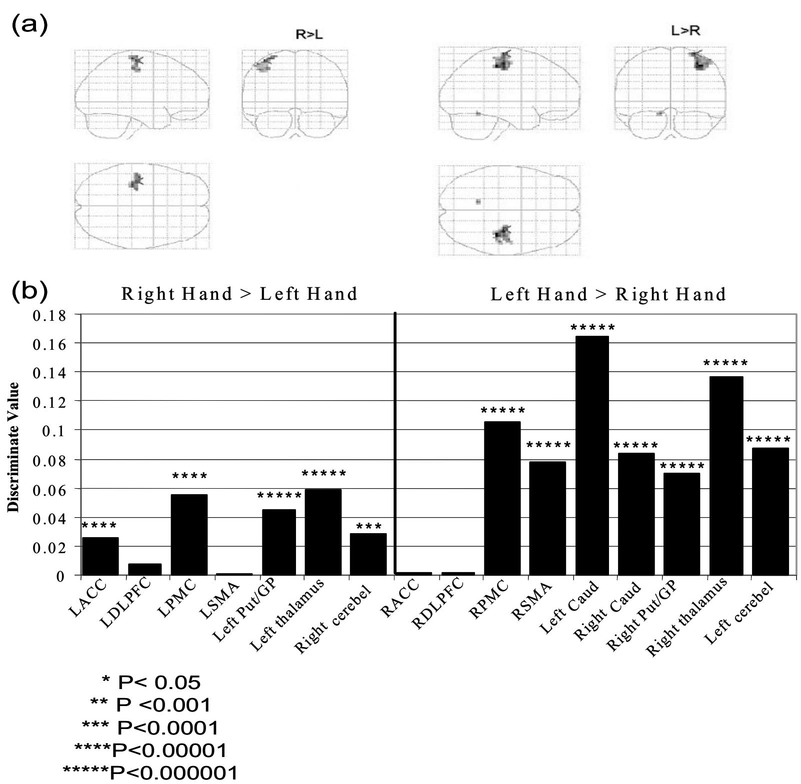

Figure 1: Performance of the proposed LLDA-based approach in fining significant ROI activations. To make a comparison, we also performed Standard SPM analysis on our data, as the results shown in (a), where clusters with at least 5 contiguous voxels exceeded a probability threshold of p = 0.001 (uncorrected) were identified as activated regions. In (b), relative contribution of the 16 ROIs between right hand and left hand finger sequential movements.