Resting State Functional Connectivity Based on Principal Component Transformation of Cortical fMRI Measurements

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Abstract— Functional brain connectivity on the basis of fMRI time series analysis is a promising research endeavor in the study of the brain in its normal state as well as under different pathologies and neurological disorders. This study introduces a new approach to constructing rest-state connectivity networks interconnection with less amount of need to a-priori assumption and without setting any specific threshold. These network topologies are shown to reflect well the fMRI measurements. This data-driven solution at constructing fMRI-based connectivity networks considers the brain as a network of networks, and defines smallest sub-network as the regions of interest made from structural segmentation of cortical areas of the brain. Principal components (PC) of these defined sub-networks are used to gauge patterns of interconnections in the hierarchy of brain networks based on a geometrical concept. Experimental evaluations were conducted on resting state fMRI recordings of a group of healthy subjects. Results of this study support the assertion that resting state networks and default mode networks can be potentially derived without the need of either thresholding or a-priori considerations.

I. INTRODUCTION

Functional magnetic resonance imaging together with the use of Blood Oxygenation Level Dependent (BOLD) contrast to investigate brain hemodynamics [1, 2, 3, 4] has led to a broad scope of research activities and applications in brain discovery research. Literature review of the past studies demonstrates that Blood Oxygenation Level Dependent (BOLD) changes, as the basis of functional Magnetic Resonance Imaging (fMRI), continue through the brain even in the absence of a controlled task as exemplified in studies [5, 6]. An investigation of resting state changes has identified spatially discrete but functionally linked regions which form widely distributed networks with coherent low frequency fluctuations in their BOLD responses [7]. Resting state methodologies are thus increasingly being employed to elicit new understanding of interwoven communications among more than fifty disjoint cortical regions identified with different functionalities [8, 9, 10].

More thorough assessments of the so-called default mode network identified with rest state (i.e. wakeful rest state without any task being performed) with contrasting analysis of task specific hypotheses together would constitute a fundamental research basis by which evaluating functional connectivity pattern of brain cortex [3, 4, 11] become more informative and deliberate. Model driven techniques such as General Linear Model (GLM) [12] versus data driven techniques [13] are both suggested methods for extracting intrinsic signatures or markers of the functional connection among the distinct cortex regions. Spatial-temporal cross-correlation between voxel time-series is the preponderant method of many of the proposed techniques [3, 9, 13, 14, 15, 16] used to create functional networks on top of the structural brain images. Kendall’s coefficient concordance (KCC) with the assumption of temporal similarity between time series of voxels located in a pre-defined neighborhood defines a regional connectivity map [13]. The main question mark of such techniques based on regional connectivity maps is about the neighborhood size to consider as a discrete region. The proposed methodology here considers that structurally homogenous areas extracted from the cortical segmentation block are the finest functional unit of the brain networks. Integrated Local Correlation (ILC) [15] and Neural Traffic (NT) [14] consider the brain as a complex network of dynamic and interactive regions, and employ the correlation coefficient corrected with a subjective threshold. Finding the right threshold is a source of variability that is yet to be understood in the evaluation of the resulting networks.

The proposed technique as conceived takes inter-subject structural variability into account by looking over regions of interests as defined based on structural segmentation of the brain. The method defines the regions of interest as the initial sub-network and merges them into a hierarchy to build the entire brain network.

II. MATERIALS AND METHODS

The suggested technique to evaluate functional connectivity network was empirically evaluated on a subset of rest fMRI data from the Autism Brain Imaging Data Exchange (ABIDE) dataset [17]. Rest fMRI data were recorded using 3T GE SIGNA at oblique data axis with the flip angle of 80 degree, with a time of repetition (TR) equal to 2 seconds and time of echo (TE) equal to 30 ms and voxel resolution of 3.125x3.125x4.5 (mm³). T1 scans were acquired with the resolution of 0.859x1.5x0.859 (mm³) with the flip angle of 15 degree at TR=8.4ms [18].
The flowchart of the technique is depicted in Fig. 1. The algorithm starts with cortical segmentation and surface reconstruction of structural images of the subject. Cortical segmentation and surface reconstruction were implemented using the well-established brain imaging software called FreeSurfer [19]. At this initial step, each location in the cortical surface model of the subject was assigned a neuroanatomical label based on probabilistic information estimated from a training set included in the FreeSurfer [19].

Sixty volumetric masks \( V_i, i = 1, \ldots, 60 \) of the mutually exclusive regions in both hemispheres are built using annotation information after cortical segmentation of subject’s anatomical scans.

\[
V_i(x, y, z) = \begin{cases} 
0 & \text{voxel located outside } i\text{'th region} \\
1 & \text{voxel located inside } i\text{'th region}
\end{cases}
\]  

(1)

Figure 1. Principle Component Functional Connectivity

Resting state functional images were brain extracted [20] and spatially filtered with a smoothing Gaussian kernel with Full Wave at Half Maximum (FWHM) at 5 mm [21]. Registration matrix was calculated from FLIRT (DOF=12; Cost Function: Normalized Mutual Information with trilinear interpolation) [22], an FMRIB Linear Image Registration Tool, to register structural images to functional images. The calculated registration matrix was employed to register each volumetric mask \( V_i, i = 1, \ldots, 60 \) into functional images to be able to extract time series of voxels located inside the specified region by the mask. Equation (2) mentions one set of time series corresponding to region \( V_i \) including \( N \) voxels

\[
V_i = \{x_{i1}(t), x_{i2}(t), \ldots, x_{iN}(t)\}; \quad i = 1, \ldots, 60
\]  

(2)

Where \( x_i(t) \) are time-series of voxels located inside region \( V_i \). After we had extracted IMR\( i \) time series corresponding to each region of interest (60 sets of a number of time series based on how many voxels encircled by each mask), Three-dimensional Principal Component Transformation (PCT) [23] was applied in each region and the component which explains the most of variability of the set was chosen as the representative vector of the region under study. AFNI routine [24] was employed to find the principal component with the most portion of energy explanation for each region of interest (ROI). We called the first principal component of each corresponding ROI as \( p_i \).

The idea of Principal Component Functional Connectivity (PCFC) is to find the pattern of interconnection among principal components calculated from ROI’s functional time-series. We first defined an adjacency matrix with its elements to be the pairwise distances among ROI’s first principal component vector in a multi-dimensional space. Cosine distance were chosen to be a meaningful tool in vector geometry for evaluation of how each region co-varies with other regions in the sense of percentage changes in BOLD-fMRI recordings. Equation (3) calculates the pairwise distance between two principal components representing two distinct ROI’s.

\[
c_{ij} = 1 - \frac{p_i \cdot p_j}{\| p_i \| \cdot \| p_j \|}; \quad \| p_i \| \neq 0 \quad \| p_j \| \neq 0
\]  

(3)

Where \( c_{ij} \) is the cosine distance between the two vectors \( p_i \) and \( p_j \) in a multi-dimensional space. Distances computed from equation (3) were converted into degrees between vectors using equation (4) and normalized into the range of [0, 90] degrees.

\[
\theta_{ij} = \cos^{-1}(1 - c_{ij}); \quad i, j = 1, \ldots, 60
\]  

(4)

The two measurements, \( c_{ij} \) and \( \theta_{ij} \), are presenting one metric but from different perspectives. We can substitute computed \( \theta_{ij} \)’s to form a matrix. The matrix is known as adjacency matrix in the computational brain network context. Each element of the matrix shows the angle between two corresponding vectors \( (p_i \) and \( p_j \).)

Next in the PCFC calculation, it is to hypothesize the topology of brain networks. To find the interconnection among sub-networks in the whole brain, PCFC includes a hierarchical clustering in bottom-up fashion. For each subject brain, this block considers each region of interest (ROI) as one sub-network (class) and merge sub networks in a bottom-up fashion to find a linkage criteria [26] by reaching a point where a network including all ROI’s is found. The benefit of implementing this clustering approach is to keep the consistency of a data-driven solution with the least number of assumptions on the connectivity model. The hierarchy topology of brain regions would represent the PCFC of the brain, thus providing a signature of how the discrete but functionally connected regions are arranged in different brain states.

I. RESULTS AND DISCUSSION

The paper introduces a data-driven solution to construct functional connectivity based on principal component transformation of BOLD-fMRI measurements by considering structure of subject’s brain with the functional context of rest state. Fig. 2 shows an adjacency matrix calculated from equation (4) for an average functional brain from the group of healthy subjects besides the histogram plot. In Fig. 3, detected network topology is visualized overlaid on a standard template using BrainNet Viewer [27]

As indicated earlier, a hierarchical clustering technique was implemented to build the topology of brain functional network. Three different linkage criteria to find the proximity

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within and between the clusters were examined to find the one with the maximum average Cophenetic Correlation Coefficient (CPCC) [26] in clustering data. CPCC is a metric to measure the fit and efficiency of a clustering technique for a set of data under examination. The higher is this CPCC measure (i.e., close to 1), the better is the matching condition of the result with the original data that could be used as an optimal solution. Fig. 4 summarizes our experimental CPCC values for “single”, “complete” and “average” linkage criteria in constructing the networks.

Given the results obtained in Fig. 5, the ‘AVERAGE’ criterion as linkage method was the one selected to calculate the proximity between sub-networks in the hierarchy because it shows higher value of CPCC value in average. Therefore the last step of the algorithm involved constructing a hierarchy of the sub-networks inclusive of the 60 regions for each subject.

Each random variable was considered to be the histogram of pair-wise distances (θ’s) across each brain. Multi Variate Normality (MVN) tests [26] were conducted on these random variables to see whether they satisfy normality. Statistical testing with the results shown in Fig. 5 support the null hypothesis, implying that the random variables calculated through the proposed technique cluster around a mean value and satisfy the MVN test at significance level of 0.05.

Fig. 6 shows the dendoram of the Principal Component Functional Connectivity (PCFC) networks constructed using the average pairwise proximities across the group of subjects on top of the corresponding average adjacency matrix. As can be observed in Fig. 5, functional cortical connectivity suggests there is a close proximity among Default Mode Network (DMN) including the structural areas, shown in bracket, of anterior and posterior cingulate gyrus, bi-lateral middle temporal and inferior temporal, middle frontal and Hippocampal regions for long term memory and parietal cortex along with prefrontal cortex, and the other key resting networks such as somatosensory cortex and visual cortex.
These results agree with the resting state functional connectivity network reviewed in [23, 28].

II. CONCLUSION

This study introduced a novel technique for constructing the functional connectivity of brain cortex that is reducing he required number of a priori assumptions or the setting of any given thresholds. This technique relates the use of principal components to rest-state connectivity networks on the basis of fMRI recordings. Independency of the method from defining a set of thresholds or assuming a model of co-activation in fMRI time series can be considered as the main contributions of this study. Default mode networks constructed using the average pairwise proximities across the group of subjects, along with the corresponding average adjacency matrix, could serve as means to identify the regions most associated with the rest state for each given subject as well as to potentially delineate patients with a given neurological disorder from a control population.

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