Mutual Information Weighted Graphs for Resting State Functional Connectivity in fMRI Data

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Target audience: Researchers, scientists and students who work in the field of resting state fMRI and multiple sclerosis

Introduction: In the analysis of resting state functional connectivity (RS-FC), functional magnetic resonance imaging (fMRI) data can be modeled as a graph of nodes and edges representing brain regions or image voxels, to capture their existing interrelationship due to functional activities **[1].** There are three key points in the analysis of the functional connectivity graphs that significantly influence inter-subject classification (to be explored in this work): 1) how to define the nodes; 2) how to define the dependency measure between time series; and 3) how to define the graph theoretical features. Traditional graph theoretical analyses of functional connectivity using RS fMRI are based on measuring the correlation between time series of predefined nodes or random voxels in the human brain. However, higher-order interactions are not captured by correlation. Moreover, in most available research works, the functional connectivity graphs were defined by their binary adjacency matrix, whereas the functional connectivity graphs can be fully characterized by undirected weighted adjacency matrix. In this study, we developed a novel analysis technique for RS-FC technique in the following steps: 1) extracting the fMRI time series for 264 nodes, selected based on neurological principals; 2) calculating normalized mutual information to capture the complex and higher order interaction between two time series; and 3) constructing the weighted graphs called mutual information weighted graphs (MIWG) for each dataset.. We utilized the proposed method to demonstrate alterations in functional communication of patients with multiple sclerosis (MS) and in comparison with healthy controls. Results were compared with the classic Pearson correlation graphs employing SVM classifier.

Methods:

Participants: A total of 25 clinically stable patients with relapsing-remitting MS and 35 healthy individuals were selected for this cross-sectional study. Inclusion criteria for MS patients included diagnosis by 2005 revised McDonald criteria.

fMRI Data Acquisition: RS fMRI data was acquired on a 3T MR scanner (Siemens MAGNETOM Tim TRIO) using gradient echo planar with following parameters: TR = 2.2sec, TE = 30$m$sec, FA = 90°, matrix size = 64×64, voxel size = 3×3×3mm^3, 40 slices per volume, slice thickness = 3mm, slice sequence: interleaved with 200 volumes.

Image Preprocessing: All preprocessing steps were performed using SPM8. We discarded first 5 volumes to avoid magnetization saturation effect, followed by slice timing correction using the first slice as reference, within subject realignment to the mean of volumes in order to correct for patient's head motion, spatial normalization to the MNI (Montreal Neurological Institute) template and smoothing by anisotropic Gaussian kernel with full width at half maximum of 8mm.

Mutual Information Weighted Graphs: Following steps were taken to implement the proposed algorithm: 1) Selecting 264 nodes according to neurobiological principles **[2]**, and extracting time series of each node (key point 1); 2)calculating pairwise normalized mutual information graphs (scenario A), as well as person correlation (P-Corr) graphs (scenario B) between the time courses of nodes, yielding 264×264 adjacency matrix for each dataset (key point 2); and 3) extracting three graph theoretical feature for each scenario (key point 3), and as follows:

a. Clustering coefficient (CC) **[3]**, which quantifies the graph segregation measure (CC of node i is geometric mean of triangles around i divided by number of all possible neighbors), b. Degree (D), which has been previously very successful for classification of schizophrenia **[4]** (D of node i is the number of links connected to the node i), and c. Eigenvector Centrality (EC) **[5]**, which is a self-referential measure of centrality (nodes have high eigenvector centrality if they connect to other nodes that have high eigenvector centrality. The eigenvector centrality of node i is equivalent to the ith element in the eigenvector corresponding to the largest eigenvalue of the adjacency matrix). A schematic of the proposed method is shown Fig. 1.

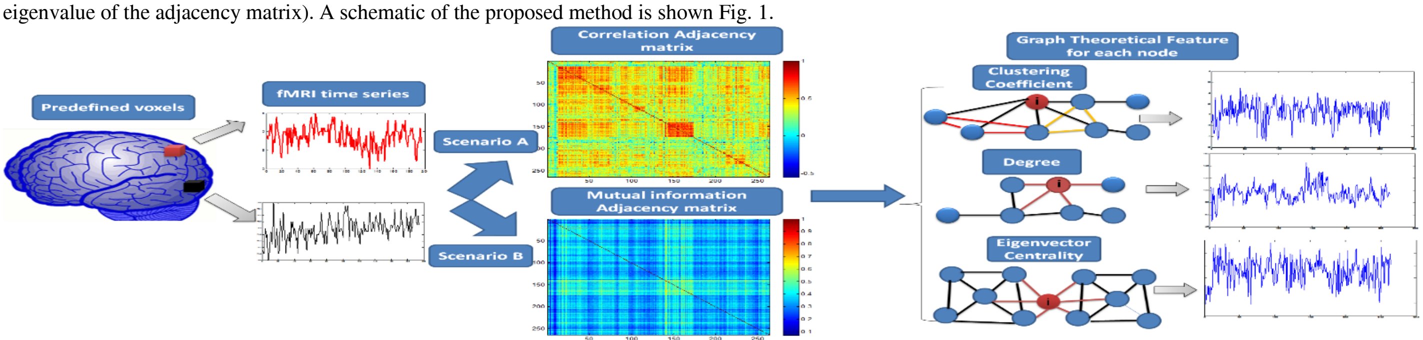

Fig. 1 Schematic of the proposed method

Results: We evaluated the classification performance based on leave-one-out cross-validation using soft margin support vector machine (SVM) with linear kernel (C = 1), and reported using the familiar measures sensitivity and specificity. Significance level was estimated by comparing with classification performance for the SVM classifiers with randomly permuted class labels (using nonparametric Friedman's test) (**Table 1**).

Table 1. Leave-one-out classification performance using SVM for each dependency measure and each graph theoretical feature

Feature	Dependency Measure	Sensitivity	Specificity	Correct Rate	P-value
CC	P- Corr	57.2%	87.8%	%72.5%	p<0.001
D	P- Corr	43.0%	77.3%	60.1%	p<0.003
EC	P- Corr	37%	69.2%	53.1%	p<0.006
CC	MI	76.7%	91.2%	83.9%	p<0.001
D	MI	78.9%	88.3%	83.6%	p<0.001
EC	MI	33.6%	74.8%	54.2%	p<0.006

Conclusions and Discussions: Analysis of RS-FC MRI based on mutual information graphs is capable to reliably classify patients with MS from the healthy controls, and on the basis of CC and D, while EC have low sensitivity. The sensitivity of classification based on MI graphs is higher than P-Corr graphs; in P-Corr graphs, clustering coefficient and degree show acceptable specificity, but low sensitivity. Thus, MI graphs have higher correct rate than P-Corr graphs. Since the alterations of functional connectivity in MS patients is complex with high moment distribution, there is possibility for MI to capture them, and to outperform P-Corr graphs. Therefore, each of three key points, selection node, defining dependency measure and graph features, is substantial for graph theoretical analysis of FC.

References:

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