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Detecting Altered connectivity patterns in HIV associated neurocognitive impairment using Mutual Connectivity Analysis

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Abstract

The use of functional Magnetic Resonance Imaging (fMRI) has provided interesting insights into our understanding of the brain. In clinical setups these scans have been used to detect and study changes in the brain network properties in various neurological disorders. A large percentage of subjects infected with HIV present cognitive deficits, which are known as HIV associated neurocognitive disorder (HAND). In this study we propose to use our novel technique named Mutual Connectivity Analysis (MCA) to detect differences in brain networks in subjects with and without HIV infection. Resting state functional MRI scans acquired from 10 subjects (5 HIV+ and 5 HIV-) were subject to standard pre-processing routines. Subsequently, the average time-series for each brain region of the Automated Anatomic Labeling (AAL) atlas are extracted and used with the MCA framework to obtain a graph characterizing the interactions between them. The network graphs obtained for different subjects are then compared using Network-Based Statistics (NBS), which is an approach to detect differences between graphs edges while controlling for the family-wise error rate when mass univariate testing is performed. Applying this approach on the graphs obtained yields a single network encompassing 42 nodes and 65 edges, which is significantly different between the two subject groups. Specifically connections to the regions in and around the basal ganglia are significantly decreased. Also some nodes corresponding to the posterior cingulate cortex are affected. These results are inline with our current understanding of pathophysiological mechanisms of HIV associated neurocognitive disease (HAND) and other HIV based fMRI connectivity studies. Hence, we illustrate the applicability of our novel approach with network-based statistics in a clinical case-control study to detect differences connectivity patterns.

Keywords

resting state fMRI; HIV; cognitive impairment; non-linear analysis; time series analysis; causality; network based statistics

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

1. INTRODUCTION

A majority of individuals infected by Human Immunodeficiency Virus (HIV) present deficits in multiple cognitive domains that are collectively known as HIV associated neurocognitive disorder (HAND). The onset of HAND is often asymptomatic with minimal impairment in overall functioning, making its detection difficult until advanced stages [1]. The neuronal damage occurring by the invasion of the HIV can be captured using neuroimaging. Resting state fMRI provides a viable non-invasive tool for detection of such damage. Though various efforts have been made [1,2,11], newer methods are needed to detect early degenerative changes occurring due to HAND and also to develop a better understanding its underlying neurophysiology, which is currently not very well understood. Commonly used neuropsychological performance tests often are difficult to administer and may miss subtle changes brain changes [1]. To overcome this limitation researchers have explored the used neuroimaging techniques to develop a better understanding of this disorder.

To this end, we investigate the use of a novel approach, namely Mutual Connectivity Analysis [3], to acquire and compare brain networks of HIV+ subjects and age matched HIV – controls. Our objective here is to detect specific sub-networks and connectivity patterns which maybe affected during the diseased state. We focus on characterization of brain network connections (edges of a network graph) obtained from parcellated resting state fMRI data for detection of differences in the two cohorts of subjects. We obtain a network graph based on the MCA framework and identify the affected connections in the patients using a graph comparison method known as Network Based Statistic (NBS) [4]. This work is embedded in our group's endeavor to expedite 'big data' analysis in biomedical imaging by means of advanced pattern recognition and machine learning methods for computational radiology and radiomics, e.g. [16–40]

In this study, we aim to model regional changes occurring in the brain networks using a non-linear and model free MCA approach and statistically test whether it can be useful in identifying impairment occurring due to HIV infection.

2. DATA

Functional MRI scans from 5 healthy controls and 5 HIV+ subjects, aged 32–53 years, 4 females and 6 males, were acquired using a 3.0 Tesla Siemens Magnetom TrioTim scanner at the Rochester Center for Brain Imaging (Rochester, NY, US). A resting state sequence, where the subject stayed still with their eyes closed, was acquired. The following parameters were used — TR = 1650 ms, TE = 23 ms, 96×96 (2.5 mm $\times$ 2.5 mm) acquisition matrix, flip angle = 84°). The acquisition lasted 6 minutes and 40 seconds, during which 250 volumes from 25 slices separated at 5 mm, were acquired. An additional high-resolution structural image was acquired using a T1-weighted magnetization-prepared rapid gradient echo sequence (MPRAGE; TE = 3.44 ms, TR = 2530 ms, isotropic voxel size = 1mm, flip angle = 7°), which was used for the registration of the functional MRI data to the standard MNI152 template [11].

3. METHODS

3.1 Preprocessing

Standard preprocessing steps were applied to the data. The first 10 volumes were deleted to remove the initial saturation effects. The volumes were then motion corrected and the brain was extracted. High pass filtering (0.01 Hz) was performed to remove the effects of signal drifts. Subsequently, the slices were registered to the standard MNI152 template [11]. These steps were carried out using the FMRI Expert Analysis Tool (FEAT) of FSL, [5]. Also, the time series were normalized to zero mean and unit standard deviation to focus on signal dynamics rather than amplitude [6]. For each dataset, 90 regional time-series were computed based on the average time series corresponding to each region of the Automated Anatomic Labeling (AAL) template (excluding the cerebellum and brain stem) [7].

3.2 Parcellation

To define the nodes of the brain we used the Automated Anatomic Labeling (AAL) template [7]. This is a commonly used atlas that defined 116 non-overlapping regions of the brain covering both the hemispheres (excluding the hemisphere). Areas of the cerebellum a discarded giving a subset of 90 distinct nodes, each of which is represented by the mean times series of all the voxel belonging to the region.

3.3 Mutual Connectivity Analysis (MCA) using a Local Simplex Model

Our first step is to build a pair-wise affinity/similarity matrix $\mathbf{A}$ for the $n = 90$ region-averaged time series obtained using Mutual Connectivity Analysis (MCA) [3]. The pair-wise affinity between two regional time series X and Y (where $X, Y \in \{X_k, k=1, \dots, n\}$) describes the degree of their dynamic coupling as a measure of their cross-prediction performance. For example, to compute matrix element $(\mathbf{A})_{X,Y}$, we break down time series X of length I into a set of vectors $\mathbf{x}_i, i \in \{1, 2, \dots, I-d+1\}$ of dimension d , which can be interpreted as a sliding window of length d moving along X . The corresponding target vectors for $\mathbf{x}_i$ are $\mathbf{y}_i$ of dimension e . In this study, the parameters d and e were chosen $d=10$ and $e = 1$. Here, $\mathbf{x}_i$ is mapped to future $\mathbf{y}_i$, e.g. the vector $\mathbf{x}_i$ that comprises of the first 10 time points of X is mapped to $\mathbf{y}_i$ which corresponds to the 11th time point of Y .

Using all (or a smaller sub-sampled set) of vectors $\mathbf{x}_i$, we can use a local simplex model, e.g. [8], to compute estimates $\hat{\mathbf{y}}_i$ of $\mathbf{y}_i$. Here, $d+1$ nearest neighbors $\mathbf{x}_j$ are identified for every $\mathbf{x}_i$. An estimate of its corresponding target vector $\hat{\mathbf{y}}_i$ is then computed as the weighted average of the target vectors for the $d+1$ neighbors. Thus,

$$\hat{\mathbf{y}}_i = \sum_{j=1}^{d+1} w_j \mathbf{y}_j,$$

where, the weights w_j are determined as -

$$w_j = \frac{e^{-\|x_i - x_j\|^2 / \|x_i - x_1\|^2}}{\sum e^{-\|x_i - x_j\|^2 / \|x_i - x_1\|^2}}$$

Note that x_j indicates the nearest neighbor for a specific x_i and $\|\cdot\|$ represents the Euclidean distance between vectors. The estimates $\hat{y}_i$ are subsequently concatenated to reconstruct $\hat{Y}$. One may also make use of other local linear or average models described in the literature for this step. $(A)_{X,Y}$ is now computed as the correlation coefficient between the prediction $\hat{Y}$ and the actual time series Y . Further details can be found in [3].

3.4 Network Based Statistics

Network profiles such as the one obtained here often need to be tested for contrast such as a comparison between a case control subjects. If these are performed using standard mass-univariate testing and a family-wise error procedure (such as a False Discovery Rate) is used, the required multiple-comparisons adjustment does not offer enough statistical power. Additionally, given the high-dimensionality of fMRI data such comparisons often are unable to arrive at any significant conclusions. This is case in our study here where in we aim to study the possible contrast occurring in the individual links of the network between the subject groups. The NBS approach offers a viable alternative to control for family-wise error when multiple comparisons are required. This has been used to study differences in connectivity profiles in different diseases such as schizophrenia [4], depression [14] etc.

Briefly, a t -statistic is computed for each link to define a set of links above a predefined threshold ($p=0.05$), using which connected components and their respective sizes are determined. A non-parametric permutation approach (5000 permutations) is applied to empirically estimate the null distribution of the component size, which can then be used to estimate the significance of the individual components. For each permutation, all subjects are randomly reallocated into two groups, and a new t -statistic is computed for each link. Finally, for a connected component of size, say M , that is found in the right grouping of controls and patients, the corrected p -value is determined by calculating the proportion of the 5,000 permutations for which the maximal connected component was larger than M . For a more detailed description of the NBS methodology, see [4].

All procedures (excluding the preprocessing described in section 3.1) were implemented using MATLAB (MathWorks Inc., Natick, MA, 2013). The NBS implementation was taken from [4].

4. RESULTS

Mean network connectivity profiles obtained using the MCA framework for HIV+ and HIV – subjects are shown in Fig 2. Subtle differences are need in these however a statistical comparison is required to detect important differences. This was performed using the NBS method. One connected network with altered connectivity between the HIV+ subjects and HIV– controls was found. This network encapsulated 42 nodes and 65 edges [Fig 3]. The specific advantage with NBS requires the p -values to be significant enough to belong to component that is formed at a particular threshold. Specifically the connections near the basal ganglia show significant differences ($p<0.05$), which correspond to the results of [13]. Another study highlights differences occurring in the posterior cingulate cortex [12], which is also a part of the network detected here. Some additional disconnections of the network within the various parcellations of the frontal lobe are identified. Additionally, We also note

a significant disconnection in the occipital cortex around the calcarine fissure to various regions of the brain indicating specific pathological changes occurring within this region.

We see here that a large connected component in the whole brain network is identified in the HIV infected individuals. We also notice that these regions have been implicated in earlier studies hence demonstrating the applicability of our methods to detect such changes. However, the interpretability of graph-based approaches is not very straightforward [4,15], especially as these are highly dependent on the definition of nodes and edges. We have defined the nodes here based on a commonly used AAL template, which has been described, based on structural grounds more than functional ones. Though, this template has been the used as the basis of various graph-based studies, various alternatives have also been suggested. Additionally, we have defined the network profile based on a non-linear metric of connectivity, which is something that has not been explored in the clinical studies in literature so far. The exact implications of the loss/alteration of connections need to be considered in a larger study. We use this work as proof of concept of the methodology that the use of non-linear connectivity measures can in fact be effective in detecting changes in the brain network, especially when combined with robust statistical methodologies, such as the NBS.

5. NEW AND BREAKTHROUGH WORK

We present an application of our novel computational framework for analysis of functional connectivity in the brain from resting state fMRI data. Although, various other methodologies for assessing functional connectivity through fMRI exist, such as seed-based approaches [9], ICA [10] etc., our non-linear Mutual Connectivity Analysis (MCA) framework overcomes certain methodological limitations, such as assumptions of linearity, dependence on external stimuli, etc. We evaluate the pair-wise cross-prediction quality between resting state fMRI time series acquired from the parcellated human brain. We also extend the concept beyond network formation and illustrate its application on a clinical study using HIV+ subjects. The regional differences obtained in the network patterns, using our method in conjunction with a statistical approach named NBS, are in line with other studies and hypotheses concerning the pathophysiology of HIV infection [12,13]. We conjecture that a non-linear and model free approach to time-series analysis has the potential to capture information flow in the brain beyond traditional methods and hence enable better clinical application, such as the one demonstrated in this study.

6. CONCLUSION

In conclusion, the results presented in this work indicate that our non-linear time-series analysis approach to connectivity analysis can be used detecting changes in connection patterns observed in patients with HIV. Hence MCA can serve as a novel method for fMRI based connectivity analyses as it avoids certain shortcomings of traditional approaches. Our preliminary results suggest that such an approach could potentially aid in improving the early detection of HAND and contribute to research focused on understanding the pathophysiological mechanisms of HAND progression.

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Figure 1.
Brief flow-chart outlining the methodology of this study

Figure 2.

The mean affinity matrices for HIV– (left) and HIV+(right) subjects generated using our MCA approach. Certain visual differences can be seen which are statistically quantified using NBS approach.

Figure 3.

A simplified view of the altered network in HIV subjects. Overall 42 nodes and 65 edges between them show significant differences with using the NBS methodology. Our non-linear method is hence able to capture specific differences in the regional profiles of the brain network. The visualization is adapted from the NBS toolbox [4].