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One side lattice memory reduced ordering function allows discrimination in resting state fMRI

***Abstract*—Currently there is a lot effort to define neurological biomarkers from resting state fMRI data for different neurological diseases. fMRI voxels are high dimensional vectors, so that dimensional reduction, to scalar values if possible, is highly desirable. At the same time, biomarkers are to be provided as brain localizations which may have an anatomical interpretation. A general procedure consists in the reduction of fMRI data to scalar values, which are then entered in a feature selection process to obtain the desired localizations of discriminant voxel sites in the brain. These voxel sites may be interpreted as biomarkers. Classification is performed on the feature vectors extracted from the selected brain voxel sites. In this paper, we follow an approach born from Multivariant Mathematical Morphology in order to obtain meaningful orderings on multivariate data. We define a supervised h-ordering defined on the fMRI time series by the response of Lattice Auto-associative Memories (LAAM) built from specific fMRI voxels. Instead of performing morphological processing based on the induced ordering, we use the LAAM supervised h-function map for feature selection and feature extraction. We perform a classification experiment on a set of resting state fMRI images of schizophrenia patients with and without a history of auditive hallucinations obtaining high accuracy with one side LAAM h-function.**

I. Introduction

The study of low frequency correlation in brain fMRI data obtained during resting state has uncover a collection of functional networks that constitute a brain fingerprint highly likely to identify image biomarkers for several brain neuronal diseases [5], [10], [18]. A big advantage of resting state fMRI experiments comes from the lack of effort on the cognitive abilities of the subjects, therefore they can be applied to a wide variety of subjects. For instance, cognitive impaired subjects are not pressed into uncomfortable situations.

The informative potential of resting state fMRI can be exploited to classify subjects and, conversely, classification can be used as a method for biomarker identification. The general method is as follows: fMRI data is transformed to a suitable low dimensional data, preferably scalar values *per* voxel. Then, these low dimensional data representations are entered into a feature selection method. Data transformations, such as Principal Component Analysis (PCA) that discard localization information do not allow to report brain localizations that can be further analyzed to identify biomarkers. Therefore, feature selection usually is based on some voxel saliency measure, such as the correlation with the categorical variable. The result of feature selection is a collection of voxels sites where feature vectors are extracted to enter the classifier training and validation process.

In this paper we follow an approach proposed for Multivariate Mathematical Morphology in order to obtain sensible orderings of high dimensional vectors. We propose a supervised h-function based on Lattice Auto-Associative Memories (LAAMs) [15], [14], which may lead to a LAAM-supervised ordering, as the fMRI data dimensionality reduction [7], [3]. The LAAM h-function provides a scalar value for each voxel. Specifically, we will demonstrate the value of the proposed approach on the discrimination of Schizophrenia patients, where we obtain encouraging results on the discrimination of patients with and without a history of auditory hallucinations.

LAAMs are auto-associative neural networks whose functional neurons perform morphological (lattice) operations. LAAMs present interesting properties such as perfect recall, unlimited storage and one-step convergence. Compared to the supervised h-orderings introduced by [19], the proposed LAAM-supervised ordering keeps multivariate morphology under the general framework of Lattice algebra. All the required calculations are defined using the Lattice algebra operators ($\vee$, $\wedge$ and $+$) and therefore, LAAM-supervised ordering is faster and imposes less computational burden than the supervised orderings previously proposed in [19].

Section II reviews the literature on resting state fMRI processing. Section III recalls the definition of Lattice Auto-Associative Memories. Section IV introduces Multivariant Mathematical Morphology based on supervised reduced orderings. Section V introduces LAAMs-based supervised ordering for multivariate data. Section VI presents some experimental results. Finally we give some conclusions and further work in section VII.

II. Resting state fMRI

Resting state fMRI data has been used to study the connectivity of brain activations [5], [10], [18]. The assumption is that temporal correlation of low frequency oscillations in diverse areas of the brain reveal their functional relations. When no explicit cognitive task is being performed, the connections discovered are assumed as some kind of brain fingerprint, the so-called default-mode network. Caution must be taken on the confounding effects of the ambient noise, the respiratory and cardiac cycles. One strong reason for resting state fMRI experiments is that they do not impose constraints on the cognitive abilities of the subjects. For instance in pediatric applications, such as the study of brain maturation [11], there is no single cognitive task which is appropriate across the aging population. Several machine learning and data mining approaches have been taken: hierarchical clustering [4], independent component analysis (ICA) [6], [13], [1], fractional amplitude of low frequency analysis [24], multivariate pattern analysis (MVPA) [11], [12]. Graph analysis has been suggested [18] as a tool to study the connectivity structure of the brain. Resting state fMRI has being found useful for performing studies on brain evolution based on the variations in activity of the default mode network [11], depression (using regional homogeneity measures) [21], Alzheimer's Disease [8], and schizophrenia.

Schizophrenia is a severe psychiatric disease that is characterized by delusions and hallucinations, loss of emotion and disrupted thinking. Functional disconnection between brain regions is suspected to cause these symptoms, because of known aberrant effects on gray and white matter in brain regions that overlap with the default mode network. Resting state fMRI studies [9], [22], [23] have indicated aberrant default mode functional connectivity in schizophrenic patients. These studies suggest an important role for the default mode network in the pathophysiology of schizophrenia. Functional disconnectivity in schizophrenia could be expressed in altered connectivity of specific functional connections and/or functional networks, but it could also be related to a changed organization of the functional brain network. Resting state studies for schizophrenia patients with auditory hallucinations have also been performed [20] showing reduced connectivity. Recent findings [16] show that focusing on the resting state network obtained by correlation with voxels in a left Heschl's gyrus (LHG; MNI coordinates -42,-26,10) regions of interest from the auditory cortex it is possible to find significative differences between schizophrenia patients with and without a history of auditory hallucinations.

III. Lattice Auto-Associative Memories (LAAMs)

Given a set of input/output pairs of patterns $(X, Y) = \left\{\left(\mathbf{x}^{\xi}, \mathbf{y}^{\xi}\right); \xi = 1, .., k\right\}$, a linear heteroassociative neural network based on the pattern's cross correlation is built up as the cross-correlation of input and output patterns $W = \sum_{\xi} \mathbf{y}^{\xi} \cdot \left(\mathbf{x}^{\xi}\right)'$. Mimicking this constructive procedure [15], [14] proposed the following constructions of erosive and dilative LAMs, respectively

$$W_{XY} = \bigwedge_{\xi=1}^{k} \left[\mathbf{y}^{\xi} \times \left(-\mathbf{x}^{\xi}\right)'\right] \text{ and } M_{XY} = \bigvee_{\xi=1}^{k} \left[\mathbf{y}^{\xi} \times \left(-\mathbf{x}^{\xi}\right)'\right], \tag{1}$$

where $\times$ is any of the $\boxdot$ or $\boxtimes$ operators, reducing the notational burden since $\mathbf{y}^{\xi} \boxdot \left(-\mathbf{x}^{\xi}\right)' = \mathbf{y}^{\xi} \boxtimes \left(-\mathbf{x}^{\xi}\right)'$. Here $\boxdot$ and $\boxtimes$ denote the $\max$ and $\min$ matrix product, respectively defined as follows $C = A \boxdot B = [c_{ij}] \Leftrightarrow c_{ij} = \bigvee_{k=1..n} \{a_{ik} + b_{kj}\}$, and $C = A \boxtimes B = [c_{ij}] \Leftrightarrow c_{ij} = \bigwedge_{k=1..n} \{a_{ik} + b_{kj}\}$.

If $X = Y$ then W_{XX} and M_{XX} are called Lattice Auto-Associative Memories (LAAMs). LAAMs present some surprising properies: perfect recall for an unlimited number of stored patterns, i.e. $W_{XX} \boxdot X = X = M_{XX} \boxtimes X$, and convergence in one step for any input pattern, i.e. if $W_{XX} \boxdot \mathbf{z} = \mathbf{v}$ and $M_{XX} \boxdot \mathbf{z} = \mathbf{u}$, then $W_{XX} \boxdot \mathbf{v} = \mathbf{v}$ and $M_{XX} \boxtimes \mathbf{u} = \mathbf{u}$.

IV. Multivariant Mathematical Morphology

Morphological operations are mappings between complete lattices, denoted $\mathbb{L}$ or $\mathbb{M}$, that are partially ordered sets where infimum and supremum are defined for all pairs of elements. For every subset $Y \subseteq \mathbb{L}$ an *erosion* is a mapping $\varepsilon : \mathbb{L} \to \mathbb{M}$ that conmutes with the infimum operation, $\varepsilon\left(\bigwedge Y\right) = \bigwedge_{y \in Y} \varepsilon(y)$. Similarly, a *dilation* is a mapping $\delta : \mathbb{L} \to \mathbb{M}$ that conmutes with the supremum operation, $\delta\left(\bigvee Y\right) = \bigvee_{y \in Y} \delta(y)$. On top of these basic operators it is possible to define image fiters such as the morphological gradient $g(Y) = \delta(Y) - \varepsilon(Y)$, or the top-hat $t(Y) = Y - \delta(\varepsilon(Y))$.

A. Multivariate ordering

Morphological operators are well defined for scalar images, however their extension to multivariate images is not straightforward since defining a total order on these vector spaces is required. One way to accomplish that mapping the multivariant values into a scalar through the definition of a reduced ordering. A h-ordering is defined by a surjective map of the original partially ordered set onto a complete lattice $h : X \to \mathbb{L}$, so that the order in the target lattice induces a total order in the source set X, that is, $r \leq_h r' \Leftrightarrow h(r) \leq h(r')$.

The reduced ordering can be defined on the basis of a supervised classifier trained with some pixel values extracted from the image [19]. Formally, a h-supervised ordering over a non-empty set X [19] is a h-ordering satisfying the conditions $h(b) = \perp, \forall b \in B$, and $h(f) = \top, \forall f \in F$, where $B, F \subset X$ are subsets of X such that $B \cap F = \emptyset$, and $\perp$ and $\top$ are the bottom and top elements of the target lattice, respectively. Erosion operators increase image regions of points close to the background, and dilation operators will increase image regions of points close to the foreground.

V. LAAMs-based Supervised Ordering

A. LAAMs-based h-function

Our contribution [2], [7], [3] to reduced supervised orderings is the definition of a h-function based on LAAMs. In [17] the use of LAAMs and the Chebyshev distance was proposed for classification tasks. Here, we propose their use to define an h-fuction that yields to a supervised ordering among multivariate data and so, allow multivariate morphological operations under the general Lattice algebra theoretical setting.

Given a multivariate data vector $\mathbf{c} \in \mathbb{R}^n$ and a non-empty training set $X = \{\mathbf{x}_i\}_{i=1}^{K}$ such that $\mathbf{x}_i \in \mathbb{R}^n$ for all $i = 1, \ldots, K$; we define the LAAM based h_X-function as:

$$h_X(\mathbf{c}) = \zeta\left(\mathbf{x}^{\#}, \mathbf{c}\right), \tag{2}$$

where $\mathbf{x}^{\#} \in \mathbb{R}^n$ is the recall result from the LAAM, can be either the min matrix product of the vector $\mathbf{c}$ and the erosive memory M_{XX}, or the max matrix product of $\mathbf{c}$ with the dilative memory W_{XX}, $\mathbf{x}^{\#} = M_{xx} \boxtimes \mathbf{c} = W_{xx} \boxdot \mathbf{c}$. $\zeta(\mathbf{a}, \mathbf{b})$ denotes the Chebyshev distance between two vectors given by $\zeta(\mathbf{a}, \mathbf{b}) = \bigvee_i |a_i - b_i|$, $i = 1, \ldots, n$.

B. One-sided LAAM supervised ordering

The LAAM-based h_X-function (2) yields directly to the formulation of the *one-side LAAM-supervised ordering*:

$$\forall \mathbf{x}, \mathbf{y} \in \mathbb{R}^n, \ \mathbf{x} \leq_X \mathbf{y} \Longleftrightarrow h_X(\mathbf{x}) \leq h_X(\mathbf{y}). \tag{3}$$

The one-side LAAM-supervised ordering induces a lattice $\mathcal{L}_X$, whose bottom is the set of fixed points of the LAAM built upon X, $\perp_X = \mathcal{F}(X)$, where $\mathcal{F}(X)$ is the set of fixed points of the LAAM. FIxed points are mapped to 0, and the LAAM h_X-function is non-negative. On the other hand, there is no upper bound for the LAAM h_X-function, thus we can not identify the the top element of $\mathcal{L}_X$, hence it is not a complete lattice. The proposed ordering (3) allows to define erosion operators increasing the image regions of voxels close to $\mathcal{F}(X)$, according to the Chebyshev distance, and dilation operators shrinking those image regions of voxels far from $\mathcal{F}(X)$.

VI. Experimental results

The aim of the experiments in this section is a proof of concept of the approach on a specific case, that of the discrimination of schizophrenia patients with and without auditory hallucinations. The experiment shows that this approach is able to perform this classification with high accuracy, sensitivity and specificity using a LAAM h-function built from selected voxel ROI located on the LHG.

A. Process

We proceed as follows:

1) Resting state fMRI data is first preprocessed to ensure that all fMRI volumes are aligned and warped to the spatially normalized structural T1-weighted data. Also, covariates are regressed out to remove noise and motion artifacts.
2) Compute the one sided LAMM h-function extracting the seed voxels from the locations shown in Figure 1 in each subject. Foreground seed is the average time signal from a selection of voxels in the LHG according to [16]. We obtain a 3D h-map from the specific seeds for each subject.
3) Compute the Pearson's Correlation Coefficient (PCC) between each voxel h-map values across subjects with the categorical variable indicating the class of the subject. Each classification experiment involves a separate correlation computation, obtaining a volume of correlation coefficients for each. We have explored the discrimination between schizophrenia patients with and without auditory hallucinations, i.e. SZAH versus SZnAH.
4) Feature selection consists in selecting the voxel sites with the largest absolute values of the correlation coefficients. Experiments cover a wide range of feature vector dimensions.
5) Feature extraction consists in building the actual feature vectors extracting the selected voxel site values from the h-map of each subject. Therefore, we have separate feature datasets for each feature vector size.
6) We perform a classification experiment with linear kernel SVM classifiers to assess the discrimination power of the feature vectors. For validation we apply a ten fold cross-validation strategy, repeated one hundred times.

TABLE I
ACCURACY, SENSITIVITY AND SPECIFICITY OF THE CLASSIFICATION SZNAH VS. SZAH FOR VARIOUS FEATURE VECTOR SIZES

	500	1 000	5 000	10 000
Accuracy	97.5	97.5	97.5	92.5
Sensitivity	100	100	100	100
Specificity	95	95	95	85

Accuracy results are assumed to provide some endorsement of the value of the image biomarkers identified by the feature masks.

B. Materials

We perform computational experiments resting state fMRI data obtained from two groups of schizophrenia patients: 26 subjects with and 14 subjects without auditory hallucinations (SZAH and SZnAH respectively). For each subject we have 240 BOLD volumes and one T1-weighted anatomical image. Details of image acquisition and demographic information are given elsewhere [16]. The data preprocessing begins with the skull extraction using the BET tool from FSL (http://www.fmrib.ox.ac.uk/fsl/). All the images were manually AC-PC transformed. The functional images were coregistered to the T1-weighted anatomical image. Further preprocessing, including slice timing, head motion correction (a least squares approach and a 6-parameter spatial transformation), smoothing (FWHM=4mm) and spatial normalization to the Montreal Neurological Institute (MNI) template (resampling voxel size = 3 mm × 3 mm × 3 mm), temporal filtering (0.01-0.08 Hz) and linear trend removing, were conducted using the DPARSF (http://www.restfmri.net/forum/DPARSF) package. All the subjects have less than 3mm maximum displacement and less than 3º of angular motion.

C. Results

Figure 2 shows the localizations of the one-side LAAM h-map computed from foreground seeds extracted from the LHG as illustrated in Figure 1 , for sample subjects in the SZAH and SZnAH populations.The colors are arbitrary, and the localizations are overlaid on the MNI152 template. Some differences on the localization spatial distribution from each population can be appreciated on inspection. The working hypothesis is that such kind of differences may be discriminant and the basis for classification of individuals into categories. The discrimination between Schizophrenia patients with and without a history of auditory hallucinations, SZAH vs. SZnAH, is difficult and has not been accomplished by statistical inference methods [16]. The classification results are summarized in Table I providing the best average Accuracy, Sensitivity and Specificity obtained in one of the repetitions of the 10-fold cross-validation experiment. Columns correspond to the feature vector size. Results are quite good, with a slight decrease for the larger feature vectors. The approach is quite sensitive to the patients without a history of auditory hallucinations.

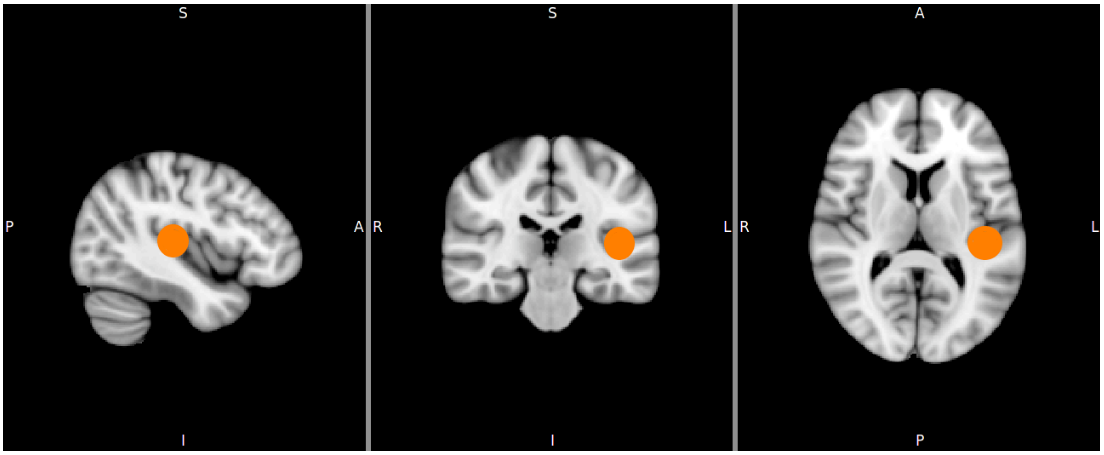

Fig. 1. Foreground voxel seed site from the left Heschl's gyrus (LHG; -42,-26,10).

VII. Conclusions

We propose a new method for fMRI data analysis inspired on multivariate mathematical morphology and supervised reduced ordering that produces a scalar representation of the fMRI data depending only on the definition of seed voxels. This method does not involve any conventional statistical techniques and assumptions, being model-free in a very extensive point of view. Moreover the method relies only in lattice computing operators, so that the only operations required for its intelligent wandering are min, max and addition which introduce less error than other arithmetic approaches. Experiments on the discrimination of schizophrenia patients with and without a history of auditory hallucinations are very encouraging, providing excellent results. Further work must be addressed to confirm these results and to perform post-hoc studies assessing the value of the voxel sites as biomarkers.

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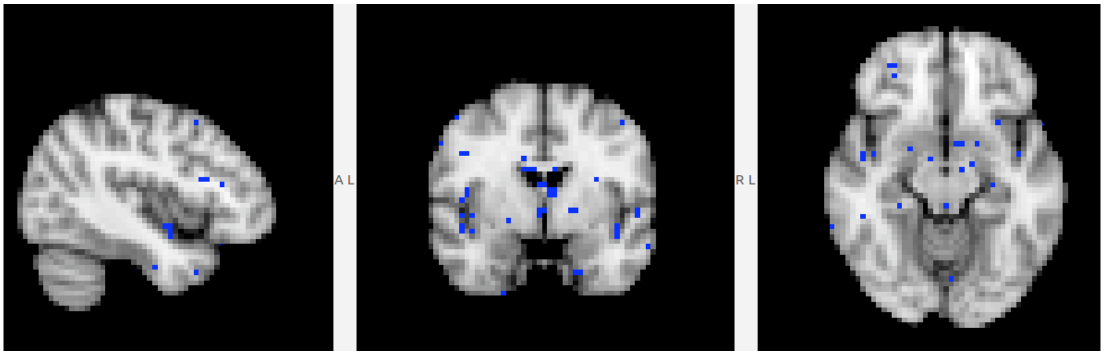
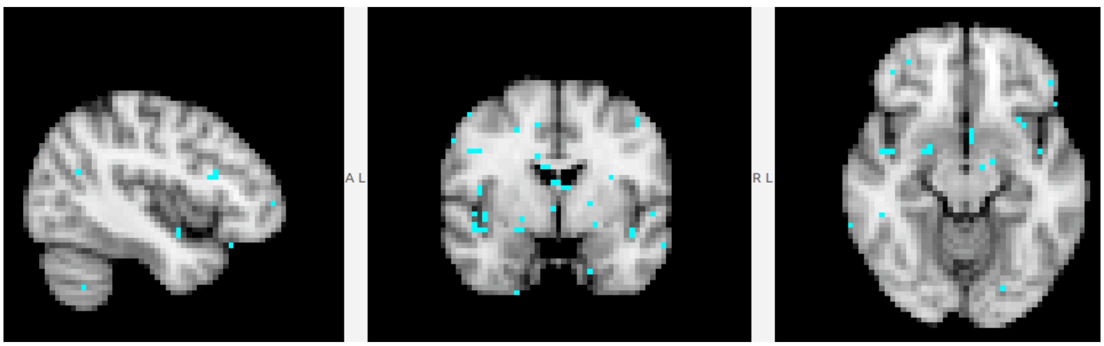


NC vs. Schiz



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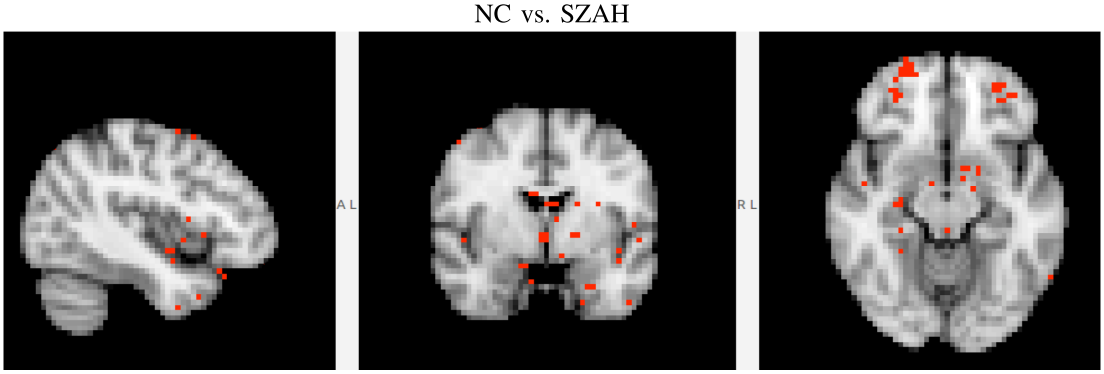
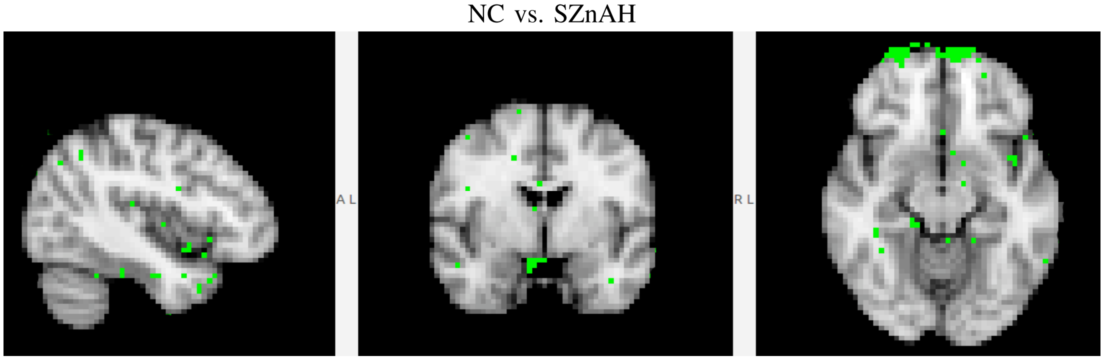


NC vs. SZnAH



SZnAH vs. SZAH

Fig. 2. Localizations of significant voxels of the one side h-map

reduced functional connectivity of the temporo-parietal area. *Biological Psychiatry*, 67(10):912 – 918, 2010. Anhedonia in Schizophrenia.

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