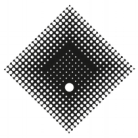
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A Survey of Graph Based Complex Brain Network Analysis Using Functional and Diffusional MRI

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American Journal of Applied Sciences

Review Articles

A Survey of Graph Based Complex Brain Network Analysis Using Functional and Diffusional MRI

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Abstract: The brain network is the function of a structurally and functionally organized complex system. Its structure and activity analysis is one of the most significant challenges. The graph based techniques of brain complex networks have been successfully used in various types of image and medical data analysis. In this survey paper, we focus on a comprehensive study of the analytical methods for complex brain network based on graph theory. This review paper is intended to provide automated brain disease diagnosis based on functional and diffusional MRI modalities. Furthermore, we discuss subjective and objective quality evaluations of complex brain networks, important tools for automated brain disease diagnosis, challenging issues and future research directions in this increasingly evolving research field.

Keywords: Functional MRI, Diffusion MRI, Graph Theory, Complex Network, Modality

Introduction

Our brain is a function of complex networks because its function is connected within different neural networks and brain regions. Almost everything we think, say and do is controlled by our brain, so when our brain is damaged, it is possibility to affect every aspect of our life (Bullmore and Sporns, 2012).

In the field of mathematics, graph theory is a major area to model relations between objects and to represent a connected network structure. Researchers are using graph theory to quantify aspects such as similarity, hierarchy and network efficiency of complex network structure in many other fields. Recently neuroscience researchers are proposed to use graph theory analysis to identify topological properties of complex brain network structure (Thirion *et al*., 2006; Bullmore and Sporns, 2009). A few years back, Grady and Polimeni (2010) published a book related to discrete calculus on graphs and described discrete calculus, matrix algebra briefly. In recent years, various researchers suggested that the combination of discrete calculus, matrix algebra on graph provides the extremely powerful computational toolbox for the analysis of human brain functions and structure. However, the ability to perform these computations on graphs was not possible even in recent history of the field.

Over the last decade, researchers have tried to improve their understanding of the functionality of human brain and machine diagnosis of mental illness. A large number of technique have been applied to learn about complex brain system and these techniques were intended to aid diagnosis and assessment of the extent of brain damage. Though hese techniques are able to detect damage to the brain, they are unable to provide the clear image in some circumstances. They have not the capacity to cover the entire brain rather provide a limited coverage of its parts. However, in the field of medical science especially in brain diagnosis research, there are various prominent techniques which have been studied and investigated to present promising diagnosis result. Functional and Diffusional magnetic resonance imaging are non-invasive techniques. These (fMRI and DMRI) advanced techniques have been used to investigate physiological disturbances and now developing leads to manifest psychiatric illness.

The purpose of this review paper is to examine existing techniques and to outline the types of challenges that can be addressed. To our knowledge, this review report represents the first effort to check impairment

Science Publications

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detection with an exact application on complex brain network. In this review, we do not consider any specific brain disorders. Rather, we aimed to identify the prominent techniques which have been applied to analyse complex brain networks based on the graph theory However, we found that many relevant tasks were mostly published in the area of neuroscience that we have focussed below. Therefore, we have elected to limit the scope of our review that can be focussed in future of neuroscience research.

The paper is organized as follows: Section 2 presents the review of related works and contributions, while the analysis of graph based complex brain network is discussed in section 3. We focus on Functional MRI as well as Diffusional MRI techniques in section 4. Finally, the guidance of future research directions and conclusion is provided in section 5.

Literature Review

Van der Horn *et al*. (2017) Illustrated on mild Traumatic Brain Injury (mTBI) that is one of the most widespread disorders in neuroscience. They found that although the complaints of post-traumatic injury are reported frequently, a consistent solution has not yet been found. To gain a comprehensive understanding, they used graph theory analysis of complex interactions between complaints, functional brain networks, depression and anxiety in the sub-acute phase after mTBI. Several recent studies present a review of advances in neuroscience focusing on the graph based research on exact areas of brain connectivity. Del Etoile and Adeli (2017) presented a detailed outline of brain connectivity and graph theory analysis as a great solutions of Alzheimer's disease. McColgan *et al*. (2017) proposed that functional and structural brain network correlates as a possible solutions of Huntington's disease. Using resting state fMRI data they examined how different functional and structural brain networks chronicle to depressive affection in premanifest HD and advantageous controls and finally got significant results. Hart *et al*. (2016) discussed about human brain as the most powerful complex system and recently this idea of complex brain networks with graph theory has entered a new era in neuroscience. Using resting state fMRI they provided new ideas in brain mapping with graph applied to neurosurgery especially to traumatic brain injury.

Bullmore and Sporns (2009) reviewed and told that recent development of graph theory analysis has changed the dimension of complex brain network research. To achieve a complete understanding of complex brain network, they provided important information of measuring the brain network organization using functional MRI, structural MRI, diffusion MRI, EEG, MEG. Chen and Glover (2015) described functional MRI shown great direction to understand cognition in both healthy and dysfunctional brain. (Hart *et al*., 2016) used functional MRI with BOLD contrast imaging to generate better-recorded images. Bullmore and Sporns (2009) explained the quantitative analysis of complex networks using graph theory to improve the patterns of human brain complex networks.

Fox and Raichle (2007) believed that resting-state BOLD fMRI studies accept broadly acclimated functional connectivity to explore the alignment of functional networks. It can accomplish admitting indirect, strong, inferences about the functional access. Song *et al*. (2008; van den Heuvel *et al*., 2009; Zhou *et al*., 2007) examined that Many exploratory readings have inspected the record between the structures of the brain network from the point of appearance of graph theory and multiplicities of behavioural phenotypes in health and disease, including calibration scores, affliction continuance and genotypic variations (Liu *et al*., 2010; Glahn *et al*., 2010). Iannetti and Wise (2007; Honey *et al*., 2009) discussed that the functional connectivity from diffusion MRI will provide good complements for modelling functional networks. Moreover, they believed that although resting-state functional connectivity is mutable and is frequently present between regions without direct structural links, its strength, spatial statistics and tenacity are nevertheless controlled by the large-scale functional structure of the human cerebral cortex.

The major contributions of our survey paper are as follows, we aim to familiarize graph based study of complex brain network. We describe brain as a complex network and graph based methods can be applied to extract the features. In addition, we discuss many of the relevant works on graph based complex brain network that has been used to "real-world" scenarios for brain disorders. Finally, with these ideas established we then explain the contributions of functional and Diffusion MRI with brain connectivity. We discuss how these technologies can help ameliorate the future guidance of complex brain network research.

Complex Brain Network Analysis

Brain network consists of a number of elements including nodes and edges that are mutually interconnected to each other (Kabbara *et al*., 2016a). These systems are not monitored centrally rather it presents collective dynamics with self-organization (Fig. 1). Overall, a network is any system with sub-units that are linked into a whole.

For example, in social relationships, individual people indicates as nodes and it expresses as V and the joint relations between two nodes are indicating whether the corresponding peoples are accompanied or not. It's artlessly accurate as a bend as *E*. The groups of nodes and edges indicate together as a graph: $G = (V, E)$ (Thirion *et al*., 2006).

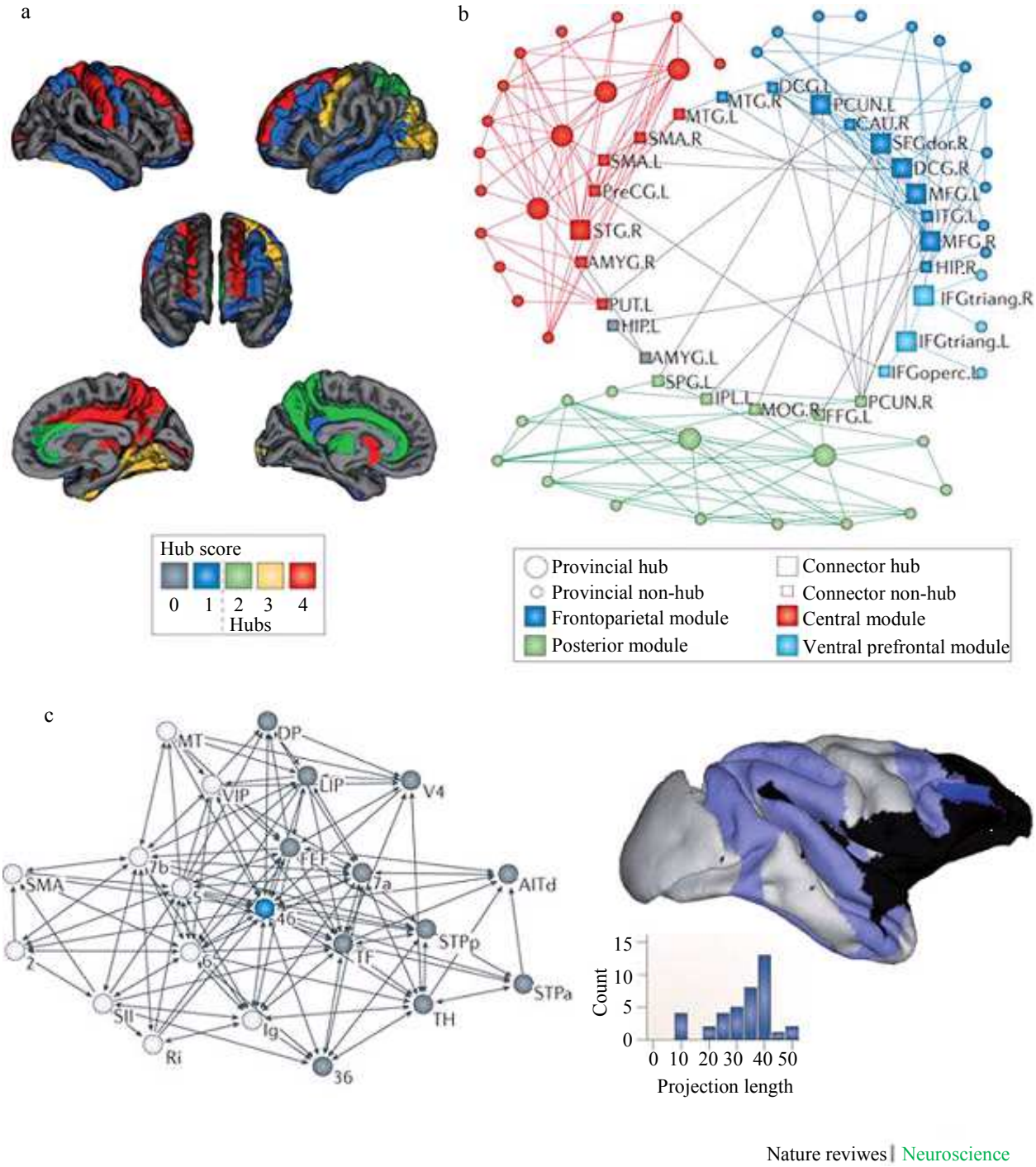

Fig. 1: Complex brain network: Hubs and modules in the brain. Image courtesy of Bullmore and Sporns (2012)

The human brain is organized into complex system allowing within individual components by structurally and functionally. But compassionate its structure and action one of the absolute accurate challenges in neuroscience. To overcome the challenges in neuroscience, many techniques have developed and already applied to make sense of the bewildering complexity of this most mysterious structure.

From past decade, many researchers tried to find the patterns of structural and functional connectivity of brain network by accumulation an array of different imaging technologies like EEG, MEG and structural, functional, Diffusion MRI with adult analytic strategies such as vivo imaging, activating causal modelling, fractional atomic squares and structural graph modelling (Table 1) (Bullmore and Sporns, 2012).

Table 1: Reviews of different automated disease diagnosis techniques applied to implement complex brain network analysis

Techniques	Application of brain networks	Acquisition	Strengths	Weaknesses
Structural MRI (Bullmore and Sporns, 2009; Guye *et al*., 2010; Sporns, 2011; Hagmann *et al*., 2007)	Analyses of structural covariance of morph-ological measures (e.g., cortical thickness or volume) between brain regions (high correlation implies a network link)	Single 3D volume of the brain (e.g., T1 MPRAGE), usually acquired as standard in most MRI protocols	Simple to acquire and not limited by artefacts to the same degree as other MRI-based sequences	Limited by degree of infe-rence one can deduce based on cortica measures
Functional MRI (Bullmore and Sporns, 2009; Guye *et al*., 2010; Wang *et al*., 2010; Maihöfner *et al*., 2005)	Analyses of statistical dependencies between brain regions.	Specific 4D sequence sensitive to BOLD contrast reflecting hemodynamic response of neuronal activity	Reasonably high temporal and good spatial resolution	An indirect measure of neuronal activity. Significant artefacts require careful pre-processing
Diffusion MRI (Iturria-Medina *et al*., 2008; Li *et al*., 2009)	Uses reconstruction of tracts to imply structural connectivity between brain regions	Measures free water diffusion.	Suggests a clear relationship with underlying structural and functional brain connectivity.	Variations in sequences and algorithms can significantly affect network para-meters.
PET (Bullmore and Sporns, 2009; Maihöfner *et al*.,2005; Power *et al*., 2011; Debaere *et al*., 2001)	Covariance in glucose metabolism bet-ween regions	Injection of a radioisotope followed by detection of gamma rays	It is a good biomarker for Alzheimer's dis-ease and provides direct metabolic data	Radiation, limits on repeatability. Potentially lower spatial resolution.
EEG (van Straaten and Stam, 2013; Rubinov and Sporns, 2010; Boersma *et al*., 2011; de Haan *et al*., 2009; Hassan *et al*., 2017a)	Measures statistical dependency between all pair wise combinations of cha-nnels, often in multiple frequency bands	To measure electrical signals in the brain directly it uses electrodes.	Direct measure of neuronal currents and best temporal resolution.	Due to skull and scalp it has some impor-tant limitations and distortion.
MEG (van Straaten and Stam, 2013; Rubinov and Sporns, 2010)	Measures statistical dependency between all pairwise combi-nations of channels	To measures magnetic field alterations using magneto-meter	Exceptionally high temporal re-solution but limited spatial resolution (particularly subcortical)	Difficulties with focusing signal spatially and for low signal-to-noise ratio

Graph Based Analysis of Complex Brain Network

Graph is simple model of complex structures, define as a set of nodes and edges which can be represented as $G = (V, E)$ (Fig. 2). This method have become a great tool in the field of technological, biological and amusing sciences such as the science of ecological networks, the World Wide Web, amusing networks and neuroscience. Onias *et al*. (2014) described that a network is a way to code a set of elements together with their connections. The elements are identified as nodes and their connections are identified as edges. When two nodes are connected by an edges, they are considered neighbours. In addition, edges can be categorized as directed , undirected and weighted (Fig. 3 and Fig. 4).

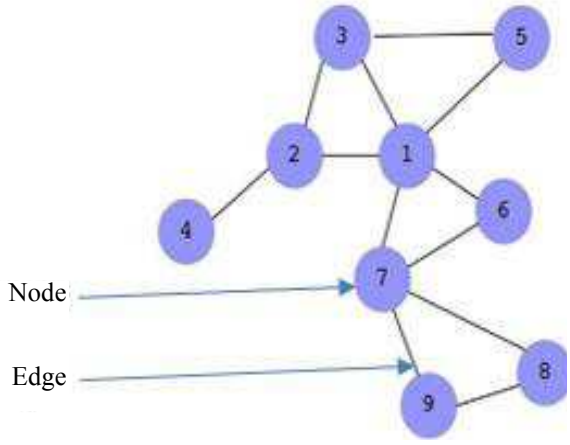

Fig. 2: Graphical representation of graph

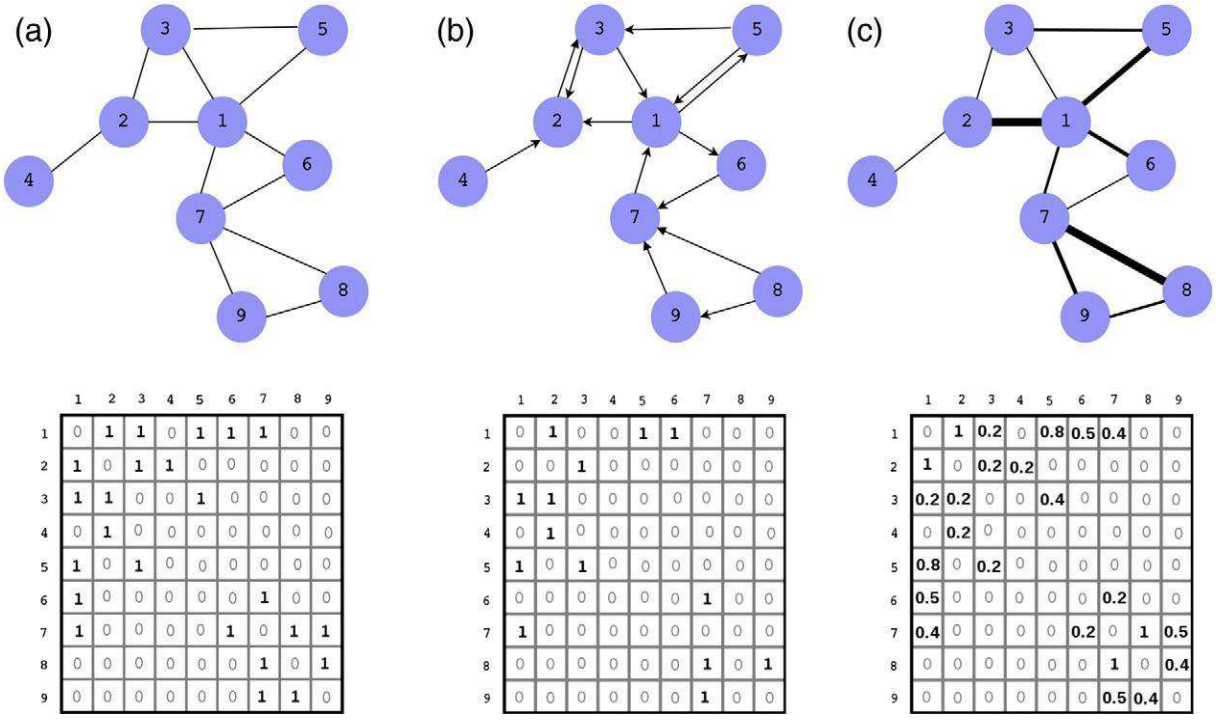

Fig. 3: Examples of (a) undirected, (b) directed and (c) weighted networks (top row) and their corresponding adjacency matrices, coded with a gray-scale colour map (bottom row). Image courtesy of (Onias *et al*., 2014)

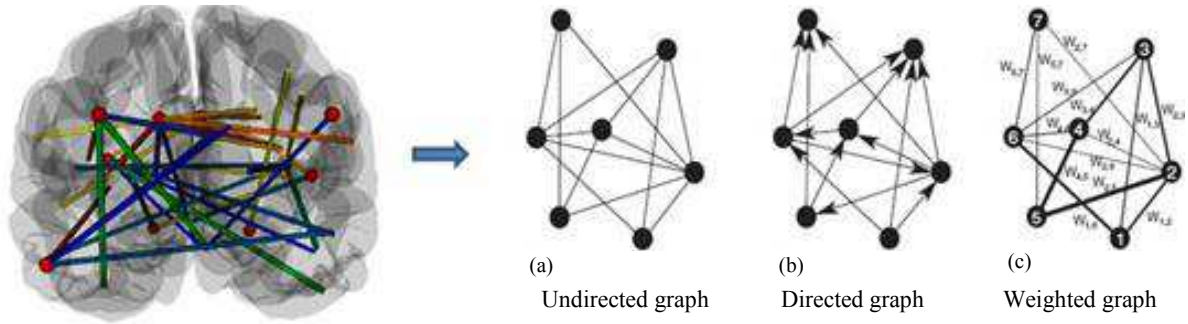

Fig. 4: Examples of complex brain network based on graph. Image courtesy of (Boccaletti *et al*., 2006; Fallani *et al*., 2014)

Moreover, a network framework with N nodes is said to accept labels N that assigns a representation (weight) to each link is called weighted network. Otherwise, if the links of a network do not accept labels, the system is named unweighted network. Previously described that the brain can be seen as a complex network: An affiliated network area where nodes represent different specialized regions and edge represent advice pathways. From the functional viewpoint, communication is coded by temporal dependence between the activities of different brain areas. The use of graph based technique in translational neuroscience has become great to measure brain dysfunctions in agreement of anomalous reconfiguration of brain networks. Besides, graph theory analysis of brain networks can be blindly activated to brain signals. The adversity with integrating data from multiple modalities is that it is computationally actual ambitious to analyse and it is acutely difficult to anticipate anticipate the relationships between objects in the data (Fallani *et al*., 2014).

Brain Network Connectivity

The human brain is organized by structurally and functionally and it is one of the most complex systems. Brain connectivity may be analysed and considered application as a broad range of network analysis methods and categorized as: Structural connectivity and functional connectivity (Fig. 5) (Ciric *et al*., 2016).

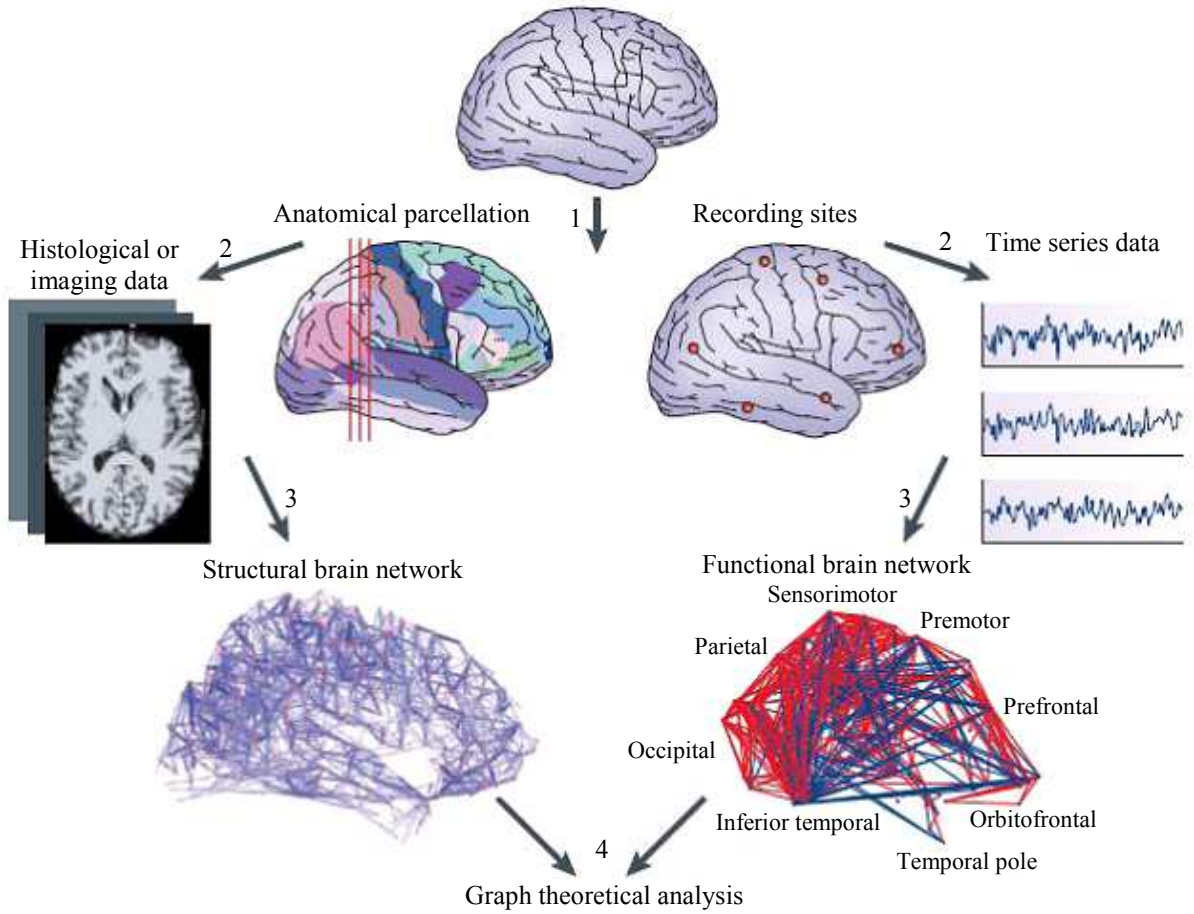

Fig. 5: Graph theory analysis of functional and structural brain network can be shown through the subsequent four phases. First, establish the network nodes. Second, Estimate connected admeasurements of affiliation between nodes. In third, Generate a connection cast by accumulation all pairwise links between nodes. In fourth, analyse the parameters of brain networks. Image courtesy of (Bullmore and Sporns, 2009)

Many of the brain connectivity methods are already activated in alongside efforts to map and call added biological systems, e.g., those of cellular metabolism, ecology or gene regulation. The approach of directed graphs is one of the most popular methods to map networks of structural and functional brain connectivity at all stages.

Graphs are collection of nodes and edges which are corresponding to brain regions and pathways. In the easiest form, graphs can be declared by a connection matrix with binary elements that identify the existence or lack of a directed edge between pairs of nodes. Generally, nodes can connect with other nodes through indirectly or directly. Indirect interaction is a connection of multiple edges and the functional effectiveness of these indirect connections are depends on the path length. Besides the distance between two nodes are corresponding to the length of the shortest path and the all-around average of all distances is called the path length.

According to formal outline of graph based analysis, complex brain network consists of a set of structural and functional connectivity and can be processed by the following several steps.

Structural Brain Network Connectivity

Structural brain connectivity represents the structural associations a part of altered neuronal elements including both the morphometric alternation and accurate anatomical connectivity. At the complex brain networks, this access about accredits to white amount projections bond cortical and subcortical regions. The structural connectivity of human brain *in vivo* can be completed by structural and diffusion MRI. (Bullmore and Sporns 2009; Van der Horn *et al*., 2017). Structural connectivity of this affectionate is anticipate to be almost abiding on under time scales (seconds to minutes) but only some of artificial experience-dependent variations at best time scales (hours to days) (Friston *et al*., 1993). In addition, in the field of neuroimaging, as the directionality of projections currently cannot be detected, the structural brain connectivity is mostly abstinent as a set of accidental relations.

Functional Brain Network Connectivity

Functional brain connectivity denotes the functional relations of brain areas accepting by quantifying the temporal correlations between spatially limited neurophysiological contest from fMRI and EEG/MEG data (Friston *et al*., 1993; Kabbara *et al*., 2016b). It is largely derived from time series analysis of complex brain networks because it is highly time-dependent and describes patterns of statistical reliance among neural elements (nodes and edge) (Joo *et al*., 2016; Zhang *et al*., 2017). A various number of neuroimaging techniques, including diffusion MRI, functional MRI, Electroencephalography (EEG), Magnetoencephalography (MEG) may be applied to analyze time series data of functional brain connectivity and can be figure out in a number of ways, including as spectral coherence, mutual information, or cross-correlation.

The future indications of functional brain connectivity is to apply an algorithm in time-evolving graphs, where the challenging factors are to extract features and to find patterns incrementally over time. Another indication of brain connectivity is if the functional brain connectivity features are extracted from the neuroimaging data, graph based techniques can be further applied to complex brain networks and examine their essential topological properties to detect abnormalities.

Role of Imaging Techniques for Complex Brain Network Analysis

Graph based analysis of complex brain networks have given significant output to find a variety of brain and mental disorders. Functional and Diffusion MRI has given rise to rich and flexible structure function relationships of complex brain network analysis. Besides these imaging techniques already contributed to developing better diagnoses and treatment options of neurodegenerative disorders like as Schizophrenia disease, Alzheimer's disease, traumatic brain injury, Epilepsy, Parkinson's disease etc., Sporns (2014). However, the studies and major contributions of functional and diffusion MRI for complex brain network analysis based on graph provides are as follows.

Funtional Magnetic Resonance Imaging (fMRI)

Functional MRI has released an important window for the non-invasive analysis of the circuitous human brain. Because it can evaluate different brain regions over times, which is the basic need to consider the brain network as a complex system. Functional MRI is a neuroimaging procedure using MRI method that measures brain activity to detect changes in blood flow. Functional MRI is also known as Blood Oxygenation Level Dependent (BOLD) MRI which is one of the most great technique to recognize activity in the human health and brain (Matthews and Jezzard, 2004). BOLD fMRI was first developed and described in 1989. It has rapidly developed as a non-invasive method to map brain activities. Although a number of methods have been applied to measure functional brain networks connectivity, functional Magnetic Resonance Imaging (fMRI), especially resting state fMRI has played great rules for identifying clinical biomarkers for brain diseases (Rodic and Zhao, 2015; Song and Jiang, 2012).

Basic Goals and Current Applications of Functional MRI

Functional MRI is a well-developed imaging technique to detect changes in the signals used to produce magnetic resonance images that are linked with neuronal action in the brain. Besides, it can be advised to abide specific hypotheses apropos the attributes of the broadcast systems amenable for assorted anatomic/functional responses of the brain. Hennig *et al*. (2003; Gore, 2003) illustrated that although many of the imaging techniques have been used to detect the brain disorder, fMRI covers all domain of systemic neurosciences. Functional MRI is just about to enter the domain of clinical applications. Daimiwal *et al*. (2012; Hennig *et al*., 2003) described that functional magnetic resonance imaging techniques have confirmed to be vital to understand the functional, cellular and molecular mechanisms of the brain (Daimiwal *et al*., 2012).

Advantages and Limitations of Functional MRI

The benefit of fMRI is that it is non-invasive and doesn't use radiation like Computed Tomography (CT) Positron Emission Tomography (PET) and X-rays scans. It can evaluate brain function securely and efficiently. Virtually fMRI has no risks. Besides, it is analogously cheap, as no trace or adverse appropriate and easy to use. Functional Magnetic Resonance Imaging (fMRI) can produce are very high-resolution images. Also, fMRI is far more objective to compare with the other traditional questionnaire methods of psychological evaluation. Although fMRI has many advantages yet it has some difficulties. First, it is costly. Second, it can alone abduction bright images contrarily its imaging action may abduction exceptionable artefacts. Third, it is an aberrant admeasurement of academician action that may be suffered by non-neural changes in the body and fourth, advisers still don't absolutely accept how it works (Chen and Glover, 2015; Ahsan *et al*., 2009). In addition the goals and clinical applications of fMRI are listed in Table 2.

Table 2: The goals and clinical applications of fMRI based on graph theory

Techniques	Goals	Applications of fMRI	Graph used	References
Functional MRI	Examine the structure of the complex brain networks.	Aging and Alzheimer's disease.	√	Bullmore and Sporns (2009; Achard and Bullmore, 2007; Meunier *et al*., 2009; Supekar *et al*., 2008; Buckner *et al*., 2009; Buckner *et al*., 2009; Hata *et al*., 2016)
	Clearly, determine which part of the brain is handling critical functions including speech, thought, movement and sensation are called brain map-ping.	Relationship of Carotid stenosis.	√	Chang *et al*. (2016)
	Help assess the effects of disease on brain function.	In migraine.	√	Colombo *et al*. (2015)
	Investigating the growth and function of brain connectivity.	Traumatic Brain injury.	√	van der Horn *et al*. (2017; Hart *et al*., 2016; Nakamura *et al*., 2009)
	Monitor the developments of surgery, radiate-on therapy, or other surgical actions for the complex brain networks.	Parkinson's disease	√	Gao and Wu (2016; Hassan *et al*., 2017b)
		Pearson correlation of brain disorder.	√	Wang *et al*. (2017)
		Drug addicts	√	Nakamura *et al*. (2009; Liu *et al*., 2009)
		Hyperactivity disorder.	√	Wang *et al*. (2009)
		Schizophrenia disease.	√	Liu *et al*. (2008)
		Epilepsy disease.	√	Liao *et al*. (2010)

Brain Network Connectivity with Functional MRI

According to the graph theory concepts brain networks connectivity can be articulated as a graph $G = (V, E)$ area where V can be the accumulating of nodes absorption the academician regions and E can be the anatomic access amid these brain regions. van Den Heuvel *et al*. (2009; van Straaten and Stam, 2013) explored a schematic amount of a graph symbol of the functional brain network in (Fig. 6).

Hagmann *et al*. (2007; Valencia, *et al*., 2009; Meunier *et al*., 2009) studied about the resting-state fMRI for measuring of the functional brain network. They also told that the functional brain networks interactions between regions are abundant because it has an intrinsically cohesive modular (community) structure and functionally linked with brain regions. Nakamura *et al*. (2009) illustrated that the topological properties (connectivity strength, small-world attributes) of functional brain networks at individual time points through the recovery from traumatic brain injury had changed using graph based resting fMRI. Liao *et al*. (2010) showed that graph based resting-state fMRI analysis of functional brain networks in epilepsy was related with smaller clustering coefficients and shorter path lengths. Liu *et al*. (2008) provided the first graph based analysis of functional brain networks in schizophrenia using resting fMRI and also showed that several topological measurements, like local efficiency, global efficiency and clustering coefficient. Supekar *et al*. (2008) reported that the unusual small-world group in functional brain networks was first demonstrated by applying resting state fMRI in Alzheimer's disease. Wang *et al*. (2009) discussed the deficit hyperactivity condition are associated with the unusual small-world topology in functional brain networks.

In Addition, several fMRI studies have examined age-related variations in the functional forms of the brain utilizing graph-based network models. Fair *et al*. (2009) reported that using a fMRI dataset (210 individuals: 66 aged 7-9 years; 53 aged 10-15 years; 91 aged 19-31 years), functional brain networks composed of 34 predefined brain areas were connected over age by the small-world measurements. In contrast, Supekar *et al*. (2009) reported that module assignments change over age because the progress of brain networks can be considered by an abrasion of short-range functional connectivity and a deepening of all-embracing anatomic connectivity. So, this suggests a dynamic developmental trajectory of brain functional network topology.

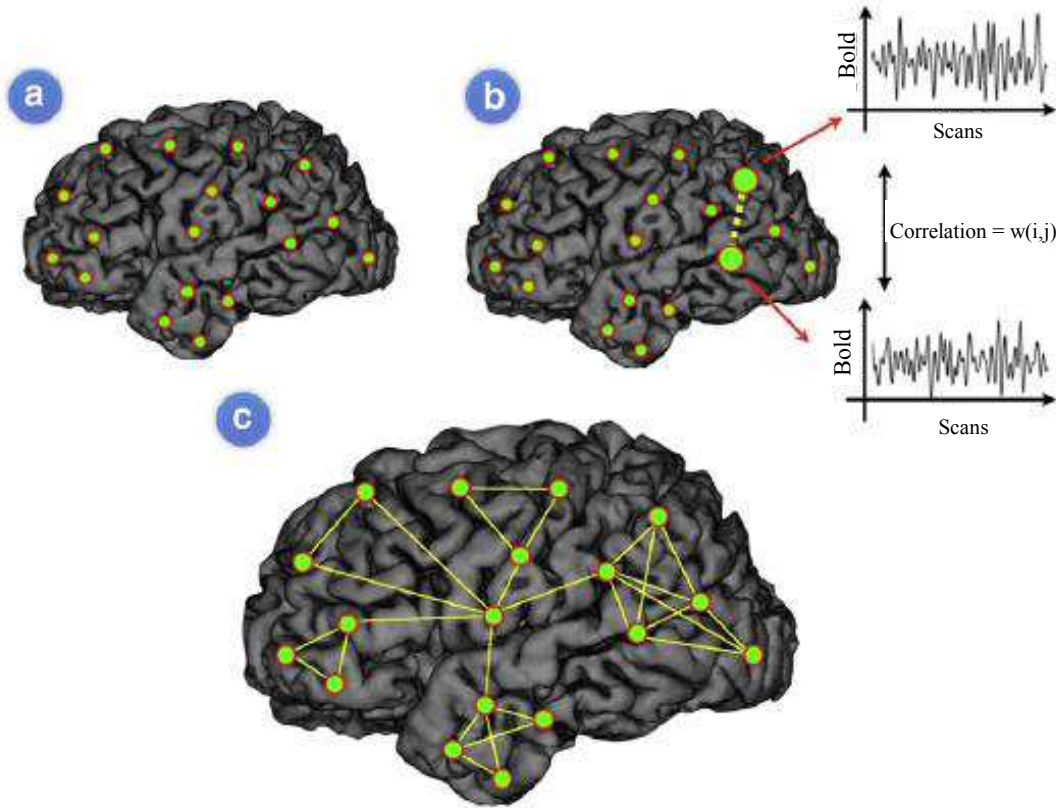

Fig. 6: The model of functional brain network consists of nodes and edges between regions that are functionally affiliated and can be bidding as a circuitous graph. In the console (a), the accumulating of nodes is represented and these can be brain regions. In the console (b), the actuality of functional interactions between the nodes in the network needs to be clear, because it represents the level of interactions between different nodes of the network. In the console (c) the actuality of interactions amid two nodes can be identified as for whether their similar of functional interactions exceeds an assertive predefined threshold. This after-effect in modelling the brain as a functional network with linked between different areas that are functionally connected. Image courtesy of (Guye *et al*., 2010)

Achard and Bullmore (2007) showed that in older adults, the interregional connectivity of functional brain networks derived from resting fMRI had reduced efficiency than in young adults. Wang *et al*. (2017) studied of Functional Brain Network (FBN) and have been introduced depression disorder classification including Pearson correlation, extracting features from constructed FBN where functional MRI shown a successful impact. To address these challenging issues they have developed a method using a sparse low-rank model to automatically remove weak relationship of FBN.

Several recent studies have shown that in the context of behaviour, development and disease states functional connectivity has proven a powerful method for analysing complex brain networks measuring by resting-state fMRI. Warren *et al*. (2017) applied functional brain connectivity to structural brain connectivity to eliminate functional connectivity with other brain regions measuring derived from the fMRI BOLD signal. Goelman *et al*. (2017) described an analysis method by using frequencies and phase of resting-state functional MRI data that have shown the correlation between coupled time-series functions. Besides they illustrated that this analysis can be applied to any coupled functions in numerous areas containing electrophysiology, EEG or MEG in neuroscience research. Xu *et al*. (2016) discussed Borderline Personality Disorder (BPD) neuroimaging research that has to appear structural and functional deviations in brain networks. To accept the topological backdrop of academician networks, they active blueprint approach by investigating anatomic alluring Resonance Imaging (fMRI) data. Although the additional a lot of accepted neurodegenerative ataxia is Parkinson's ache (PD) primarily affecting the aging populations, its neurophysiological mechanisms still unclear.

Gao and Wu (2016) proposed that the development of neuroimaging techniques can be allowed to detect Parkinson's Disease (PD) in patients. Especially they described the functional MRI neuroimaging technique for detecting of the functional connectivity of brain networks in patients with Parkinson's Disease (PD). Traumatic Academician Injury (TBI), after-effects from

accident to academician tissue acquired by an external force. The neurobiological mechanisms of Traumatic Brain Injury (TBI) underlying specific disorders still are not fully clear. Several of the neuroimaging techniques have been applied to detect these disorders. To find a clear image, Diffusion MRI, Diffusion tensor imaging and Functional MRI provided new insights of the animal academician in both health and disease focussing on structural and functional connectivity patterns. Xiao *et al*. (2015) identified several studies that many of functional connectivity abnormalities in brain networks, but researchers are still working to identify abnormalities. Colombo *et al*. (2015) discovered functional connectivity abnormalities in migraine by resting-state fMRI which is a new field of neuroscience research. Because, to explore the functional connectivity of brain areas, resting-state fMRI is one of best methods.

Functional brain connectivity is a relatively new research topic in the field of complex brain networks. Several studies found that the function of brains can be changed by aging and Alzheimer's Disease (AD) and shown recent innovations neuroimaging techniques have detected abnormalities in functional networks. To detect diseases and analyse functional connectivity Dennis and Thompson (2014) applied three primary methods including seed-based, ICA and graph theory. In the field of neuroscience, especially in brain complex network graph theory is playing a great role. Chang *et al*. (2016) identified that Carotid stenosis changes the functional connectivity and decline the cognitive functions. To evaluate the relationships between hemodynamic injury and cognitive decline, they applied graph theory based on resting state fMRI.

Diffusion Magnetic Resonance Imaging (DMRI)

Diffusion MRI uses the diffusion of water molecules to generate contrast in MR images. Although over the last 30 years various technologies have been developed to detect physiological illness, Diffusion MRI has become an accustomed address with an abundant appulse on bloom affliction and neurosciences (Gallichan, 2017). From the mid-1980s, Diffusion MRI is as well-known as Diffusion-Weighted Magnetic Resonance Imaging (DWI or DW-MRI) (Delouche *et al*., 2016; Le Bihan *et al*., 2006).

Goals and Current Applications of Diffusion MRI

Diffusion MRI is a quickly establishing the experimental tool for the evaluation of brain diagnosis. Its goal is to examine the white matter in the brain and to determine diffusion coefficient in-vivo which has great potential for further understanding of normal and abnormal physiology (Bammer, 2003; Mori and Barker, 1999). Recently, Diffusion MRI is an imperative technique that already widely used for the study of stoke and other neuroimaging disorders. This technique is very important to apprehend the baptize circulation in academician which allows us to abstraction academician fibre structures (Mori and Barker, 1999; Booth and Hamarneh, 2010; Mueller *et al*., 2015)**.** The applications of Diffusion MRI in brain disorder and clinical neuroscience which are summarized in Table 3.

Advantages and Limitations of Diffusion MRI

Diffusion alluring Resonance Imaging (DMRI) is one of a lot of rapidly developing diagnosis tools in the field of MRI which image adverse is based on the circulation of baptizing molecules in tissue. Besides, Circulation MRI can appraise white amount in the brain. As DMRI has been activated to studies of brain disorders so it can have some advantages and limitations (Table 4) (Jones, 2010; Chenevert *et al*., 2000).

Brain Network Connectivity with Diffusion MRI

Kahn *et al*. (2017) described that to allow for actual information transmission, human expertise learning has to need to fine-scale coordination of distributed networks of brain areas associated with white matter tracts. For testing this hypothesis they collected structural imaging data and to identify streamlines linking cortical and subcortical brain areas, they used deterministic tractography which has made structural networks for each participant. Finally, they decided that enlarged white matter connectivity linking early visual areas was related with a faster learning level.

Hagmann *et al*. (2007) proposed that mapping of the structural brain network connectivity with circulation MRI is an action fabricated of four accomplish which apparent in beneath (Fig. 7). First, they acclimated Circulation Spectrum MRI (DSI) which is performed on a sample abstracts set. This accretion provided a 3D circulation action at anniversary abode in the brain. This abstracts set is alleged a circulation map. It is formed by the bounded tissue features, in accurate by the acclimatization of axonal bundles absolute in the brain. Second, based on this map they generated an amount of 3D curves (called fibres) that followed the aisle laid by the white amount axonal bundles. Third, alone from the beforehand step, they acclimated a heuristic that far the academician white matter gray amount interface into baby zones of according apparent (called Regions Of Interest-ROIs) accoutrement the accomplished case and abysmal bookish nuclei boundaries. In the fourth step, they abutting the achievement of accomplishing two and three: The ROIs become nodes and the fibres are adapted into edges in the consistent graph. Finally, they appropriate that this blueprint estimates the body of white amount access amid any two regions of gray matter.

Table 3: Applications of diffusional MRI based on graph

Technique	Applications of DMRI	Graph used	References
Diffusion MRI	Diffusion Tensor Imaging (DTI) in brain development.	√	Hüppi and Dubois (2006; Neil *et al*., 2002; Vakhtin *et al*., 2013)
	Diffusion in acute stroke.	√	van Gelderen *et al*. (1994; van Everdingen *et al*., 1998; Warach *et al*., 1995; Kamalian *et al*., 2011)
	Diffusion in chronic stroke and small vessel disease.	√	Wardlaw *et al*. (2013; Schaefer *et al*., 2000; Hachinski *et al*., 2006)
	Diffusion imaging in brain tumors.	√	Hachinski *et al*. (2006; Holodny and Ollenschlager, 2002; Maier *et al*., 2010; Provenzale *et al*., 2006)
	Diffusion tensor MRI in multiple sclerosis.	√	Rovaris and Filippi (2007; Li *et al*., 2013)
	Diffusion MRI in Epilepsy.	√	Bullmore and Sporns (2009; Govindan and Chugani, 2010; Engel Jr. *et al*., 2013; Arfanakis *et al*., 2002)
	DTI and Tractography in neurosurgical planning.		Clark and Byrnes (2008)
	Diffusion MRI in psychiatric disorders.	√	White *et al*. (2008; Johansen-Berg and Behrens, 2013)
	DTI in crumbling (Aging) and age related neurodegenerative disorders.	√	Sullivan and Pfefferbaum (2011; Brown *et al*., 2011; Sun *et al*., 2012)

Table 4: Advantages and Limitations of diffusion MRI

Technique	Advantages	Limitations
Diffusion MRI	Able to aces up tears in the white amount that added imaging browse including (MRI and CT) scans do not aces up.	Images distortion
	Containing added abyss advice from MRI scans and allows us to access images of white matter.	The low spatial resolution which agencies a of pixels so the images may appear out cryptic at times.
	DMRI is an effective technique for comprehensive, noninvasive, functional anatomy mapping of the human complex brain networks.	Extremely sensitive to motion and can cause mis-registration if the patient moves.
	Can help solve the mystery of concussions through its deeper and in depth scan of the brain.	Requires extensive computing power, man-hours and expertise.
	Provides outstanding details of the structural brain connectivity.	
	Provides a 3D visualization of neuronal pathways.	
	Can help doctors predict recovery times for concussion patients.	

Structural brain connectivity mapping techniques are playing a very significant role to identify abnormal connectivity in psychiatric and neurologic disease, particularly Small animal connectivity techniques are very important to find anomalies in the disease model . Calabrese *et al*. (2015) showed small animal diffusion tractography that can be significantly improved through the groupings of ex vivo MRI with exogenous adverse agents, containing with innovative diffusion accretion and face-lifting address and probabilistic fibre tracking.

Schultz *et al*. (2016) illustrated, although many of the researchers has been studied an affluence of research into brain connectivity, we are far from a complete understanding to change over the development of human brain. They studied and described Computational Diffusion MRI to insights into human brain development. They have presented some recent findings on academician connectivity in autism, 22q11.2 abatement syndrome, Fragile X, Turner syndrome, Williams's syndrome and ADHD. Mostly they have been focused to find the features of brain networks development and biological methods engaged for detecting brain impairment. The study of brain mapping connectivity is still in its infancy. For imaging and analyzing brain connections. Li *et al*.

(2016) proposed Diffusion Magnetic Resonance Imaging which noninvasively maps academician connectivity at an arresting calibration by barometer baptize molecules. Besides in recent years, there has been studied a lot on network modeling of brain connectivity seriously. Analyzing human brain networks, many of the researchers applied graph theory by using a various number of imaging techniques including functional MRI, Structural MRI, diffusion MRI and EEG/MEG separately.

He and Evans (2010) studied all of these techniques and shown many crucial properties of complex brain networks which can be applied to detect the abnormalities of brain regions especially focusing on Alzheimer's and Schizophrenia disease. To map the structural access of the human brain, Thomas *et al*. (2014) proposed Tractography based on diffusion-weighted MRI (DWI) which is one of the most prominent widely used technique. Besides, to investigate they applied this method and showed the highest sensitivity. Overall, for developing brain network analysis with fMRI and DMRI , different authors applied different software packages. The number of software packages for brain network analysis with fMRI and DMRI are listed in Table 5.

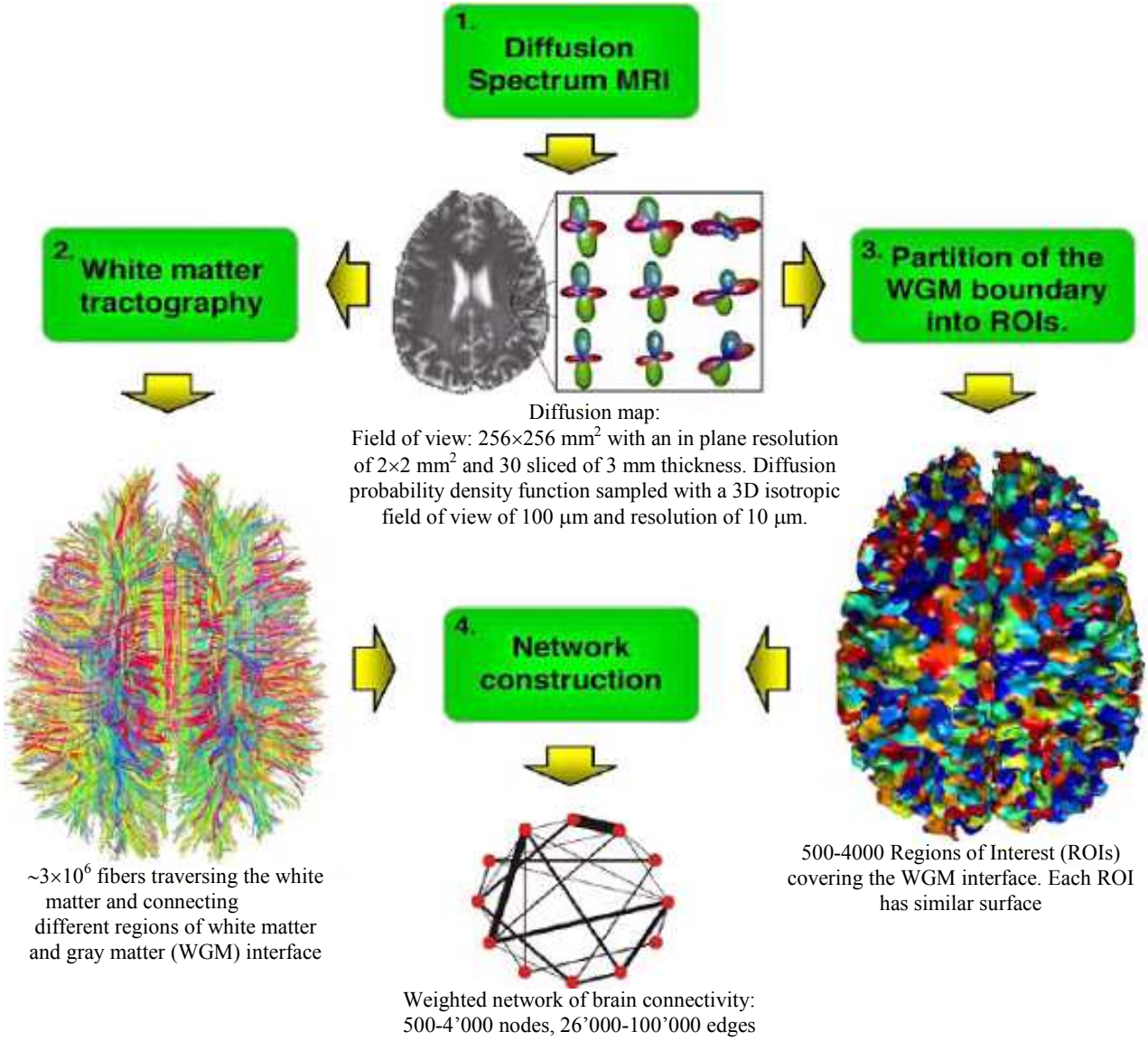

Fig. 7: Structural Brain network connectivity with diffusion MRI. Image courtesy of (Sporns, 2011)

Table 5: Review of different Software packages for brain network analysis with fMRI and DMRI

Package name	Descriptions	Category	Website	Refs.
SPM	SPM has been designed for the analysis of brain imaging data sequences. The current release of SPM is designed for the analysis of fMRI, PET, SPECT, EEG and MEG.	Segmentation, time domain analysis, spatial transformation, statistical operation, haemodynamic response.	www.nitrc.org/projects/spm or www.fil.ion.ucl.ac.uk/spm/	Power *et al*. (2011; Liao *et al*., 2010)
AFNI	AFNI is a technique for mapping human brain activity.	Analysing, processing and displaying functional MRI data	www.afni.nimh.nih.gov/afn/	Cole *et al*. (2014; Zhang *et al*., 2003)
FSL	FSL is a comprehensive library of analysis tools for FMRI, MRI and DTI brain imaging data.	Diffusion application, functional application, structural application	www.fsl.fmrib.ox.ac.uk/fsl/	Iturria-Medina *et al*. (2008;Alexander-Bloch *et al*., 2012)
GIFT	GIFT can implement multiple algorithms for independent component analysis and blind source separation of group fMRI data.	Independent module analysis	www.mialab.mrn.org/software /gift/index.htm	Vakhtin *et al*. (2013; Stevens *et al*., 2009)
REST	REST is a convenient toolkit to calculate Functional Connectivity, Regional Homogeneity, Amplitude of Low-Frequency Fluctuation Fractional ALFF, Granger causality, degree centrality, voxel mirrored homo-topic connectivity and perform statistical analysis.	Data Processing of Resting-State fMRI	www.restfmri.net/forum/index.php	van Den Heuvel and Pol (2010)
CONN	CONN is a Matlab-based cross -platform software for the computation, display and analysis of functional connectivity in fMRI (fcMRI).	Connectivity analysis, modelling, multivariate, principal component analysis, regression, correlation, visualization	www.conn-toolbox.org	van Den Heuvel and Pol (2010)
Brain voyager	Brain Voyager is a tool for the advanced analysis and visualization of structural and functional MRI data and for combined EEG/MEG distributed source imaging.	Visualization	www.brainvoyager.com	Watson *et al*. (2009)
FLASCO	FIASCO is a collection of software designed to analyse fMRI data using a series of processing steps.	Statistical analysis	www.stat.cmu.edu/~fiasco/	Lazar *et al*. (2001)
Brain Net Viewer	BrainNet Viewer is a brain network visualization tool, which can help researchers to visualize structural and functional connectivity patterns from different levels in a quick, easy and flexible way.	Visualization	www.nitrc.org/projectsbnv/	Xia *et al*. (2013)
NODDI	NODDI is a new diffusion MRI technique for imaging brain tissue microstructure.	Atlas application, diffusion application	www.nitrc.org/projects/noddi _toolbox	Inglese *et al*. (2005; Lemkaddem *et al*., 2014)
MRIcron	MRIcron is a cross- platform NIfTI format image viewer. It can load multiple layers of images, generate volume renderings and draw volumes of interest.	Volume rendering, centre of mass regression, clipping, two dimensional display	www.nitrc.org/projects/mricron	Molenberghs *et al*. (2012; Figee *et al*., 2013)
REX	REX is a stand-alone toolkit for the rapid and flexible exploration of ROI response waveforms and other signals from across large fMRI datasets.	Time domain analysis, visualization, workflow	www.nitrc.org/projects/rex/	Hosseini *et al*. (2012)

Quality Evaluation of Complex Brain Networks

In this study, we have examined structural and functional connectivity in the human brain using features from graph theory. Because Structural and Functional Connectivity (SC and FC) have received great attraction over the last decade, as they offer unique insight into the coordination of brain functioning. To demonstrate the evaluations of complex brain network, we presents structural and functional graph theory analyses in two separate studies.

Objectives Evaluations

Mijalkov *et al*. (2017) measured the differences in global and nodal network topology in healthy controls, patients with amnestic MCI and patients with Alzheimer's disease. They carried out a graph theory

analysis on the resting-state fMRI data of healthy controls and PD patients with MCI from the Parkinson's Progression Markers Initiative. They evaluated resting-state functional images that were acquired using an echo planar imaging sequence (repetition time = 2400 ms; echo time = 25 ms; flip angle = 80°; matrix = 68×68; voxel size = 3.25×3.25×3.25 mm^3). Bassett and Sporns (2007), illustrated that graph theory has proven to be an extremely productive framework in which to understand the structure and function of large-scale brain network and their implications for human cognition (Bassett and Sporns, 2007); alternative approaches that build on this framework-such as network control theory-necessarily require sceptical evaluation to clearly delineate value added. Now we just focus different equations on this table to measure connectivity of complex brain networks (Table 6).

Graph theory have provided a toolbox of diagnostics to describe the organization of graphs or networks. Gu *et al*. (2015) evaluated that using graph theory, they can identify regions of high (low) degree, while using network control theory. Moreover, they can understand the functional role of these regions as being critical for guiding the movement of the brain into many easy-to-reach (difficult-to-reach) states.

Table 6: Complex brain network measure: Equations and definitions

Measures	Ref.	Equations	Definitions
Degree of node	Liu *et al*. (2008)	$k_i = \sum_{i \in G} a(i,j)$	G denotes the complete set of network and $a(i,j)$ represents the element of adjacency matrix. when $a(i,j) = 1$, there is a link between nodes i and j. otherwise, $a(i,j) = 0$.
Degree distribution	Caldarelli (2007)	$P(k) = \frac{n_k}{N}$	n_k represents the whole number of nodes with degree k and N denotes the whole number of nodes.
Transivity	Honey *et al*. (2009)	$T(G) = \frac{\sum_{i \in G} 2a(i,j)a(i,h)a(j,h)}{\sum_{i \in G} k_i (k_i - 1)}$	This metrics is represent only to a full network.
Cluster coefficient	Honey *et al*. (2009)	$C(G) = \frac{1}{N}\sum_{i \in V} C(i) = \frac{1}{N}\sum_{(i,j,h) \in G} \frac{2a(i,j)a(i,h)a(j,h)}{K_i (k_i - 1)}$	$C(i)$ denotes the cluster quantity of nodes i. $C(i) = 0$ when $k_i < 3$
Local efficiency	Iannetti and Wise (2007)	$E_{lobal}(i) = \frac{1}{N_{G_i}(N_{G_i} - 1)} \sum_{j,k \in G_i} \frac{1}{d(j,k)}$	G_i represent the set of neighbors of i.
Global efficiency	Iannetti and Wise (2007)	$E_{global}(G) = \frac{1}{N(N-1)} \sum_{i \neq j \in G} \frac{1}{d(i,j)}$	E_{global} evaluates in the full network. Where N denotes the total number of nodes.
Cost or probability of connection	Iannetti and Wise (2007)	$P_{cost}(G) = \frac{1}{N(N-1)} \sum_{i \in G} k_i$	This metrics is evaluated in the full network. Where G represents the network.
Shortest path length	Latora and Marchiori (2001)	$L = \frac{1}{N(N-1)} \sum_{i,j \in G, j \neq j} d(i,j)$	$d(i,j)$ represent the shortest path length between i and j.
Small-worldness	Fallani *et al*. (2014; Humphries and Gurney, 2008)	$\sigma = \frac{C/C_{rand}}{L/L_{rand}}$	C_{rand} and L_{rand} are cluster coefficient and shortest path length evaluated to randomly network from original network. The network is small-world if $\sigma \gg 1$

The development of graph-theory based complex network analysis provides an important mathematical framework to characterize the global and regional topology in brain connectivity networks (Ribeiro de Paula *et al*., 2017). Using graph-theory based complex network analysis and network based statistic approach, Xu *et al*. (2016) examined the topology and connectivity in resting-state functional brain networks of adults with BPD versus healthy controls. As hypothesized, patients with BPD provided evidence for abnormalities both in topological structure and in connectivity in the intrinsic functional brain networks.

These abnormalities appear to be related to specific symptoms of BPD and can be used as features to distinguish patients with BPD from healthy controls using a machine learning classifier. These findings add to prior neuroimaging studies that have reported abnormal connections between specific brain regions in BPD and may provide new, clinically-relevant knowledge about the neurophysiology of the disease. Their graph analysis identified significant changes of small-world properties and network efficiency in patients with BPD versus healthy controls at the 0.03–0.06 Hz frequency band, including increased size of Largest Connected network Component (LCC), clusteringcoefficient, small-worldness and local efficiency (Table 7).

Recently, Gong *et al*. (2008; Hagmann *et al*., 2008), maps of about 80 cortical and subcortical gray matter regions were constructed from DWI data and analysed with fMRI data using graph theory. They also found the same result. But Eguiluz *et al*. (2005) found controversial result although no statistical test was used. To our knowledge, only one study investigated the graph properties in both structural and functional connectivity. More recently, Messé *et al*. (2012) have investigated with the total of 132 nodes, distributed over the whole cortical (n = 92) and subcortical (n = 24) gray matter and the cerebellum (n = 16) were defined by all functional networks identified (Fig. 8).

In order to investigate similarities between structural and functional aspects of the full-brain network across subjects, the structural and functional connectivity indices were uniformly thresholded to obtain binary graphs of varying density or cost. They performed an analysis of variance and found the approximately same results (Fig. 9) of the node degrees for Structural and functional connectivity of brain network.

Table 7: Number of nodes and edges and the corrected p-value of the connected subnetwork in 0.03- 0.06 Hz that show lower connectivity in BPD patients, under different primary threshold in NBS test

Primary threshold	No. of nodes	No. of links	Corrected p-value
t = 1.75, p ≈ 0.05	No significant result		
t = 2.05, p ≈ 0.025	68	205	0.048
= 2.5, p ≈ 0.01	49	87	0.0408
t = 2.75, p ≈ 0.005	40	57	0.0298
t = 3.05, p ≈ 0.0025	26	26	0.0304
t = 3.4, p ≈ 0.001	No significant result		

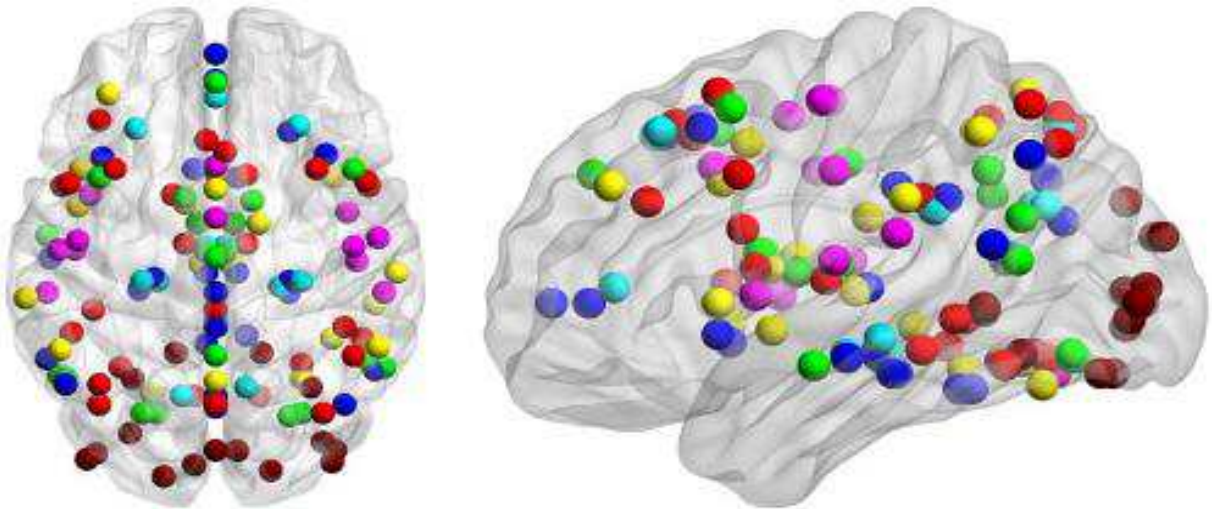

Fig. 8: Regions of interest location in axial (left) and sagittal (right) views superimposed on a brain template surface. Image courtesy of Messé *et al*. (2012)

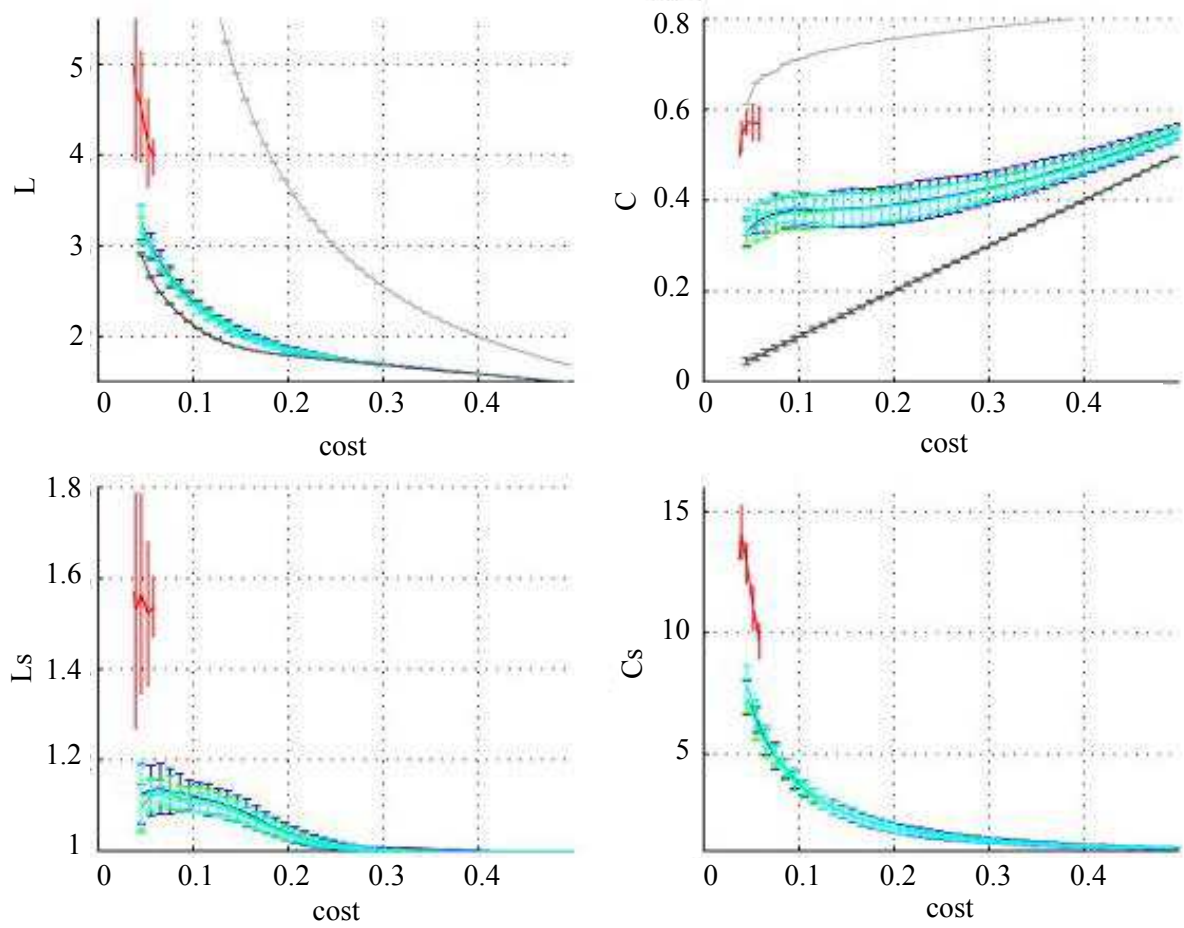

Fig. 9: Mean and standard deviation across subjects of the characteristic path length L (top left), scaled characteristic path length L_s (bottom left), clustering coefficient C (top right) and scaled clustering coefficient C_s (bottom right) as a function of the cost value for structural connectivity (red), functional connectivity at rest (dark blue), functional connectivity during the motor task (green) and functional connectivity for the visual stimulation (light blue) and the corresponding values for typical networks: Random (light grey) and lattice (dark grey), with the same size and density as those of the networks analysed. Image courtesy of Messé *et al*. (2012)

Subjectives Evaluations

Both structure and function can be indirectly imaged *in vivo* using magnetic resonance imaging (MRI). Structural connectivity using Diffusion-Weighted Imaging (DWI) (Mori and Zhang, 2006) and functional connectivity using functional Magnetic Resonance Imaging (fMRI) (Logothetis *et al*., 2001). DWI provides information about white matter organization, allowing the reconstruction of fibre bundles (Hagmann *et al*., 2007; Iturria-Medina *et al*., 2007) and fMRI uses Blood-Oxygenation Level-Dependent (BOLD) contrast to indirectly map neuronal activation (Raichle and Mintun, 2006). Various approaches have been used to investigate the nodes and edges, relaying either on structural or functional information. Strogatz (2001; Watts and Strogatz, 1998; Reijneveld *et al*., 2007) were applied graph theory to characterize quantitatively the structural and functional features of the complex brain network. Previous studies, in references, have shown that functional imaging (Achard *et al*., 2006; Salvador *et al*., 2005) and structural imaging (Gong *et al*., 2008; Hagmann *et al*., 2008) with as common results the small word properties of the analysed complex brain networks.

Future Research Directions

In the field of neuroscience, Graph-theory analysis of brain network is one of the complex task. Although many researchers already engaged with this research field still there are some challenging issues need to be identified. Complex brain network analysis b used on the graph could be both useful and feasible for more profound studies but still required for more systematic assessment. Besides, in complex brain networks, there are deficiencies of a gold standard for the meaning and descriptions of network nodes and edges or links.

Ensuring the suitable use of network analysis, researchers still have to need to take attention when choosing the right network demonstration of the brain connectivity. The most prominent area of expansion is, structural brain connectivity had modelled for structural associations among different neuronal elements derived from resting fMRI and functional brain connectivity had modelled for the functional associations among brain regions measured with diffusion MRI but nobody tried for the whole-brain network. So, the combination of both structural and functional connectivity can be modelled as networks with different neuroimaging modalities. Because the combination of different imaging modalities to determine the relationship of the structural and functional connectivity of the brain. We hope this multimodal imaging techniques of the future will provide integrative evidence to map the patterns of whole brain connectivity.

Conclusion

Graph based analysis of Complex brain network has emerged as an important technique to visualise functional and structural brain connectivity. We characterized two prominent procedures that measure local and global properties of complex brain networks. The associated brain connectivity prominent technique allows researchers to begin exploring network features of complex functional and structural imaging datasets. We also show some challenging issues that will be playing an increasingly important role in the evolvement of brain's network in near future.

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Author's Contributions

All authors equally contributed in this work.

Ethics

This review article is original and have never been published anywhere. The corresponding author confirms that all of the authors have read and approved the manuscript and no ethical issues involved.

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Abbreviations

MRI	Magnetic Resonance Imaging
PET	Positron Emission Tomography
FMRI	Functional Magnetic Resonance Imaging (fMRI)
DSI	Diffusion Spectrum Imaging
DMRI	Diffusion Magnetic Resonance Imaging
WM	White Matter
DTI	Diffusion Tensor Imaging
FA	Functional Anisotropy
DKI	Diffusion Kurtosis Imaging
MD	Mean diffusivity
FODF	Fiber Diffusion Orientation Distribution Function
TBI	Traumatic Brain Injury
CSD	Constrained Spherical Deconvolution
BOLD	Blood oxygenation level dependent
EEG	Electroencephalography
FC	Functional Connectivity
DMN	Default mode network
GCS	Glasgow Coma Scale
SWI	Susceptibility Weighted Imaging
DWI	Diffusion Weighted Imaging
FlAIR	Fluid Attenuated Inversion Recovery
NMR	Nuclear Magnetic Resonance
GMD	Gray Matter Density
ADC	Apparent Diffusion Coefficient
NAWM	Normal-Appearing White Matter
WMD	White Matter Density
NAGM	Normal-Appearing Gray Matter
NABT	Normal-Appearing Brain Tissue
SDP	Slow Diffusion Phase
FDP	Fast Diffusion Phase
SC	Structural Connectivity
MEG	Magnetoencephalography