Published in final edited form as:

Proc SPIE Int Soc Opt Eng. 2017 March 13; 10137: . doi:10.1117/12.2254189.

Investigating Changes in Resting-State Connectivity from Functional MRI Data in Patients with HIV Associated Neurocognitive Disorder Using MCA and Machine Learning

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Abstract

Infection of the brain by the Human Immunodeficiency Virus (HIV) causes irreversible damage to the synaptic connections resulting in cognitive impairment. Patients with HIV infection, showing signs of impairment in multiple cognitive domains, as assessed by neuropsychological testing, are said to exhibit symptoms of HIV Associated Neurocognitive Disorder (HAND). In this study, we use resting-state functional MRI (fMRI) data to distinguish between healthy subjects and subjects with symptoms of HAND. To this end, we first establish a measure of interaction between pairs of regional time-series by quantifying their non-linear functional connectivity using Mutual Connectivity Analysis (MCA). Subsequently, we use a classifier to distinguish patterns of interaction between healthy and diseased individuals. Our results, quantified as the mean Area under the ROC curve (AUC) over 75 iterations, indicate that, using fMRI data, we can discriminate between the two cohorts well (AUC > 0.8). Specifically, we find that MCA (mean AUC = 0.89) based connectivity features perform significantly better ($p < 0.05$) when compared to cross-correlation (mean AUC = 0.82) at the classification task. A higher AUC using our approach suggests that such a nonlinear approach is better able to capture connectivity changes between brain regions and has potential for the development of novel neuro-imaging biomarkers.

Keywords

Resting-state fMRI; functional connectivity; mutual connectivity analysis; vector quantization; HIV; neurological disorders

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This work is not being and has not been submitted for publication or presentation elsewhere.

1. INTRODUCTION

Analysis of patterns in spontaneous fluctuations of brain activity during rest can potentially be used to detect a cognitive or diseased state in human subjects [1, 2]. Studies, utilizing data driven Multi-Voxel Pattern Analysis (MVPA) have gained momentum in recent years as they have demonstrated the potential to provide neuro-imaging based biomarkers for neurological and psychiatric disorders. MVPA extracts patterns from functional connectivity profiles by training a classifier to discriminate between the profiles of healthy individuals and individuals with a neurological disorder such as depression [2]. Such studies have commonly used functional connectivity profiles constructed by the simple cross-correlation of fMRI time-series extracted from different regions of the brain. In this paper, we investigate the use of Mutual Connectivity Analysis (MCA) [3] with Local Models (LM) [3, 4], as an alternative approach to study interactions between regional time-series recorded from resting-state fMRI and capture useful information regarding connection patterns between two cohorts of subjects.

Changes in cognitive performance of individuals infected with Human Immunodeficiency Virus (HIV) are a result of the irreversible viral damage to the brain, gradually leading to neuronal dysfunction. HIV Associated Neurocognitive Disorder (HAND) can occur in individuals infected with HIV once the virus enters the nervous system, crosses the blood brain barrier and eventually damages the activity of nerves involved in different domains of cognition. Neurological exams and neuropsychological tests are used to diagnose symptoms of HAND. These diagnostic approaches do not reveal much about how connectivity within infected individuals is affected. With our study, we introduce an approach to investigate changes in functional connectivity patterns between healthy controls and subjects with HAND.

In this paper, using fMRI analysis, we try to non-invasively capture changes in the patterns of connectivity in healthy and diseased subjects. We study the applicability of MCA to extract connectivity profiles followed by MVPA to identify subjects showing symptoms of HIV Associated Neurocognitive Disorder (HAND). MVPA is performed with a prototype-based learning algorithm called Generalized Matrix Learning Vector Quantization (GMLVQ) [5] for discriminating connectivity patterns of the two subject groups. GMLVQ is a classifier that inherently performs feature selection followed by classification. Traditionally, MVPA is performed by either separating the feature selection step and classification step or performing classification without reduction in the number of features. We also compare the classification performance of MCA with cross-correlation, which is the conventionally used approach for establishing functional connectivity. This work is embedded in our group's endeavor to expedite 'big data' analysis in biomedical imaging by means of advanced machine learning and pattern recognition methods for computational radiology and radiomics, e.g. [6–36].

2. DATA

2.1 Functional MRI data

Functional MRI scans were obtained from 29 subjects, 15 controls and 14 subjects with symptoms of HAND (HAND+) at the Rochester Center for Brain Imaging (Rochester, NY, USA) using a 3T, Siemens Magnetom TrioTim scanner, with fMRI scan parameters: Echo time (TE) = 23 ms, repetition time (TR) = 1650 ms, flip angle (FA) = 84°, 96 × 96 acquisition matrix. A total of 250 volumes of resting-state data were acquired from each subject, where the subject was instructed to lie down with their eyes closed. Twenty-five slices separated by 5 mm were acquired from the 6.67 minutes scan. A T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) sequence (TE = 3.44 ms, TR = 2530 ms, FA = 7°, isotropic voxel size of 1 mm) was used to acquire a high-resolution structural scan needed to co-register functional sequences to the standard MNI152 template. Written consent was given by the scanned individuals according to protocol approved by the IRB.

The fMRI data were pre-processed to correct for motion, extract the brain and adjustment for interleaved acquisition using the FSL toolbox (FSL version 5.0) [37]. In addition, the datasets were registered to the MNI152 standard space and a nuisance regressor was used to remove the whole brain time-series. Furthermore, the first 10 temporal volumes were discarded and high-pass filtering was performed to allow for T1 equilibration and remove signal drifts respectively. Finally, the voxel time-series were normalized to zero mean and unit standard deviation to focus on dynamics rather than amplitude [38]. The brain was divided into 90 regions using the Automated Anatomic Labelling (AAL) template [39]. Each region was represented as the average time-series of all voxels within it.

3. METHODS

3.1 Connectivity Analysis

The following two subsections describe the two approaches we use to quantify connectivity from resting-state fMRI data. Both these approaches produce high dimensional connectivity profiles, called features, providing a representation for every subject in both the cohorts.

3.1.1 MCA – Pair-wise nonlinear interaction using Local Models—To quantify the relationship between every pair of regional time-series acquired from each subject, we use mutual connectivity analysis (MCA) [3] with local models, as a measure for characterizing non-linear dynamic interaction between time-series. Here, we aim at capturing the underlying dynamics in a resting brain from fMRI data as an instrument to identify disease induced changes in connectivity of a resting brain. For comparison, we also computed cross-correlation of low-pass filtered (cut-off frequency at 0.1 Hz) time-series as a conventional measure of establishing functional connectivity.

Local Models (LM) [4] are used to establish a measure of nonlinear directed interaction in terms of cross-predictability between every pair of voxel time-series. To obtain a measure of, say, time-series $\mathbf{X}$ cross-predicting time-series $\mathbf{Y}$ (time-series of length T) we use windows $\mathbf{x}_t$ of length d from $\mathbf{X}$ to predict a point $\mathbf{y}_t$ in $\mathbf{Y}$ where, $t \in \{d, 2, \dots, T-1\}$. The windows $\mathbf{x}_t$

and $\mathbf{y}_t$ have dimension d and one respectively. Here, l is 1 as we predict one time-point, $\mathbf{y}_t$ using d dimensional $\mathbf{x}_t$. Here, $\mathbf{x}_t = [\mathbf{X}(t-(d-1)), \dots, \mathbf{X}(t-1), \mathbf{X}(t)]$ and $\mathbf{y}_t = \mathbf{Y}(t)$.

The cross-predicted estimate of $\mathbf{Y}$, i.e. $\hat{\mathbf{Y}}_{\mathbf{X}}$, is established with weighted average local models to detect non-linear dynamics. To estimate $\mathbf{y}_t$ first, we find the n nearest neighbors of $\mathbf{x}_t$ at time indices $t_i (i \in \{1, 2, \dots, n\})$, where, $n = d + 1$ for local simplex models.

$$\hat{\mathbf{Y}}_{\mathbf{X}}(t) = \sum_{i=1}^n \mathbf{w}_i \mathbf{y}_{t_i}, \quad i=1, 2, \dots, n$$

$$\mathbf{w}_i = \frac{e^{-\|\mathbf{x}_t - \mathbf{x}_{t_i}\|^2 / \|\mathbf{x}_t - \mathbf{x}_{t_1}\|^2}}{\sum e^{-\|\mathbf{x}_t - \mathbf{x}_{t_i}\|^2 / \|\mathbf{x}_t - \mathbf{x}_{t_1}\|^2}}$$

Similarity in the prediction estimate $\hat{\mathbf{Y}}_{\mathbf{X}}$ of $\mathbf{Y}$ by $\mathbf{X}$ is computed using Pearson's correlation between the estimated $\hat{\mathbf{Y}}_{\mathbf{X}}$ and the original $\mathbf{Y}$. This value is a measure of how well $\mathbf{X}$ predicts $\mathbf{Y}$ quantifies a directed non-linear measure of interaction, which is stored in an affinity matrix $\mathbf{A}$, at $\mathbf{A}_{(\mathbf{x}, \mathbf{y})}$. More details about how local models can be used to cross-predict one time-series from another can be found in [4]. This procedure is repeated for all pairs of 90 regional time-series, resulting in a connectivity matrix for each of the 29 subjects.

3.1.2 Functional Connectivity with Cross-Correlation—Correlation measures the linear statistical association between two time-series. We use the Pearson cross-correlation coefficient on the low-pass filtered (0.1 Hz) fMRI data, which is the most widely used approach for functional connectivity analysis [2]. The Pearson coefficient normalizes the covariance of the two time-series by the product of their variance.

The upper triangular entries above the main diagonal of the symmetrized connectivity matrices can then be represented as a high-dimensional feature vector of connection strengths. Such feature vectors are obtained for both MCA-LM and cross-correlation. As cross-correlation results in a symmetric matrix, the symmetrization step need not be performed. However, to make a fair comparison between the two approaches and to ensure that the same number of representative features are used, the symmetrized MCA-LM matrix is used.

3.2 MVPA – Classification using GMLVQ

Subsequent to obtaining such high-dimensional vectors from connectivity profiles, we use them as input to the Generalized Matrix Learning Vector Quantization (GMLVQ) classifier and test its ability to predict the two subject groups. We hypothesize that HIV associated neurodegeneration could manifest as differences within both the MCA-LM and correlation-derived matrices when compared between the two groups. To characterize such differences, we use GMLVQ, which is a prototype-based local distance learning approach, which is known to demonstrate good generalizability for high-dimensional data [5]. Strict separation between training and testing data was carried out, with 90%/10% train/test separation within

an iterative cross-validation scheme. The data set was divided in such a way that the classifier received an equal number of subjects from both groups during training in order to prevent bias towards a particular class. Furthermore, the test set had at least one instance from both classes.

All procedures were implemented using MATLAB 8.4 (MathWorks Inc., Natick, MA, 2014). The MATLAB implementation of GMLVQ was taken from [41]. Wilcoxon signed-rank test was used to test for significant differences between the methods. A flow chart of the steps involved in this analysis is shown in Figure 1.

4. RESULTS

Figure 2 shows the connectivity profiles constructed using LM and cross-correlation from the fMRI sequence of one of the subjects. These matrices are vectorized and used as features for classification. We use the Area Under the Receiver Operator Characteristic Curve (AUC) to evaluate the ability of MCA-LM and cross-correlation to predict the disease state. An $AUC = 1$ indicates a perfect classification, $AUC = 0.5$ indicates random classification and $AUC = 0$ indicates complete reversal in predicted class from the true class.

Figure 3 shows the plot of the means and standard error of means for 75 different combinations of training/test data when correlation and LM were used to generate connectivity profiles. The four results for LM correspond to four different values of d . We summarize the mean AUC value of the histograms shown in Figure 2 in Table 1. Observe that MCA-LM performs significantly better than cross-correlation for $d = 3$. The above results suggest that LM is able to model the dynamics in a resting human brain and better capture the non-linear interaction in BOLD fMRI.

5. NEW AND BREAKTHROUGH WORK

We investigate the effectiveness of Mutual Connectivity Analysis (MCA) using Local Models (LM) to quantify non-linear interactions of regional time-series obtained from fMRI data and use such a characterization for classification between healthy subjects and subjects presenting with symptoms of HIV Associated Neurocognitive Disorder (HAND). We have previously shown how the MCA framework could be used to extract underlying functional brain network structure, such as the motor cortex, in resting state fMRI [40]. The high AUC values using MCA derived feature vectors suggest that MCA-LM can be more useful than correlation in effectively capturing the disease state of subjects with and without any cognitive impairment as a result of HAND. In addition, we use Generalized Matrix Learning Vector Quantization (GMLVQ), which does *not* require an explicit feature selection/feature extraction step prior to classification and is specifically applicable to high-dimensional data analysis problems. This is in contrast to previous work on MVPA, which uses feature selection for dimensionality reduction prior to classification [2].

6. CONCLUSION

We present an approach for classifying healthy controls from subjects showing HIV Associated Neurocognitive Disorder (HAND) by establishing a measure of non-linear

interaction between regional brain activities measured in resting-state fMRI using Mutual Connectivity Analysis (MCA). The ninety regions from the Automated Anatomic Labelling (AAL) template were extracted after registering every subject to the MNI152 standard space. This registration and use of a standard template is carried out to ensure that every subject is represented by a set of features (connectivity profiles) that represent interactions between the same pair of regions.

We train a classifier to recognize differences in MCA-LM derived connectivity patterns (features) and test its performance on an independent test set. The high AUC value obtained using MCA-LM as compared to cross-correlation demonstrates the applicability of our nonlinear approach to capture relevant changes in the connectivity profiles. We hope that this type of study paves the path to understanding those interactions in the brain that may be different between healthy controls and subjects presenting with HAND symptoms. In conclusion, our MCA method has the potential to provide clinically useful information about how the underlying dynamics of the resting human brain differs between subjects presenting with symptoms of HAND and healthy controls. Besides HIV related brain disease, we conjecture that our method may be applicable to serve as a diagnostic biomarker for other neurologic conditions as well.

Acknowledgments

This research was funded by the National Institutes of Health (NIH) Award R01-DA-034977. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Health. This work was conducted as a Practice Quality Improvement (PQI) project related to American Board of Radiology (ABR) Maintenance of Certificate (MOC) for Prof. Dr. Axel Wismüller.

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Figure 1.

Flowchart of the steps involved to classify patients and controls using resting-state fMRI. First, the resting-state fMRI data is preprocessed following which regional time-series are extracted. Subsequently, we obtain the connectivity matrix using MCA. Connectivity matrices are obtained for every subject. These vectorized matrices represent every subject as the resting-state connectivity of their brain. Since HIV associated Neurocognitive Disorder (HAND) causes neurodegeneration, we classify the two groups.

Figure 2.

Symmetrized connectivity matrices obtained from a sample subject. The matrix on the left is constructed using MCA-LM, $d=3$. The connectivity matrix on the right is constructed using cross-correlation.

Figure 3.

Plot comparing the AUC results for correlation and MCA-LM for different model orders d . The (x) represents the mean of the distribution and the error bars represents standard error of means. (*) indicates significant difference between LM ($d=3$) and cross-correlation.

Table 1

Mean AUC for 75 different sets of training and test data. Significant difference ($p < 0.05$) is observed between correlation and LM for $d=3$.

Method	Mean AUC
Correlation	0.82
LM ($d=2$)	0.83
LM ($d=3$)	0.89
LM ($d=4$)	0.87
LM ($d=5$)	0.87