Published in final edited form as:

Proc SPIE Int Soc Opt Eng. 2015 ; 9417: . doi:10.1117/12.2082565.

Investigating the use of mutual information and non-metric clustering for functional connectivity analysis on resting-state functional MRI

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Abstract

Functional MRI (fMRI) is currently used to investigate structural and functional connectivity in human brain networks. To this end, previous studies have proposed computational methods that involve assumptions that can induce information loss, such as assumed linear coupling of the fMRI signals or requiring dimension reduction. This study presents a new computational framework for investigating the functional connectivity in the brain and recovering network structure while reducing the information loss inherent in previous methods. For this purpose, pair-wise mutual information (MI) was extracted from all pixel time series within the brain on resting-state fMRI data. Non-metric topographic mapping of proximity (TMP) data was subsequently applied to recover network structure from the pair-wise MI analysis. Our computational framework is demonstrated in the task of identifying regions of the primary motor cortex network on resting state fMRI data. For ground truth comparison, we also localized regions of the primary motor cortex associated with hand movement in a task-based fMRI sequence with a finger-tapping stimulus function. The similarity between our pair-wise MI clustering results and the ground truth is evaluated using the dice coefficient. Our results show that non-metric clustering with the TMP algorithm, as performed on pair-wise MI analysis, was able to detect the primary motor cortex network and achieved a dice coefficient of 0.53 in terms of overlap with the ground truth. Thus, we conclude that our computational framework can extract and visualize valuable information concerning the underlying network structure between different regions of the brain in resting state fMRI.

Keywords

Resting-state functional MRI; functional connectivity analysis; mutual information; non-metric clustering; topographic mapping of proximity

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

1. MOTIVATION/PURPOSE

Currently, functional MRI (fMRI) is being investigated as a tool that can assist in interpretation of brain network activity and evaluation of disease states in response to behavioral or pharmacological intervention. A fundamental problem in this research context is to provide a comprehensive representation and accurate quantification of functional connectivity in regions of interest or the whole brain [1]. Some of the previous functional or effective connectivity analytic approaches involved linear methods only (e.g., Granger causality [2,3]). Others transformed a high-dimensional system into a lower dimensional system using different approaches (e.g., principal component analysis [4], independent component analysis [5]), the drawback being that the identified interactions are hard to transfer back into the original high-dimensional system.

This study was conducted to investigate the non-linear functional connectivity structure in the brain on fMRI images while avoiding assumptions that promote such information loss. We are specifically interested in establishing pair-wise network connectivity between time series ensembles from resting state fMRI data. The subsequent application of non-metric clustering approaches can enable the recovery of underlying networks in the human brain. This approach is termed mutual connectivity analysis and has been previously proposed with local simplex models and neural networks [6,7]. Here, we establish such pair-wise connectivity through the use of mutual information (MI). Such information theory measures have been previously used for investigating information structure and stimulation induced changes in task fMRI data [8,9]. However, we apply this approach to resting-state networks, which reflect the fluctuations in brain activity and the underlying connectivity of the brain when the subject is at rest. 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, e.g. [10–40].

We start by computing the pair-wise MI for all pixels within a single slice of the brain (where regions of the primary motor cortex are expected to be found) on resting-state fMRI data. The resulting affinity matrix is then subject to non-metric clustering with topographic mapping of proximity (TMP) to recover functionally connected structures, as discussed in the following sections.

2. DATA

The functional MRI imaging system employed a 1.5 T GE SIGNA™ whole-body MRI scanner (GE, Milwaukee, WI, USA). The experiment enrolled four healthy subjects (one female and three males, between the ages 25 and 28). Two image sequences, one task activation sequence and one resting-state sequence, were acquired from each subject. During the task sequence, a sequential finger-tapping motor paradigm (20 seconds fixation, 20 seconds task) was applied. The task data were then used to identify primary motor cortex (right motor cortex – RMC, left motor cortex – LMC and supplementary motor area - SMA) in brain that showed stimulation-related changes in activity (Figure 1).

During the resting-state sequence, the subject was instructed to keep eyes closed while staying still and awake. Each functional MRI (EPI-BOLD) sequence acquired 512 images (TR = 500 ms, TE = 40 ms, FA = 90°). The slice thickness was 10 mm and then in-plane resolution was 3.75 mm × 3.75 mm. The first 24 image acquisitions (12 seconds) of the resting-state were discarded because of spin saturation effects and adaptation of subjects to their immediate environment. The final time series length for each pixel on the resting-state fMRI data was 488.

3. METHODS

3.1 Image processing

Motion artifacts were compensated by using an automatic image alignment (AIR) software package [41]. To remove the effects of the scanner or physiological changes in the subjects on the fMRI signal, we applied linear de-trending. For resting-state data, a low-pass filter with a cut-off frequency of 0.08 Hz was further applied to reduce the effect of high-frequency noise [42]. For the task sequence, time series were smoothed using a 5 mm FWHM Gaussian kernel. Finally, the time-courses were further normalized to zero mean and unit standard deviation to focus on signal dynamics rather than amplitude [43].

3.2 Mutual information based pairwise connectivity analysis

Here, we aim to establish inter-regional and functional information structure in the brain using pair-wise connectivity analysis based on mutual information. The first step is to construct a pair-wise affinity matrix $\mathbf{A}$ for all pixels from the brain on a single slice.

Let N denote the total number of pixels that are under consideration. For two pixel time series X and Y (where $X, Y \in \{1, \dots, N\}$), their dynamics can be expressed as time-series of length L -

$$X(t) = \{X(1), X(2), \dots, X(L)\} \text{ and } Y(t) = \{Y(1), Y(2), \dots, Y(L)\}.$$

Their mutual information $I(X, Y)$ is defined as -

$$MI(X; Y) = \sum_{x, y} p(X, Y) \log \frac{p(X, Y)}{p(X)p(Y)},$$

where $p(X, Y)$ is the joint probability distribution of X and Y , while $p(X)$ and $p(Y)$ are the marginal probability distributions of X and Y respectively [44].

In this study, the conditional mutual information is applied to quantify the shared information transfer and to infer causality relations between time series $X(t)$ and $Y(t)$. For this purpose, time delayed embedding vectors according to Takens [45] are used. We first map the time series X and Y into state spaces of dimensions m and n , thus generating a set of m - and n -dimensional vectors -

$$x(t) = \langle X(t), X(t-\tau), X(t-2\tau), \dots, X(t-(m-1)\tau) \rangle,$$

$$y(t) = \langle Y(t), Y(t-\rho), Y(t-2\rho), \dots, Y(t-(n-1)\rho) \rangle,$$

for $t = 1$ to $t = L - d$, where $d = m, n$, and τ and ρ are the time delays used for the embedding of systems $X(t)$ and $Y(t)$, respectively. The conditional mutual information between future vectors of Y and the past state of X , conditioned on the past state of Y is expressed in [44] as

$$MI(X(t); Y(t+\eta) | Y(t)) = MI((x(t), x(t-\tau), \dots, x(t-(m-1)\tau)); y(t+\eta) | (y(t), y(t-\rho), \dots, y(t-(n-1)\rho))).$$

For fMRI investigation, we focus on short-term interactions that depend exclusively on the current value and the immediate previous state vectors. Only information about one component in the future of the system is predicted. Therefore, we set $\eta = 1$. The opposite conditional MI is defined analogously. In this study, the embedding dimension and time delay are optimized according to the Ragwitz criterion [46]. A k -nearest neighbor technique is applied to estimate the probability distribution in mutual information. For this study, $k = 4$ was used [47]. In this manner, a pair-wise MI-based affinity matrix is built for all time series under consideration.

3.3 Non-metric clustering

In order to assess functional connectivity and recover network structure, we applied non-metric topographic mapping of proximity (TMP) [48] to the pair-wise connectivity results obtained by the methods described in section 3.2. TMP is a soft topographic vector quantization algorithm that can handle arbitrary distance measures, specifically non-metric data. The algorithm processes the data based on a dissimilarity matrix $\mathbf{D}$ that describes mutual relationships between data items as pair-wise dissimilarities, and thus does not require that the data items are located in a feature space that fulfills the mathematical properties of a metric. For example, the dissimilarities do not have to satisfy a triangle inequality.

Since TMP requires a dissimilarity matrix, the MI-based affinity matrix $\mathbf{A}$ was converted to a symmetrized dissimilarity matrix $\mathbf{D}$ using exponential scaling -

$$\mathbf{D} = e^{-5\mathbf{A}}.$$

Note that any monotonically declining function can be used in place of the exponential scaling. This dissimilarity matrix $\mathbf{D}$ was then processed with TMP to reconstruct the topographic neighborhood, by treating $\mathbf{D}$ as a matrix of transition probabilities.

3.4 Clustering Quality Evaluation

The clustering results from TMP were compared to the ground truth and the performance was assessed using the dice coefficient to evaluate the degree of overlap between the two. Here, the number of expected clusters is set manually to 25 for TMP. Different clusters were

then subsequently merged in an iterative process to achieve the maximum dice coefficient value possible.

All procedures were implemented using MATLAB 8.1 (MathWorks Inc., Natick, MA, 2013). The mutual information analysis implementation was taken from TRENTOOL [49].

4. RESULTS

4.1 Clustering analysis based on mutual information

As specified in section 3.4, the number of clusters to be detected by TMP in the MI-based pair-wise affinity matrix was specified as 25. Thus, each pixel within the brain was assigned to one of these clusters. Figure 2 shows the TMP cluster assignment maps of one subject. Pixels that belong to each cluster are highlighted in red on these maps. As seen here, cluster no. 22 closely resembles the primary motor cortex network.

4.2 Functional connectivity map obtained from mutual information

Figure 3 shows the ground truth for one subject obtained by the motor stimulation fMRI task and the functional connectivity map obtained from mutual connectivity analysis based on mutual information on resting-state fMRI data. Here, clusters originally detected by TMP are selectively merged for maximizing the Dice coefficient comparing the ground truth and the cluster segmentation result. The Dice coefficient obtained by comparing ground truth and the final motor cortex map from resting-state fMRI is 0.53. As seen here, such pair-wise MI-based analysis combined with non-metric TMP clustering can detect the motor cortex structure even in the absence of stimulation-related activation.

5. DISCUSSION

Functional MRI (fMRI) has recently found use in establishing effective/functional connectivity in the human brain. Given the need to quantify information transfer and establish the structure of functionally connected networks, this study describes a model-free fMRI connectivity analysis method aimed at network structure recovery. Specifically, we investigate the use of mutual information in establishing pair-wise network connectivity in time series ensembles extracted from resting-state fMRI. The mutual information estimator allows the quantification of nonlinear functional connectivity of high-dimensional time series ensembles directly, which eliminates the need for any dimension reduction prior to functional connectivity analysis. Such information theoretic measures are computed for all pixels on a single slice of fMRI data in this study, but can easily be extended to include all voxels within the entire brain.

The pair-wise similarity/dissimilarity matrix constructed by such MI-based analysis was subsequently subjected to non-metric clustering for purposes of recovering the underlying network structure. For this task, the approach of topographic mapping of proximity (TMP) data was pursued. As seen in Figure 3, such a methodology enables the recovery of the primary motor cortex network with a high degree of resemblance to the ground truth, as established with a finger-tapping stimulus in a task-based fMRI sequence. It should be noted

that our results are also in agreement with studies where other non-metric clustering approaches have been investigated [6,7].

6. CONCLUSION

This study investigated the ability of mutual information based pair-wise connectivity analysis to recover network structure in the human brain on resting-state functional MRI data. Our results show that such analysis, in combination with non-metric TMP clustering, is able to extract the primary motor cortex network. The results gathered in our study showcase the potential for such model-free approaches in uncovering the underlying structure of functionally connected networks in the human brain.

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. The authors would like to thank Dr. Martina Hasenjäger, University of Bielefeld, Germany, for contributing the implementation of the TMP algorithm, and Prof. Dr. Dorothee Auer at the Institute of Neuroscience, University of Nottingham, UK, for her assistance with the fMRI data acquisition process. The authors would also like to thank Dr. Lutz Leistritz and Prof. Dr. Herbert Witte of Bernstein Group for Computational Neuroscience and the Institute of Medical Statistics, Computer Sciences, and Documentation, Jena University Hospital, Friedrich Schiller University Jena, Germany, Dr. Oliver Lange and Prof. Dr. Maximilian F. Reiser, Institute of Clinical Radiology, Ludwig Maximilian University, Munich, Germany for their support.

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Figure 1.

The ground truth example for one subject. The identified primary motor cortex (left and right motor cortex) and pixels corresponding to the supplementary motor area (shown in red) are superimposed on the original slice.

Figure 2.

Cluster assignment maps from TMP for 25 clusters. Pixels belonging to each cluster are highlighted in red. Subsequent cluster merging reveals the underlying network structure. However, the primary motor cortex network is already noticeable in cluster no. 22, as seen above.

Figure 3.
(LEFT) “Ground truth” for one subject representing brain activity in a motor stimulation task. Regions showing stimulation-related activation are highlighted in red. (RIGHT) Clustering results from mutual information with TMP algorithm; the Dice coefficient with ground truth is 0.53.