Spectral Clustering of Resting State fMRI Reveals Default Mode Network with Specifically Reduced Network Homogeneity in Major Depression

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Abstract— **Although resting state fMRI seems an ideal tool for investigating clinical populations, especially in case of reduced cooperation or tolerance, unbiased methods with high sensitivity for disease relevant pathologies remain to be identified. In this paper, we perform spectral clustering on the mean time series of automated anatomical labeling regions of interest for comparing the resting state networks in healthy volunteers and major depression disorder (MDD) patients. A new network homogeneity measure is suggested as a criterion for evaluating the level of homogeneity in a network. We found reduced network homogeneity specifically within the default mode network in MDD subjects compared to age-matched controls. In contrast to previously proposed methods investigating network homogeneity, we fully relied on data-driven definition of clusters of interest to fill an important gap between ROI based network analyses and those using ICA.**

Keywords-Resting State fMRI; Spectral Clustering; Major Depression Disorder; Network Homogeneity

I. INTRODUCTION

In recent neuroimaging studies, spontaneous slow fluctuations (ranging from 0.01 to 0.1 Hz) of Blood Oxygenation Level Dependent (BOLD) signal are observed to be significantly coherent in the resting human brain [1]. Functional connectivity analysis tries to identify the coherency of these signals among different brain regions. There are two major approaches to extract the functional connectivity in resting state fMRI: model based, and data driven. The simplest traditional method, in the model based aspect, is seed voxel method that determines the temporal correlation between BOLD time series of a region and that of other regions. Seed voxel analysis is widely used to identify brain networks because of its simplicity, sensitivity, and ease of interpretation [2]. However, the resulting networks are limited by selection of the seed voxels. In contrast, data driven methods explore the functional connectivity without the assumption of a model. Several data driven methods have been suggested for detecting reliable functionally connected resting-state networks such as independent component analysis (ICA) [3], principle component analysis [4] and methods based on clustering approaches [5]. Clustering approaches are mainly used to group fMRI time series according to their similarities. Some of the conventional clustering approaches such as C-means and Fuzzy C-means use a measure of distance that affects the shape of clusters [6]. For instance, Euclidean distance and Mahalanobis distances force the shape of clusters to be hyper-spherical and hyper-ellipsoidal, respectively. For overcoming this deficiency, spectral clustering was proposed to achieve arbitrary shapes according to the data structure, by clustering in the space of eigenvectors of the similarity matrix constructed from the data points [7]. Moreover, spectral clustering is a simple and efficient algorithm and can be solved by standard linear algebraic methods.

Heuvel et al. [8] proposed a method based on spectral clustering. In their method, inter-voxel correlations of time-series are grouped at the individual level. At the group level, the consistency of the resulting networks across subjects is used for clustering, and group resting state networks are defined.

In this paper, we perform spectral clustering on the mean time series of automated anatomical labeling (AAL) regions of interest. As the result of individual clustering, an affinity matrix is constructed for each subject. The individual affinity matrix shows whether or not two assumed regions are in the same cluster. At the group level, spectral clustering is done on the mean of individual affinity matrices across subjects of each group. The obtained clusters represent functional networks that are consistently present across the healthy subjects or Major Depressive Disorders (MDD).

The aim of this study was to compare resting state networks in healthy volunteers and MDD patients. Network

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homogeneity is a criterion quantifying the degree of similarity between the regions' time courses of a specific network. Uddin et al. [9] have previously suggested a measure for network homogeneity which is defined as the mean of correlation between any given voxel's time courses with all other voxels in the network. This criterion as a bivariate measure, is based on the similarity between two time series and does not consider similarity between all of the time series simultaneously. In contrast, we here suggest Kendall's Coefficient of Concordance (KCC) as a measure of network homogeneity. KCC was previously used as a measure of homogeneity between neighboring voxels [10]. This criterion provides us with an ability to measure network homogeneity in a single level and consequently, specificity increases. In addition to this modification, we propose to estimate network homogeneity on purely data-driven networks: Once a network of activated regions is selected by the clustering algorithm, KCC is applied to the time courses of the network's regions in order to obtain the network homogeneity.

As one major network with disturbed functional architecture at rest in MDD, the default mode network, encompassing ventromedial prefrontal as well as posterior cingulate and parietal regions, is characterized by high resting state activity, which decreases as a function of task load. However, it has been shown that the degree of its deactivation can be modulated by self relevant or affective load in specific conditions [11]. Especially, the medial prefrontal cortex has been characterized by abnormal histological as well as metabolic findings in MDD which can be directly related to abnormal brain function during task and rest [12, 13].

II. Materials and Methods

The procedure proposed for extracting and evaluating resting state networks for both healthy subjects and MDD patients includes four main steps: data acquisition and preprocessing, individual clustering, group clustering, and evaluating the results by network homogeneity. The scheme in Fig. 1 illustrates these steps in detail.

A. Resting State fMRI Data Acquisition

Sixteen healthy subjects (mean age: 32.5; Gender: 13 male, 3 female) and Sixteen MDD patients (mean age: 41; Gender: 10 male, 6 female) participated in this study. The healthy subjects without any psychiatric, neurological, or medical illness were self-referred from study advertisements. All volunteers completed the mini-international neuropsychiatric interview (MINI) to specifically ensure the absence of any ICD-10 psychiatric disorders [14]. The subjects with an acute MDD episode were recruited from the inpatient Department of Psychiatry at the University of Magdeburg. These patients were clinically diagnosed according to the ICD-10 criteria [15].

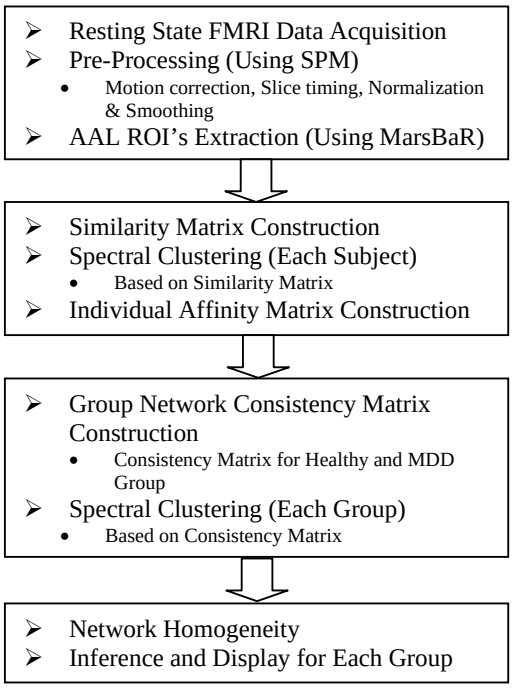


Figure 1. Overal scheme outlining the analysis steps presented for clustering and evaluating networks in resting state fMRI data.

Data was acquired using a 3 Tesla Siemens MAGNETOM Trio scanner (Siemens, Erlangen, Germany) with an eight channel phased-array head coil. For acquisition of the resting state fMRI data, the subjects were told to lie still in the scanner with their eyes closed. Functional time series of 488 time points were acquired with an echo-planar imaging sequence. The following acquisition parameters were used: echo time = 25 ms, field of view = 22 cm, acquisition matrix = 44×44, isometric voxel size = 5×5×5 mm^3. Twenty six contiguous axial slices covered the entire brain with a repetition time of 1250 ms (flip angle = 70).

B. Preprocessing

The first eight acquisitions were discarded to reach the steady state MR image contrast and limit T1 effects. Then, the 480 remaining volumes were slice-time corrected and head motion corrected. In the next steps, normalization to MNI template and smoothing (FWHM = 8mm) has performed for all subjects. Each of these steps was performed by SPM8 (UCL, London, UK). After these, mean time course for each AAL ROIs was extracted using MarsBaR.

C. Individual Clustering

We want to cluster regions of the brain such that regions in different clusters are dissimilar to each other and regions within the same cluster are similar to each other. Similarity graph is a way of representing regions and their similarities to each other. Spectral clustering is based on partitioning the similarity graph. Here, the similarity matrix is constructed by calculating the correlation between the time series of each region with the time series of all other regions (functional connectivity map). Then, this similarity matrix is grouped via

spectral clustering. Spectral clustering is performed by eigen-decomposition of the similarity matrix. The spectral clustering analysis algorithm is as follows:

i) Construct the similarity matrix (S), where $S(i,j)$ is the correlation between time courses of regions i and j.

ii) Define D to be the diagonal matrix where:

$$D(i,i) = \sum_{j=1}^{R} S(i,j) \quad (1)$$

(R=90, the total number of regions)

iii) Construct L:

$$L = D^{-1/2} S D^{-1/2} \quad (2)$$

iv) Compute the first k eigenvectors of L ($x_1, x_2, ..., x_k$) and form the matrix X as follows:

$$X = [x_1, x_2, ..., x_k] \in R^{R \times k} \quad (3)$$

v) Form the matrix Y from X by normalizing the rows to have unit norm:

$$Y_{i,j} = \frac{X_{i,j}}{(\sum_j (X_{i,j})^2)^{1/2}} \quad (4)$$

vi) Consider rows of Y as points in R^k and cluster them into k clusters via a clustering algorithm.

The construction of the affinity matrix for all subjects is the final step in the individual clustering. The affinity matrix is the $R \times R$ binary matrix in which a 1 in location (i,j) indicates that i and j regions are in the same cluster.

D. Group clustering

Individual affinity matrix is the result of individual clustering and shows whether or not two regions are in the same cluster. Mean of individual affinity matrices across the subjects of one group declares the consistency of extracted connectivity between two regions in that group of subjects. Therefore, this consistency matrix is clustered via spectral clustering for both healthy and MDD groups to find consistent networks across subjects in each group.

E. Network Homogeneity

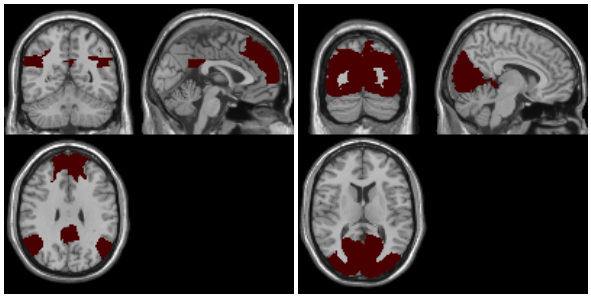
Network homogeneity is a measure for evaluating the amount of similarity between the regions' time courses of a specific network. Network homogeneity is derived by calculating the KCC between the time series of the regions constructing that network. The proposed network homogeneity is derived as follows:

$$Network\ Homogeneity = \frac{\sum_{i=1}^{n} (S_i)^2 - n(\bar{S})^2}{\frac{1}{12} K^2 (n^3 - n)} \quad (5)$$

where n is the total number of time points, S_i is the sum rank of the i'th time point, $\bar{S}$ is the mean of the S_i's, and K is the number of regions within that network. Thus, network homogeneity is assigned to each extracted network and for each subject. Group differences were assessed using two sample T-tests. To evaluate our proposed network homogeneity measure and the previous one based on correlation between time courses, the result of two sample T-tests were compared.

III. Results and Discussion

As one major finding, we could reveal previously described networks by our clustering mechanism such as the default mode network (DMN) or visual network (see Fig. 2). More importantly, we found decreased network homogeneity (NetHo) in DMN and visual network, while NetHo was not different in the patient group for other networks (see Table 1). The proposed measure of network homogeneity captures this reduction with more statistical power (less p-value) than the previous measure based on correlation as shown in Table 2. It has to be noted that the other clusters revealed by the spectral clustering step are not of less functional significance but also represented meaningful clusters of brain regions. However, no specific hypothesis regarding their malfunction in major depression existed. This specificity thus strengthened our results and excluded other potential confounds, such as medication. The reduced NetHo in DMN is compatible with findings based on ICA [16] but also those from task studies [17]. Dysfunction in this network is thought to be important for clinical symptoms such as increased ruminations, abnormal self focus or anhedonia.



(a) Default mode network (b) Vision Network

Figure 2. Brain networks obtained by spectral clustering in both healthy and MDD gorups.

TABLE I. Mean network homogeneity for healthy controls and MDD patients

Network	Mean homogeneity Healthy	Mean homogeneity MDD
DMN	0.695	0.640
Vision	0.744	0.692

TABLE II. Comparison of two sample T-test for different network homogeneity measures in DMN, (Degree of Freedom=30)

	Network homogeneity based on KCC	Network homogeneity based on correlation
T-value	1.72	0.88
P-value	0.05	0.20

IV. Conclusion

In our study, we propose a combination of spectral clustering techniques identifying networks which subsequently are compared between patient and control populations using network homogeneity measures. We could show that our method is robust and more specific. The combination allows for minimum bias of NetHo comparison and the specificity of group differences should be regarded both in support of the technical feasibility as well as the key role, DMN resting state abnormalities may play in the pathology underlying MDD.

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