Abstract—This study introduces a novel data-driven approach for constructing large-scale functional brain networks. These networks are constructed by converting raw functional magnetic resonance imaging data into graphs using independent components analysis (ICA). Empirical evaluations were performed using data collected from three sites, which are part of a pediatric epilepsy consortium. The test data contained 30 control subjects and 29 pediatric epilepsy patients all of which were performing an auditory decision descriptive task, a language task paradigm. This approach is augmented by a unique graph thresholding technique based on the graph density function. The constructed networks were then analyzed using graph theoretical measures. The proposed network construction approach is weighed in merit to the traditional correlation approach and a modified version of it. The obtained results show that the ICA-based approaches improve considerably the delineation process of the patients’ population from the controls’ population, whereas the traditional methods show considerable overlap between the two populations. Furthermore, an investigation on the topology of the networks constructed show that all methods lead to a small-world topology conforming to previous brain functional studies.

I. INTRODUCTION

The advent of recent neuro-imaging modalities in the last few decades has spurred many brain functional studies [1]-[4]. Particularly, Functional Magnetic Resonance Imaging (fMRI) has been widely used because of its safety (no radioactive materials), its balanced spatial/temporal resolution, and its non-invasiveness. fMRI is a technology that relies on detecting Blood Oxygenation Level Dependent (BOLD) signals as an indirect hemodynamic measurement of neuronal activity. The accessibility of fMRI and its use in clinical practice has generated studies of brain functional changes and shifts associated with particular neurological disorders, such as epilepsy. Moreover, recent studies [5] have confirmed that the brain is a highly integrated structure of functional units, as opposed to being composed of isolated compartments responsible for independent tasks. Therefore, it is crucial to investigate the brain as an intricate network of interwoven elements where brain dynamics in its normal state or as caused by specific neurological disorders could be assessed in a more meaningful way.

The focus of this study was placed on constructing a functional brain network by connecting different spatially independent units generated by Independent Component Analysis (ICA) [6] and investigating the topology of this network using Graph Theory [7]. As an example, we studied the effect of a neurological disease, namely pediatric epilepsy, on language networks.

Functional brain networks are traditionally constructed by correlating the temporal BOLD signal between several voxels in the gray matter [8]; alternatively, causal models can be used to investigate the connection between a limited number of predefined regions in the brain [9] to yield a partial depiction of the entire brain network. The functional network construction methods as proposed in this study are novel in that they define isolated individual brain units generated by a blind source separation method (ICA) and connect these independent units into an intricate network representing the entire functional brain network. More importantly, the identification of the independent units is completely data driven. These units hypothetically perform different functions that are integrated to perform a given task.

II. METHODS

A. Participants and Data Collection

A total of 29 pediatric epilepsy patients and 30 age/sex matched control subjects were recruited from three leading pediatric hospitals: British Columbia Children’s Hospital, Children’s Healthcare of Atlanta, and Children’s National Medical Center. All three locations used a 3 Tesla Siemens Trio MRI scanner. The fMRI language paradigm used was the Auditory Descriptive Decision Task as described in [10].

In addition to the fMRI scan, a high resolution structural T1 MRI scan was acquired for each subject to aid in registering each subject’s fMRI space to a common stereotaxic space defined by a brain template.

B. fMRI Preprocessing

Each subject’s fMRI dataset was preprocessed as follows: temporally high pass filtered with a cutoff of 100 seconds to remove the MRI scanner’s baseline effect, head motion corrected using MCFLIRT [11], slice time corrected, deskulled to remove non-brain tissues using Brain Extraction Tool (BET) [12], and spatially smoothed with a 5 mm full width at half maximum (FWHM) to increase the signal to noise ratio. The preprocessing was performed using the FMRIB Software Library (FSL) [13], [14].

C. Independent Components Analysis (ICA):

ICA is a blind source separation algorithm that transforms a set of signals into their associated latent sources. ICA does not assume any a priori knowledge of these sources. The only constraints imposed on the sources are that they are statistically independent and at most one of them is Gaussian. There are several ICA algorithms as exemplified in [15], [16] with the most prominent being an elegant fixed-point algorithm (FastICA) that uses negentropy as its cost function.
ICA in fMRI appeared in 1998 as the first model-free method used to generate activation maps [18]. Typical results of applying ICA to the four dimensional fMRI data [19] are spatially independent components each with a corresponding temporal profile as shown in Fig. 1.

Each preprocessed fMRI dataset will be passed to the probabilistic independent component analysis (PICA) algorithm [20] to get its latent sources. PICA is an ICA approach that uses FastICA as its backend algorithm and includes a noise term in the model; additionally PICA has a model order estimation step [21] that estimates the optimal number of independent components. The output of PICA is optimal in that each spatial map is optimally integrated and represents one activation unit as opposed to being separated into several maps that are harder to interpret. PICA was performed using MELODIC, which is part of the FSL software library [13], [14].

D. Coregistering the Brain Atlas to the fMRI Space:

The Automated Anatomical Labeling (AAL90) atlas [22], which includes 90 cerebral regions in the MNI152 space, was registered to the subject’s fMRI space then superimposed over each spatially independent component. For each subject the registration was as follows: deskulling of the fMRI dataset, deskulling of the its corresponding T1 both using BET, registering the deskulled fMRI to the deskulled T1 using an affine transformation (12 degrees of freedom), registering the deskulled T1 to the MNI152 brain also using an affine transformation. The two aforementioned registration steps were concatenated into a single transformation matrix. This single matrix was then inverted and applied to register the AAL90 atlas to subject’s fMRI space. It is noted that each registration step was performed using the FMRIB’s Linear Image Registration Tool (FLIRT) [11].

D. Functional Network Construction:

Networks or graphs consist of a group of nodes connected by edges. The goal in this implementation step was to determine a functional brain network, which is essentially defining the nodes and connecting them by valid edges. The nodes were defined as the different 90 regions of the AAL90 atlas. Thus, these nodes will be comparable across subjects. In this study, four methods to connect these nodes are proposed:

1) ICA-based Capturing Extent of Activation

After coregistering the AAL90 atlas to the subject’s fMRI space, the atlas is superimposed over each spatial independent component (IC). For each of the 90 regions in the atlas we count the number of activated voxels at each IC. The temporal profile of the IC with the highest activated voxel count is associated with the particular atlas region. Eventually, every region in the atlas will be associated with a single temporal signal. A 90x90 correlation matrix is constructed using Pearson’s correlation between the temporal signals. The resulting matrix is a graph adjacency matrix representing the functional brain network of the subject at hand while capturing its extent of activation.

2) ICA-based Capturing Intensity of Activation

Similarly, an adjacency matrix capturing the intensity of activation can be constructed by repeating the same steps in 1 but instead of counting the number of activated voxel, the average absolute z values of the activated voxels is computed. The resulting graph adjacency matrix represents the functional brain network of the subject at hand while capturing its intensity of activation.

3) Traditional

For each subject the AAL90 atlas is registered to the fMRI space and then superimposed over the preprocessed fMRI as described above, then for each of the 90 regions we compute the average of all BOLD signals within that region, the averaged signal represents that region. We construct a 90x90 correlation matrix using Pearson’s correlation. The resulting adjacency matrix represents the traditional functional brain network.

4) Modified Traditional

Likewise, instead of averaging the BOLD signals within each region in the traditional method, the first principal component of the BOLD signals within a region, which captures the largest variance, can now represent that region instead. The resulting adjacency matrix represents the modified traditional functional brain network.
E. Thresholding the Adjacency Matrix:

All graphs constructed using any of the four connectivity methods, were undirected weighted graphs. In this study the focus was placed on connectivity whether two nodes were connected or not; therefore, the absolute value of the adjacency matrix was thresholded in an unweighted form. In this section, a thresholding scheme is designed for facilitating the selection of an objective threshold comparable across all subjects.

A graph density can be defined as:

$$D = \frac{\text{Number of edges}}{\text{Number of all possible edges}}$$  \hspace{1cm} (1)

For a fully connected graph, where all nodes are connected directly to all other nodes, \(D = 1\). On the other extreme, a disconnected graph will yield \(D = 0\).

Density is a measure of a network’s wiring cost. Therefore, thresholding using this measure facilitates comparison across networks. For example, two brain networks with the same density will have the same number of nodes and the same number of edges (same wiring cost). However, the edges are shifted reflecting the state of the subject’s network. Fig. 2 shows the relation between thresholding using Pearson’s correlation coefficient and the graph density (for a control subject). Clearly, higher correlation threshold values lead to lower density graphs. We use a bidisectional algorithm to calculate the corresponding correlation threshold value given a selected density. This means a density threshold that guarantees a connected graph with the cheapest wiring cost. A connected graph is thus a network where every node will have a path to any other node in the networks, directly or indirectly.

III. RESULTS

To measure a graph connectedness, we use the normalized size of the largest connected component. A connected component in a graph is a group of nodes that can reach each other within the component; i.e. in a connected graph all nodes can reach each other and the largest connected component contains all nodes, hence it’s normalized size is 1. Similarly, if there are several connected components within the network, which do not have any connecting links, then the size of the largest connected component will be less than 1.

For each network construction method, we compute the normalized size of the largest connected components for every subject across a density range from 10% to 70%. Fig. 3 a, b, c, d show the results for method 1, 2, 3, 4 respectively.

Fig. 3 shows that ICA based methods were able to delineate the patients from the controls better than the traditional methods. To confirm these observations statistically, we calculate the area under the curve for each subject then we compare the patient population to the control population using a boxplot and a \(t\)-test. The \(t\)-test confirms that ICA based methods can separate the patients/controls groups with a \(p = 0.001\), whereas the other two traditional methods where not able to separate the groups \(p = 0.295\) for the traditional method, and \(p = 0.14\) for the modified traditional method. The boxplots are shown as insets in Fig. 3.
Furthermore, we investigated the topology of the networks constructed by calculating the small-world parameter [23], [24]. We found that each network method thresholded with the cheapest wiring cost results in small-world network topology with $p = 1.0E-13$. Small-World networks topology is known to have higher information transfer efficiency and better synchronization. These findings match other studies that found that typical and atypical brain networks have a small-world architecture and that neurological disorders introduce changes to the network while maintaining the overall small-world networks architecture [8], [25], [26].

IV. DISCUSSION

The ICA based construction methods used in this study were data driven. The methods can be used with resting state fMRI as well as task-based fMRI. These ICA-based methods with the help of graph theoretical analysis were capable of delineating to a great extent the pediatric epilepsy patients from the control groups of our study. A fact that will allow us to enhance our investigation of the language network reorganization introduced in [1], [2], [4].

Furthermore, the density thresholding scheme used is objective in that it selects a correlation threshold that guarantees a connected graph with the cheapest wiring cost. In addition, thresholding all subjects with the same density level allows for easy comparison across networks, since such thresholded graphs will have the same number of nodes and the same number of edges. It should be noted however, although, the networks have the same number of edges the edge distribution would be altered reflecting the state of the subject’s network.

Future investigations on this research endeavor should include rigorous statistical tests and graph theoretical analysis of the constructed networks using different measures such as: degree centrality, betweenness centrality, average clustering coefficient, and average shortest path length.

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