

Labeling Graph connectivity patterns in the human brain network using fMRI data

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Abstract- Exploring the human brain from the viewpoint of connectivity patterns reveals important information regarding the structural, functional, and causal organization of the brain. Among the connectivity techniques, functional, and effective connectivity have been the focus of the computational studies in recent years. The main purpose of this paper is to review the recent studies utilizing Labeling graph methods to analyze connectivity patterns in the human brain network using fMRI data and expect to see whether the recognition of brain connectivity properties by Labeling graph theory (as measured by fMRI) has been effective in understanding the mechanisms underlying human cognition compared to the traditional approaches.

Index Terms- brain connectivity, functional connectivity, effective connectivity, fMRI, labeling graphs.

I. INTRODUCTION

The human brain is one of the most complex networks in the world, and studies on its static and dynamic properties have undergone explosive growth in recent years [5], [6], [7], [20], [26]-[31]. The advances in graph theory and network neuroscience (i.e., the study of the structure or function of the nervous system) offer an opportunity to understand the details of this complex phenomenon and its modeling [32], [33]. Graph theoretical approaches have set up a mathematical framework to model the pairwise communications between elements of a network. In human neuroscience, graph theory is generally applied to either functional or effective connectivity. However, most studies have been devoted to functional connectivity [5]. Graph-based network analysis reveals meaningful information about the topological architecture of human brain networks, such as small-worldness, modular organization, and highly connected or centralized hubs [5], [6], [7], [18], [32]. Small-worldness is a property of some networks in which most nodes are not neighbors of each other but can be reached from every other node by a small number of steps. This characteristic is well suited to the study of complex brain dynamics, and it confirms underlying human cognition compared to the traditional approaches.

II. THEORETICAL BACKGROUND: CONNECTIVITY PATTERNS USING FMRI

Brain connectivity investigations using fMRI time-series were initiated in the mid-1990s and provided a new tool for

efficient information segregation and integration in the human brain networks with low energy and wiring costs. Recent studies demonstrate that the small-world property of brain networks experiences topological alterations under different cognitive loads and during development [1]-[3], as well as in neurological and mental disorders [21]-[26]. These alterations may provide novel insights into the biological mechanisms underlying human cognition, as well as health and disease.

Recent advances in neuroimaging have enabled mapping of the human connectome in different applications [32], [33]. Brain function can be localized through neuroimaging techniques that assess changes in metabolism via positron emission tomography (PET) or changes in blood oxygenation level-dependent (BOLD) responses via fMRI. Structural pathways can be captured using diffusion tensor imaging (DTI), in which MRI is applied to trace white matter tracts. Finally, the timing of brain activity and its locus can be determined from electroencephalogram (EEG) or magnetoencephalogram, which respectively, measure electrical and magnetic signals outside the skull. Used separately or together, these techniques constitute the neuroimaging toolkit of scientists investigating the physiology of human brain networks. fMRI and PET offer a relatively low temporal resolution but have a significant spatial resolution, making them particularly useful for determining where neural signals are generated. However, PET scanning can measure the blood flow changes in an area of ~5–10 cubic millimeters while fMRI can resolve down to 3 cubic millimeters and even lower. Moreover, PET scanning is much more expensive than fMRI and requires radioactive isotopes to work [12]. During the last two decades, there has been an explosion of fMRI studies mapping neural functions to distinct parts of the brain at rest or during task performance, however, more attention has been directed toward resting-state fMRI (rs-fMRI) data. The main purpose of this paper is to review the recent studies utilizing Labeling graph methods to analyze connectivity patterns in the human brain network using fMRI data and expect to see whether the recognition of brain connectivity properties by Labeling graph theory (as measured by fMRI) has been effective in understanding the mechanisms

researchers, especially neuroscientists, to study the human brain network with high precision. Computational methods available for brain connectivity are divided into two general categories:

functional connectivity and effective connectivity [12], [13]. Briefly, functional connectivity provides information about the statistical dependencies or temporal correlations between spatially remote neurophysiological events, whereas Now it is the time to articulate the research work with ideas gathered in above steps by adopting any of below suitable approaches: effective connectivity is concerned with the directed influence of brain regions on each other [13]. In the following, we will review the computational methods that are presented in the literature for investigating both types of connectivity with a greater focus on graph theoretical approaches in separate sections (Figure 1).

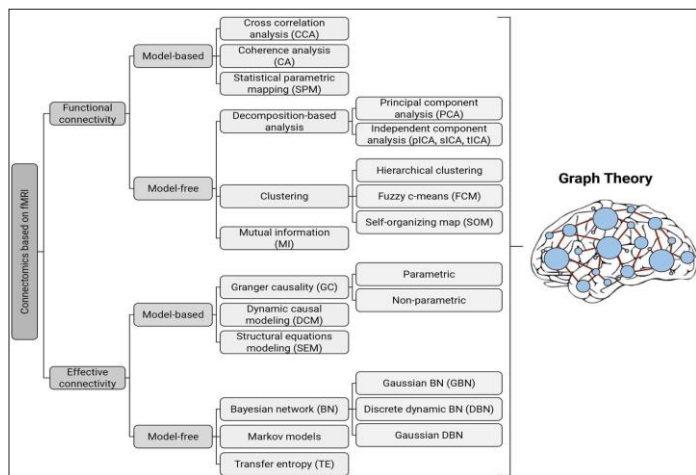


Figure 1

Functional Connectivity

Functional connectivity refers to the temporal correlations between BOLD signals from spatially remote brain regions [11]. Functional connectivity methods in fMRI studies are broadly divided into model-based (e.g., cross-correlation, coherence analysis, and statistical parametric mapping) and model-free (e.g., decomposition-based analysis, clustering, and mutual information) groups.

Model-Based Methods

Model-based methods typically identify brain connectivity networks by selecting one or more “seed” regions and then determining whether there is a linear link between seed regions and other regions using predefined criteria [23], [24]. Despite their widespread use and simple interpretation in identifying functional connectivity, the requirement for prior knowledge (particularly in rs-fMRI), dependency on the seed selection, and the inability to detect non-linear forms of interaction, restrict the discovery of all plausible functional architectures [10].

ICA and PCA is that the components in ICA should be as independent as possible. Note that a violation of component independence would reduce the efficiency of ICA. Furthermore, finding the optimal number of independent components is

Cross-correlation and coherence

Cross-correlation analysis is the most traditional method for testing functional connectivity, which is defined by measuring the correlation between the BOLD signals of any two brain regions. The computational complexity of this method is extremely high when calculating the correlation of two series at all lags. Fortunately, a large number of fMRI studies have overcome this drawback by computing only the correlation with zero lag due to the short duration of the hemodynamic response of blood [12]. Moreover, correlations are sensitive to the shape of the hemodynamic response function (HRF), which causes variations across different individuals and different brain areas. Furthermore, a high correlation may be observed among regions that practically have no blood flow fluctuations. Uncontrolled physiological noise in the brain (e.g., from cardiac and respiratory variations) can also result in high correlations between brain regions [11], [12] suggested a new measure, termed coherence, which is the spectral representation of correlation in the frequency domain.

Statistical parametric mapping (SPM)

SPM is another model-based approach used to detect region-specific effects (e.g., brain activation patterns) in neuroimaging data, such as fMRI and PET, using a combination of the general linear model (GLM) and Gaussian random field (GRF) [13]. The GLM helps estimate the parameters describing the spatially continuous data by performing a univariate test statistic on each voxel. GRF theory is applied to address the multiple comparisons problem for continuous data (i.e., images) when making statistical inferences over a volume of the brain, an approach similar to the Bonferroni correction for the analysis of discrete data.

Model-Free Methods

In contrast to seeds-based methods, model-free methods need no seeds selection. Also, model-free methods may be beneficial in studies where there are no temporal or spatial patterns, as well as in quantifying non-linear neuronal interactions [10].

Decomposition-based analysis

PCA can express the fMRI data with a linear combination of orthogonal contributors that have the greatest impact on the data variance. Each contributor contains a pattern of time variability (or a principal component) multiplied by a pattern of spatial variability (or an eigen map). The created eigen maps reflect the connectivity architecture of the brain. Despite the ability to explore the whole-brain connectivity, PCA fails to detect activations when the contrast-to-noise ratio is low. Also, how to select the optimal number of components has become an open question. Thus, PCA commonly serves as a preprocessing step in fMRI studies through dimension reduction [21]. Another decomposition-based method, called independent component analysis (ICA), attracted the attention of researchers in rs-fMRI studies. The major difference between

controversial because choosing a small number of components can have a significant effect on ICA results, particularly when used for decoding purposes. Finally, ICA cannot discriminate between signals of interest and signals of no interest (e.g.,

physiological noise, unexplained signal variations), leading to overfitting and invalid assessment of statistical significance. To

Clustering

The primary goal of clustering algorithms is to group voxels or regions of interest into different clusters based on the similarity between their BOLD time courses. Hierarchical clustering, k-means, fuzzy clustering (fuzzy c-means), self-organizing maps, graph-based, and bootstrap analysis are the most well-known algorithms used in fMRI studies [21], [22]. Among these methods, the largest volume of studies utilizes hierarchical and fuzzy clustering. Hierarchical clustering seeks to construct a hierarchy of clusters based on an agglomerative or divisive strategy. Although this method exhibits good efficacy in the presence of respiratory or cardiac noise, its high computational complexity is a serious limitation when examining the whole brain connectivity. Fuzzy c-means (FCM) is a method in which each data point has a membership value to each cluster, rather than entirely belonging to one cluster as k-means. This algorithm performs optimization by updating memberships and cluster centers until convergence [22]. It's worth noting that, given the non-Euclidean nature of MRI data, the use of Euclidean distance in FCM-based algorithms may lead to an invalid result [10], [32] compared the results of clustering algorithms to those of decomposition-based methods and reported a high level of overlap. Future studies may, therefore, pay more attention to these algorithms and, by eliminating the above issues, achieve more acceptable performance in human neuroscience.

III. WHAT IS A BRAIN GRAPH?

A brain graph is a model of a nervous system as a number of nodes interconnected by a set of edges. For example, the edges can represent functional or structural connections between cortical and subcortical regional nodes based on analysis of human neuroimaging data. Once a brain graph has been constructed by defining the nodes and edges, its topological properties can be measured by a rich array of metrics that has been developed recently in the field of statistical physics of complex networks [14] and historically built on the concepts of graph theory [15], [16]. Since the nodes of a brain graph can be spatially localized, or physically embedded, its geometrical properties can also be estimated and potentially related to network topology.

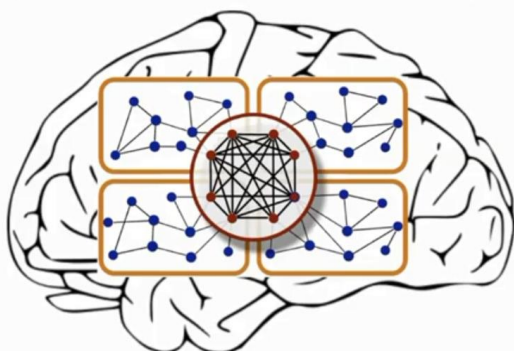


Figure 2

address this pitfall, proposed a probabilistic ICA that allows for non-square mixing when there is Gaussian noise.

The first application of graph theory and network analysis can be traced back to 1736 when Leonhard Euler solved the Königsberg Bridge Problem [14]. In this regard, a graph consists of a finite set of vertices (or nodes) that are connected by links called edges (or arcs). Euler studied the problem of Königsberg bridge and constructed a structure to solve the problem called Eulerian graph.

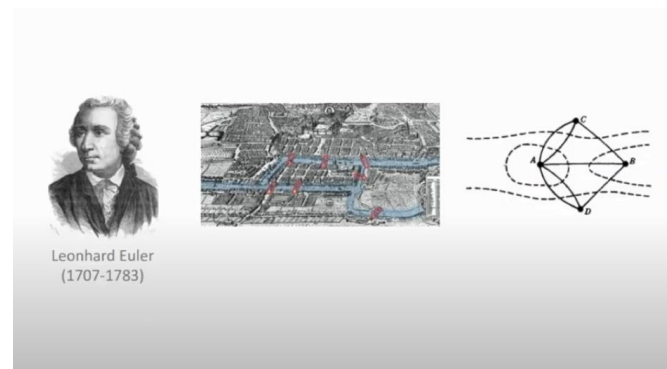


Figure 3

One of the most interesting problems in the area of Graph Theory is that of labeling of graphs. Graph labeling was first introduced in the last 1960s. A graph labeling is an assignment of the vertices or edges or both, subject to subject to certain conditions have been motivated by practical problems. Many practical problems in real life situations have been motivated the study of labeling of a graph. Labeled graphs are becoming an increasingly useful family of Mathematical Models for a broad range of applications.

Graph labeling ideas are highly utilized by structural models that gained popularity in the 19th and 20th century. For each kind of application, depending on problem scenario a kind of graph is used for representing the problem. A suitable labeling is applied on that graph in order to solve the problem. This structural arrangements of various objects or technologies lead to new inventions and modifications in the existing environment for enhancement in highly interdisciplinary, having important applications mainly it allowed to describe phenomena from very different fields: network structure, dynamics of network structure, dynamical processes running over networks, modeling of network topologies. The main purpose of this paper is how brain properties can emerge through the interactions of distinct neuronal units in various cognitive and neurological applications using graph labeling methods and to analyze connectivity patterns in the human brain network.

Harary [15]-[17] introduced the concepts of sum and integral sum graphs. A graph G is a sum graph if the vertices of G can be labeled with distinct positive integers so that $e = uv$ is an edge of G if and only if the sum of the labels on vertices u and v is also a label in G . He extended the concept to allow any integers and called them as integral sum graphs. To distinguish between the two types, we call sum graphs that use only positive integers N -sum graphs and those with any integers Z -sum graphs [17].

If G is a properly labeled sum graph, then the vertex with the highest label in a sum graph cannot be adjacent to any other vertex. Thus every sum graph must contain isolated vertex or vertices. If G is a sum graph or an integral sum graph with respect to a label set S , then G can be denoted as $G+(S)$.

Harary introduced a family of integral sum graphs that are defined by $G_{n,n} = G+(s)$ where $S = \{-n, \dots, -2, -1, 0, 1, 2, \dots, n\}$ we find the number of edges of $G_{n,n}$. We generalize the graph $G_{n,n}, n \in \mathbb{N}$ and define the graph $G_{m,n} = G+(s)$ where $S = \{-m, \dots, -2, -1, 0, 1, 2, \dots, n\}$ and prove that these graphs are integral sum graphs and also find their sizes.

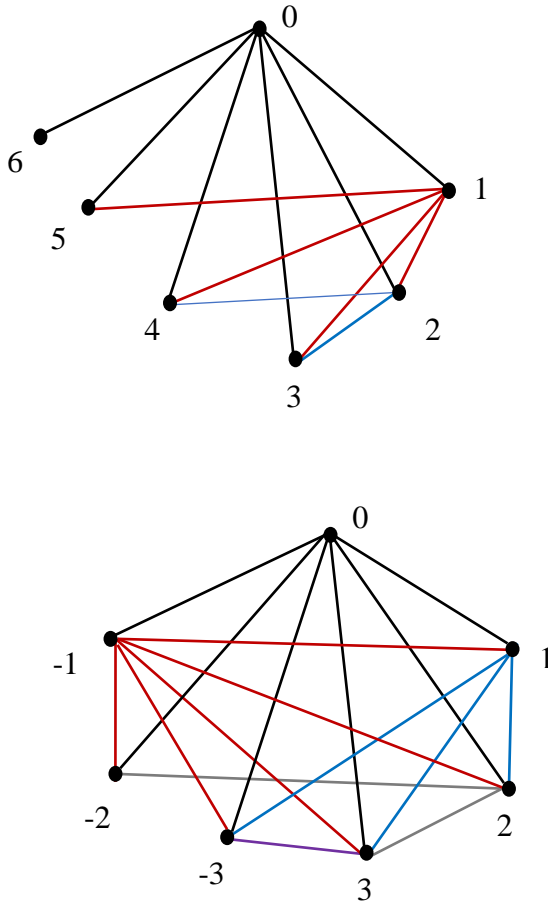


Figure 4

While discussing sum and integral sum graphs we could notice that the complement of a sum and integral sum graph G satisfies the property that $e=uv$ is an edge of G^c if and only if the sum of the labels on vertices u and v is not vertex label. From this idea, we define anti-sum and anti integral sum graphs and give some properties. The concept of integral sum and anti-integral sum labeling helps to decompose complete graphs.

We define anti-sum and anti-integral sum graphs. The concepts of sum, anti-sum, integral sum and anti-integral sum labeling are used to decompose complete graphs.

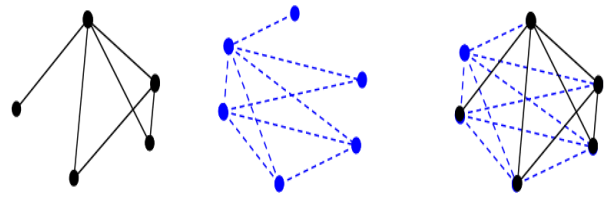


Figure 5

Comparing the brain topological alterations during a cognitive task and resting-state using fMRI data helps identify areas that affect human behavioral performance. used graph labeling methods and to analyze connectivity patterns approach to explore variations in functional brain organization during semantic decision making compared with rest in healthy participants. They observed that differences were generally associated with the language-related and DMN regions. More importantly, they found greater intra-modular communication in these regions during decision making (i.e., a decrease in distributed connectivity), whereas the inter-modular communication was stronger at rest.

Moreover, it analyzed whether cognitive behavior correlates with the functional connectivity of the DMN in healthy subjects, both while at rest and during an attentional task. Quantifying the static and dynamic nodal properties within the DMN, they revealed the importance of the default network, especially the posterior cingulate areas, on human cognitive performance. Finally, it investigated the relationship between ongoing alterations in baseline connectivity patterns and behavioral performance through a continuous auditory detection task. Interestingly, their results indicated a reduction in modularity (i.e., increasing integration efficiency) before misses compared with hits and task-free rest, mostly in the DMN areas and visual networks. These findings augment our understanding about the key role of the DMN in behavioral performance at rest and during a task; however, its association with other brain regions in more complex cognitive tasks, such as reasoning and executive functions, requires further studies.

Disconnection in a brain made up of localized but linked specialized regions results in functional impairment, associating with atypical integration of distributed brain areas. Elaborated the rises and fall of disconnection syndromes and pointed out that many neurological disorders can be explained via these syndromes, in line with the studies of pioneers in neurology and psychiatry such as Meynert, Wernicke, and Dejerine. Studies in the field of complex brain networks have demonstrated that analyzing the network properties and metrics derived from brain topology using rs-fMRI can help neurologists distinguish patient groups from control subjects in mental disorders. In the following, several studies that have used graph theory to investigate common neurological disorders, comprising epilepsy, Alzheimer's disease (AD), multiple sclerosis (MS), autism spectrum disorder (ASD), and attention-deficit/hyperactivity disorder (ADHD), are discussed. However, other mental disorders were also found in recent graph-based literature, including schizophrenia, Parkinson's disease, insomnia, major depression, obsessive compulsive disorder (OCD), borderline personality disorder (BPD), and bipolar disorder, but their contribution is negligible and more attention is required in future research using labeling graph connectivity patterns.

IV. CHALLENGES AND FUTURE DIRECTIONS

In general, the consistency of results across similar experiments that employed a Labeling graph methods to analyze connectivity patterns approach indicates that this perspective is promising for establishing a comprehensive and sustainable model in future fMRI studies. However, it is sometimes difficult to integrate all of the reported findings of pathological brain networks because the results do not coincide with each other when the factors affecting the experiments are different. For instance, patient demographic factors (such as age, gender, educational level, etc.), disease-specific characteristics (such as duration, course, severity, disability level, etc.), sample size, and network construction greatly vary across the studies. As an example of network construction, ignoring the negative entries in the connectivity matrix is very likely to result in the loss of valuable information. To overcome these heterogeneities and increase the reliability of the findings, more consistent comparisons can be made across the studies. In addition, there are several image repositories for pairwise studies in the area of brain network connectivity that can be explored by various packages based on Labeling graph methods to analyze connectivity patterns. Although the importance of computational approaches in fMRI analysis has been evident over the last decade, it has not always matched the richness of fMRI data. Early methods mostly neglected the ability of predictive models to better understand the distributed and dynamic nature of neural representations. Recently, several theory-driven techniques have commenced to highlight the salient role of machine learning, algorithmic optimization, and parallel computing in fMRI analysis. Hence, adoption of modern techniques, such as multivoxel pattern analysis (MVPA), convolutional neural network (CNN), generative models, and real-time analysis, then aligning them with graph theoretical concepts might open a new generation of experiments that could transform our understanding of complex properties in the human brain networks.

Another challenge in Labeling graph methods to analyze connectivity patterns research is developing a consensus about which of the brain parcellation schemes is optimal for defining network nodes and constructing the brain network. Different parcellation methods may lead to different topological properties in the human brain networks, and the results depend on the network resolution. However, for better insight, one can appraise the reproducibility of the primary findings by applying multiple parcellation schemes at different spatial scales, particularly those with high resolution. Moreover, node specification in developmental research is extremely important as it is possible for nodes to be dissimilar across a sample, which may distort the brain network. Therefore, a fundamental condition for ensuring the reliability of graph analysis in brain connectivity studies is the precise definition of network nodes, which itself requires the adoption of an appropriate parcellation strategy.

Although structural pathways are thought to underlie functional connectivity patterns, one cannot claim that

there is a one-to-one correspondence between topological properties in functional and structural organizations. In some neurological diseases such as schizophrenia, small-world network abnormalities may even display opposite directions over functional and structural organizations. Concerning this matter, van den Heuvel et al. recognized evidence of reduced local efficiency and segregation (i.e., clustering and modularity) together with increased global efficiency in several functional studies of schizophrenia. However, their review of structural studies resulted in contradictory findings, such as increased segregation along with reduced integration and global efficiency. Moreover, they examined the structural and functional disruptions in the earliest stage of MS and MS patients by combined use of DTI and rs-fMRI. Studies exhibited structural changes in the earliest stage of MS, while functional patterns remained stable at that stage. Hence, structure-function relationship studies are needed to help elucidate such existing deviations for labeling graph connectivity patterns.

The dynamics of brain function seem to result in numerous cognitive, emotional, and behavioral changes that occur during brain development. However, the majority of studies cannot interpret brain network dynamics because their design is typically cross-sectional and the calculated measures of the brain graph are only capable of displaying a snapshot of the disease over time. Therefore, the progression of neurodegenerative disorders may not be well-understood, and subsequently, treatment strategies exhibit poor performance, reported that longitudinal fMRI studies with labeling graph connectivity patterns provide a suitable means for understanding the development of pathological conditions, as well as tracking temporal correlations between topological alterations in the brain network.

V. CONCLUSION

The main focus of the current paper, comprehensive information on Labeling graph methods to analyze connectivity patterns in the complex brain network along with its applications in neuroscience is presented. The brain network topology is expected to be responsive to cognitive performance, behavioral variability, experimental task, and neurological disorders such as epilepsy, Alzheimer's disease, multiple sclerosis, autism, and attention-deficit/hyperactivity disorder. However, Labeling graph methods analysis in human neuroscience faces a number of issues that remain unaddressed, restricting its interpretation and application. Some examples are heterogeneity of the results, sensitivity to parcellation strategy and node specification, statistical variability of brain graphs due to noise, lack of attention to the structure-function relationship, neglecting the variations in network density and connection strength, and dynamics of the brain network. Addressing any of these limitations in future studies will help advance our understanding of functional neural networks in the human brain.

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