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fMRI activation pattern recognition: A novel application of PCA in Language Network of Pediatric Localization Related Epilepsy

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Abstract— **In this study, a novel application of Principal Component Analysis (PCA) is proposed to detect language activation map patterns. These activation patterns were obtained by processing functional Magnetic Resonance Imaging (fMRI) studies on both control and localization related epilepsy (LRE) patients as they performed an auditory word definition task. Most group statistical analyses of fMRI datasets look for "commonality" under the assumption of the homogeneity of the sample. However, inter-subject variance may be expected to increase in large "normal" or otherwise heterogeneous patient groups. In such cases, certain different patterns may share a common feature, comprising of small categorical sub-groups otherwise hidden within the main pooling statistical procedure. These variant patterns may be of importance both in normal and patient groups. fMRI atypical-language patterns can be separated by qualitative visual inspection or by means of Laterality Indices (LI) based on region of interest. LI is a coefficient related to the asymmetry of distribution of activated voxels with respect to the midline and it lacks specific spatial and graphical information. We describe a mathematical and computational method for the automatic discrimination of variant spatial patterns of fMRI activation in a mixed population of control subjects and LRE patients. Unique in this study is the provision of a data-driven mechanism to automatically extract brain activation patterns from a heterogeneous population. This method will lead to automatic self-clustering of the datasets provided by different institutions often with different acquisition parameters.**

I. INTRODUCTION

Through Functional Magnetic Resonance Imaging (fMRI) it is possible to produce brain activity patterns that represent the execution of a given task, such as the Auditory Decision Description Task (ADDT). This language paradigm is used in this study. Several investigators have described reorganization of language networks from canonical areas to distinct locations either in the same or contra lateral hemisphere due to the effect of structural lesions (e.g. stroke) or functional processes (e.g. epilepsy) [1]–[3]. Typical language regions include Broca's and Wernicke's areas. Atypical fMRI activation patterns were defined as those cases in which brain activation found in one or two regions is right or bilateral; left dominance is considered typical if both regions are left, or one left and the other bilateral or non-canonical [4]–[6].

Most group statistical analyses of fMRI datasets look for "commonality" under the assumption of the homogeneity of the sample, or use control group as standard by excluding healthy controls with atypical dominance [7]. However, inter-subject variance may be expected to increase in large "normal" or otherwise heterogeneous patient groups.

In this paper we develop an objective PCA-based data-driven method to segregate populations, without selecting region of interest(ROI) or normalizing the Z-score range, seeking distinct language activation patterns among the heterogeneous group that might be associated with normal variant and LRE pathological variant conditions, which may help to study brain changes that reflect brain plasticity [1]–[3], and also improve our understanding about the language compensation mechanism by associating clinical variables with these distinct activation patterns, such as seizure foci location, age of epilepsy onset. PCA enables computation of a linear transformation that maps data from a high dimensional space to a lower dimensional orthogonal space that maximize variability [8]. One advantage of the PCA is that it is a data-driven method as opposed to regular (ROI) methods that are based on prior assumptions, and to subjective visual methods that are prone to bias.

II. METHODS

Our university in collaboration with several pediatric hospitals with established epilepsy programs, developed a multisite repository for control and pediatric epilepsy data to facilitate fMRI group studies in LRE patients. The long term goal is to obtain data from a large group of patients in order to characterize subtypes of the heterogeneous expression of atypical language networks and relate them to clinical variables such as age of brain injury, age of epilepsy onset, underlying etiology, and location of seizure focus.

A. Data Collection

At the current stage this research endeavor, 133 fMRI datasets with 11 null activation datasets have bee processed. Data sets from 64 control and 58 children with LRE (patient population) were thus included in this study (see Table I). Control subjects were required to be right handed and free of any current or past neurological or psychiatric disease. Each subject was asked to perform a word definition task.

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TABLE I

PATIENT AND SUBJECT DISTRIBUTION BY INSTITUTION AND SCANNER TYPE *

Subjects	Inst.	Scanner	TR	Num
	Hospital for Sick Children, Toronto , Canada	GE 1.5 T	2	19
	Miami Children's Hospital, Miami,FL	Phillips Intera 1.5 T	2	10
LRE	Children's National Medical Center,Washington,DC	Siemens Trio 3 T	2	14
	BC Children's Hospital, Vancouver, Canada	Siemens Avanto 1.5 T	3	4
	Children's Hospital of Philadelphia,PA	Siemens Trio 3 T	3	11
Control	Children's National Medical Center,Washington,DC	Siemens Trio 3 T	3	64

* No-activation cases were not taken into account

During the "on" period, the participant listened to a definition of an object followed by a noun. Participants were instructed to press a button each time they judged that the description matched the noun. During the "off" period,the subject listened to the task definitions digitally presented in reverse speech [9].

B. Data Preprocessing

Each hospital is likely to provide fMRI datasets using distinct file formats, plane of exam, view orientation, slicing, voxel size, repetition time (TR), and number of time points. Consequently, orientation, slice number, voxel size and field of view were corrected and standardized. Further more, datasets were converted into Neuroimaging Informatics Technology Initiative (NIFTI) format using the transversal view and radiology convention, and were finally mapped into the standard Montreal Neurological Institute (MNI) brain with 3mm voxel size and dimensions of 63x71x63.

A set of scripts in MATLAB was developed to perform the needed correction and standardization. The fMRI Software Library (FSL) was used to perform the pre- and post-processing required for obtaining the resulting 3-D activation maps. In the first level of analysis, each subject's data was motion corrected, high-pass filtered, and smoothed using a full width at half maximum (FWHM) of 7 mm. All the images used in the experiments were Z (Gaussianised T/F) statistic images using cluster threshold $Z > 2.3$ and a corrected cluster significance threshold of $p = 0.05$ [9], [10].

C. PCA on Activation Maps

Previous publications have reported PCA as the core analysis method for Scale Subprofile Model (SSM), which was presented as a PCA approach for modeling regional patterns of brain function [12]–[14]. The relationship between the so-called subject loading and regional covariance pattern (eigen-image) has been widely proved [15]. According to the concept and merit of subject loading, we performed PCA on our 122 fMRI activation maps without masking and intensity normalization, utilized the top two components (subject loadings) to self-cluster 3 activation patterns through the Euclidean distance method. The following are the detailed steps:

1. Each individual's 3D dataset was transformed into a 1D dataset with n voxels, where n is defined by $M \times N \times L$, where M , N and L are the resolutions of the activation map image in the x , y and z axes respectively. The whole population of subjects was organized on a 2D matrix X, where each subject contributes a specific column in the matrix. The mean value for each voxel across all subjects, which composes the mean vector $\overrightarrow{m}$ of these k subjects, was computed.

2. Each activation map was centered by subtracting the mean vector for all subjects. The covariance matrix Cx was then calculated from (1).

$$Cx = \Psi^T \Psi \tag{1}$$

where $\Psi = [\Phi_1 \Phi_2 .. \Phi_n]$ and each Φ is defined as $\Phi = x_i - m_i, i = 1, 2...k$ with x_i being the vector containing the activation of a given subject.

3. MATLAB's eigen-function was used to compute the eigenvector matrix (E) of the covariance matrix (Cx) Then, the eigenvectors were sorted by the corresponding eigenvalues. Each subject was represented by a row vector $e_{.i} = [e_{1i} .. e_{ji}]$ where j corresponded to the eigenvectors being used. Notice the E matrix here is equivalent to the subject loading matrix as in SSM and U matrix calculated in (2) is equivalent to the regional covariance pattern, but instead of "regional", our U is the covariance patterns of the whole 3D brain region with normalization such that $\parallel u_i \parallel = 1$.

$$U = \Psi E \tag{2}$$

4. Based on the e_i distribution in the matrix E, three primary clusters with far distances from each other were first determined linearly. Then the new mean (m_{mean}) vector of these clusters was generated with subjects only chosen from the three primary clusters, and the principal components of these clusters were calculated, generating the new matrix U_{mean} following (2) .

5. To cluster subjects' activation maps not falling in any of the primary clusters (undecided regions),Each undecided subject will be assigned to the closet cluster using the distance method. Vector x_{new} will now represent the activation map of the subject. The following steps are undertaken:

a). Project Φ_{new}, which is the new centered x_{new} ($\Phi_{new} = x_{new} - m_{new}$), onto the primary clusters defined eigenspace using (3).

$$\hat{\Phi}_{new} = \sum_{l=1}^{j} u_l^T \Phi_{new} u_l \tag{3}$$

Where each u_l represents a column vector of the U_{new} matrix as described in step 4.

b). Calculate the Euclidean distance feature using (4) below:

$$D_i = ||\widehat{\Phi}_{new} - \Phi_i|| \tag{4}$$

for $i = 1, 2, ..., q$, where q is the number of primary cluster members, with $\Phi_i = x_i - m_{new}$ and where j ($j < k$) is the number of eigenvectors selected. In this study, j was

assigned the value of 2 since 2 eigenvectors were found most relevant for meaningful clustering results.

c). The new subject Φ_i was assigned to the cluster whose member had the minimum distance calculated through (4). In other words, the new subject is assigned to the cluster where the closest identified subject Φ_i was located.

III. RESULTS

A. PCA clustering Results

The distribution of the three final clusters found by the distance method among the first two eigenvectors (Subject Loadings) are depicted as in Fig.1.

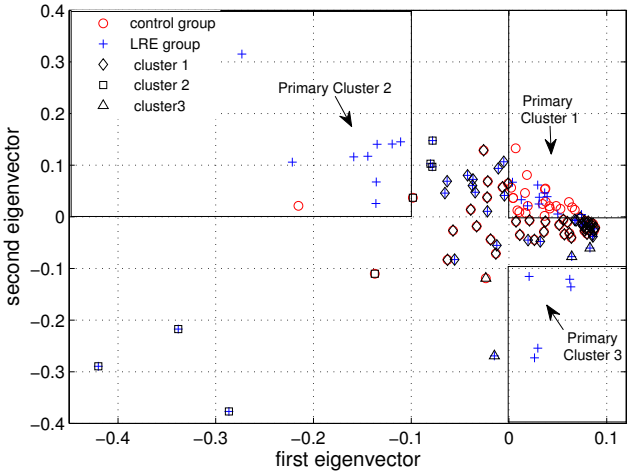

Fig. 1. Final clusters using two eigenvectors.These first 2 dominant eigenvectors are used to select three primary clusters based on the criteria: cluster 1:$e_{1i} > 0 \cap e_{2i} > 0$ (which is the most condensed cluster region with 32 data points); cluster 2: $e_{1i} < -0.1 \cap e_{2i} > 0$ (with ten data points); cluster 3: $e_{1i} > 0 \cap e_{2i} < -0.1$ (with five data points). The remaining region outside these three clusters contains 75 data points undecided. After distance method, 63 are now assigned to cluster 1 marked as diamonds; four are now assigned to cluster 2 marked as squares; and eight are now assigned to cluster 3 marked as triangles. There are mixed LRE and control subjects in cluster 1. However, the majority of the members in clusters 2 and 3 belong to LRE group.

B. activation patterns by PCA clustering

The final clusters' mean activation patterns are shown in Fig.2 after the automatic self-clustering through distance methods on the top two subject loadings. The strongly activated areas found in these three types of activation patterns (in relation to the three clusters) broadly encompass Broca's and Wernicke's areas. As anticipated, cluster 1 (Fig.2a) was the typical language response on the left hemisphere while cluster 3 (Fig.2c) had an atypical right hemisphere dominant response. Most of the subjects from cluster 2 and 3 were patients, 15 patients out of 18 for cluster 2 and 8 out 9 for cluster 3, while control subjects are dominant in cluster 1 (60/95) (Fig. 1). Cluster 2 (Fig.2b) consisted of a group of cases that shared the same areas as cluster 1. However, our method was able to distinguish cluster 2 from cluster 1 because cluster 2's intensities were much higher than those of cluster 1, especially in Broca's area, also it has greater right sided cerebellum activation. Note that clusters 2 and 3 are variants compared to major cluster 1, and cluster 3 is closer to current notion of atypical language activation pattern which is atypical bilateral or right dominant.

IV. DISCUSSIONS AND FUTURE WORKS

A. Discussions

In this study we introduced a PCA procedure designed to automatically identify sub-groups of distinct language activation patterns in control and LRE patients from different sites, who performed the same word definition fMRI task. PCA also identified two subgroups with left lateralization. The two left dominant subgroups differed on the intensity level of regional activations. The typically developing control children primarily were in the first subgroup while mostly patients belonged to the second subgroup. These findings may represent an effect of epilepsy or its underlying substrate on language network expression or may represent different strategies in performing the task [16]. The intensity difference suggests that patients may remain left dominant but draw upon the distributed language network in a different way than the control group. This implies antiepileptic drug interaction for the patients or their compensatory mechanism to perform the task, which means they may rely on a different cognitive strategy. Simple and advanced PCA methods have been utilized to identify fMRI activation patterns. Though the concept and merit of subject loading is similar as SSM [14], our method is simpler and the major difference relies on the fact that we applied PCA without masking nor intensity normalization, which is important for recognizing the distinct patterns of different intensity. The relevance of this finding was discussed above.

Differences in scanner manufacturer, magnetic strength and acquisition parameters are perceived as limitations that hinder any group analysis on the datasets collected from a variety of sites. Indeed, standard group analysis post-processing discourages the utilization of different scanners, different settings, and different image resolution, because the methods are dominated by models of assumptions. In contrast, our adaptation of the PCA method is entirely data-driven.

Since it's both cost-effective and objective, the automatic cluster tool presented here may help the assessment of large data sets in which visual or ROI rating may be unpractical or difficult. It could also be used as a means to interrogate data for clinical variables.

B. Future Works

The next challenges are to determine a reasonable cluster number, to define other patterns of atypical language activation such as those localized in the neighboring non-canonical areas, and also investigate the differences in extent and peak intensities within the same hemisphere. Future research may also take advantage of the sensitivity of the PCA for group separation in order to overcome human rating errors or rigid paradigms of interpretation which perhaps too narrowly limit brain language activation into simple patterns of left , bilateral or right.

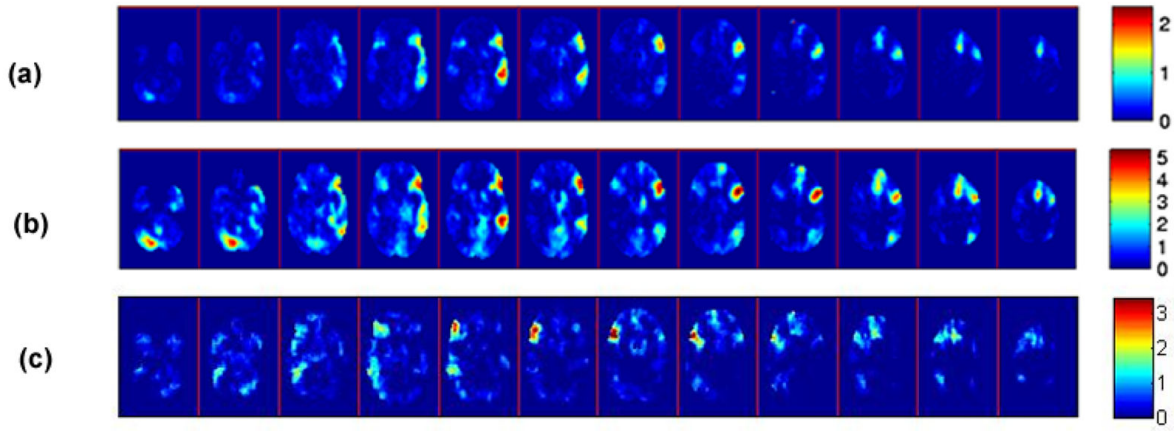

Fig. 2. Mean activation maps for each cluster. 2D array of selected axial cuts color coded for activation intensities. Higher activations are in red color. Brain oriented in radiological convention: left hemisphere on the right side. (a) Mean activation map for cluster 1. Notice the strong left lateralization of anterior (Broca) and posterior (Wernicke) clusters. (b) Mean activation map for cluster 2. The z value range is higher than (a). This explains the better definition of Supplementary Motor Area (SMA).Also note greater activation in right cerebellum and in mid frontal gyrus. (c) Mean activation map for cluster 3 with an atypical right hemisphere dominant response. Notice the strong right lateralization of anterior (Broca) cluster.

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