Cognitive Neurodynamics (2021) 15:389–403
https://doi.org/10.1007/s11571-020-09630-5

REVIEW PAPER

Brain functional network modeling and analysis based on fMRI: a systematic review

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Received: 16 January 2020 / Revised: 5 August 2020 / Accepted: 20 August 2020 / Published online: 31 August 2020

Abstract

In recent years, the number of patients with neurodegenerative diseases (i.e., Alzheimer's disease, Parkinson's disease, mild cognitive impairment) and mental disorders (i.e., depression, anxiety and schizophrenia) have increased dramatically. Researchers have found that complex network analysis can reveal the topology of brain functional networks, such as small-world, scale-free, etc. In the study of brain diseases, it has been found that these topologies have undergoed abnormal changes in different degrees. Therefore, the research of brain functional networks can not only provide a new perspective for understanding the pathological mechanism of neurological and psychiatric diseases, but also provide assistance for the early diagnosis. Focusing on the study of human brain functional networks, this paper reviews the research results in recent years. First, this paper introduces the background of the study of brain functional networks under complex network theory and the important role of topological properties in the study of brain diseases. Second, the paper describes how to construct a brain functional network using neural image data. Third, the common methods of functional network analysis, including network structure analysis and disease classification, are introduced. Fourth, the role of brain functional networks in pathological study, analysis and diagnosis of brain functional diseases is studied. Finally, the paper summarizes the existing studies of brain functional networks and points out the problems and future research directions.

Keywords Brain functional networks · Complex network · Topological properties · Neurological and psychiatric diseases

Abbreviations

AAL	Anatomical automatic labeling
BOLD	Blood oxygenation level dependent
CAD	Computer aided diagnosis
EEG	Electroencephalogram
fMRI	Functional magnetic resonance imaging
ICA	Independent component analysis
MEG	Magnetoencephalography
PCA	Principal component analysis
ROI	Region of interest
SVD	Singular value decomposition
SVM	Support vector machine
SPM	statistical parametric mapping toolkit
TSCI	Traumatic complete spinal cord injury.
WHO	World Health Organization

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Introduction

As the aging of the population becomes more pronounced and the pressures in life gradually increase, the number of patients with neurodegenerative diseases (Alzheimer, Parkinson, mild cognitive impairment, etc.) and mental disorders (depression, anxiety and schizophrenia, etc.) have increased dramatically (Enzhong et al. 2015). Brain diseases are not only issues of individual countries, but also a global problem. According to the 'World Alzheimer Report

2016 (Prince et al. 2016)', Alzheimer's disease affects 46.8 million people worldwide by 2015 and will nearly double every 20 years. It will reach 74.7 million in 2030 and 131.5 million in 2050. According to statistics from the World Health Organization (WHO), there was 18.4% increase between 2005 and 2015. What is more serious is that this number has changed significantly in the past few years. According to the 'World Alzheimer Report 2018 (Patterson 2018)', around the world, there will be one new case of dementia every 3 s. In 2018, about 50 million people worldwide suffer from dementia, and by 2050, that number will rise to 152 million. Compared with the previous statistics in Report 2016, there are 20.5 million increased in 2018. It is estimated that the global social dementia-related costs will be 1 trillion dollars in 2018 and this figure will rise to 2 trillion dollars by 2030.

Neurodegenerative diseases cause abnormal death and atrophy of specific neurons in the central nervous system, leading to severe neurological deficits, cognitive or motor dysfunction. Mental disorders lead to persistent and obvious abnormalities in patients' cognition, emotion, volition, behavior and other activities. Neuropsychiatric diseases (including neurodegenerative diseases and mental disorders) not only affect the normal life and work of patients, but also bring heavy burden to family and society (Atluri et al. 2016; Beckmann 2010).

To better understand the brain function, researchers have conducted more than two decades of research in the field of exploring invasive and non-invasive brain imaging techniques (Bassett and Sporns 2017). Invasive methods are usually only applicable to the study of animal brains. Although invasive methods have high temporal and spatial resolution, they can only cover a limited spatial range (Yao et al. 2020). Therefore, these methods do not apply to the study of the human brain. The more mature non-invasive brain research techniques include electroencephalogram (EEG) (Khajehpour et al. 2019), magnetoencephalography (MEG) (Pfurtscheller and da Silva 1999), and functional magnetic resonance imaging (fMRI) (Mp and Hulshoff Pol 2010). These methods have different advantages and disadvantages in measuring brain activities. EEG and MEG provide excellent temporal resolution, but their low spatial resolution makes them unsuitable for studying the entire brain activity pattern effectively. fMRI is a method of studying the neural activity in certain parts of the cerebral cortex through physiological activity and obtaining a series of images through magnetic resonance. fMRI based on blood oxygenation level dependent (BOLD) signals has the advantages of non-invasive, repeatable and high temporal and spatial resolution and it is an ideal method to study the whole brain activity patterns and their relationships (Lord et al. 2013).

With the further research, it has been found that there are significant differences in the working model of the brain between healthy subjects and neuropsychiatric diseases. For example, it has been found that there were differences in the intensity of interaction between the brain regions of healthy subjects and subjects with mental disorders during rest and task execution (Wei et al. 2015; Mwansisya et al. 2017). This provides that the function of the brain stems from the interactions between brain regions. The highly complex structures and functions of the brains are the focus of research. Topologies between neurons or clusters of neurons form complex brain networks and the complex networks are closely related to how the entire brain works (Wang et al. 2010; Zhu et al. 2018). With the development of modern brain imaging technology and the development of complex network theory (i.e., graph theory), it provides the basis and analysis methods for human brain network research (Power et al. 2010; Wang and Wang 2014).

This paper focuses on the study of human brain functional networks and reviews the previous studies. The research background of the brain network is introduced in "Background of brain functional network research" section. The foundation of the construction of brain networks is introduced in "Brain functional network construction" section. The common analysis methods of brain networks are introduced in "Brain functional network analyses" section. The role of brain networks in the analyses of brain diseases is reviewed in "Application of brain functional networks for brain diseases research" section. The relevant references in this paper are summarized in "Summary of related brain functional network research" section. Finally, the problems in the study of brain networks are summarized in "Problems and possible research directions in brain functional network research" section.

Background of brain functional network research

In 2005, Salvador et al. (2005) for the first time constructed the brain functional network of healthy subjects in resting state through a priori anatomical automatic labeling (AAL). In this study, brain was divided into 90 regions and then the partial correlation coefficients of BOLD signals between each brain region were calculated to establish the relationship between brain regions. Finally, the significant connections were located by statistical test and a brain functional network was obtained. Based on this research, they found that the brain networks of these normal people showed "small world" properties, higher network efficiency, optimized connection structure and higher topology stability through further analysis of the networks. Among the properties, small world describes a state between regular network and random network, which shows the complex situation of combining default physiological state and task state of brain. When the attribute of small world changes, brain network will develop to the regular network or random network (Yao et al. 2015). Network efficiency describes the effectiveness of network information transmission. Brain network information transmission is efficient in normal state(Liang et al. 2018). Optimized connection structure and higher topology stability describes that the brain has the optimal and most stable working state when it works. When brain diseases occur, it will break this inherent state, which has become one of the contents of brain functional network research (Bassett and Sporns 2017; Lord et al. 2013; Wang et al. 2017).

At present, a large number of studies have been produced in the research of brain functional networks (Tian 2010; Liang et al. 2010). In the study of brain diseases, especially neuropsychiatric diseases [Alzheimer's disease (John et al. 2017), Schizophrenia (Mwansisya et al. 2017), depression (Wang et al. 2015), etc], the researchers found that the topology of the brain functional networks such as properties mentioned above changed abnormally (Wang et al. 2015; Bullmore and Sporns 2012; Cecchi et al. 2007; Pruttiakaravanich and Songsiri 2016). For example, the loss of small world attribute, the decline of network transmission efficiency, the change of transmission path and so on. These studies not only provide a new perspective for understanding the pathogenesis of neuropsychiatric diseases, but also provide assistance in the early support and treatment of the diseases.

With the development of neuroimaging technology, the scale of brain functional networks is also increasing. The size of the network has evolved from larger brain regions to voxel levels (Bullmore and Sporns 2009; Hipp et al. 2011). The number of nodes defined in the network has increased from several dozens to more than 20, 000. It has been found that, with the gradual increase of the scale of functional networks, the features of brain functional networks become more and more abundant. These features provide more support for the study of new connection patterns in human brain functional networks. At the same time, it has become an effective biomarker in the study of brain diseases (Khalili et al. 2017; Drysdale et al. 2017). Therefore, data mining has gradually emerged in the field of brain network analyses. The complex composition of brain function network data introduces many unique challenges faced by data mining research. In the research methods of traditional brain function networks, topological statistics (Yao et al. 2015) (small-world, scale-free, etc.) are used as important indicators to measure changes and working patterns of brain functional networks. The topological statistics, such as small world, are used as statistical properties of networks. With the increase of defined brain node numbers, the calculation of the topology statistics has also become increasingly difficult.

As a graph, brain network is not a whole. It contains a number of sub-graphs, as sub-networks. The subgraph has its own transmission structure while participating in the whole brain network function. The analysis sub-graph, as an important component of the network, can effectively reduce the complexity of the operation. In actual research, it is very meaningful to extract the sub-graph working mode in the brain functional networks (Kong and Yu 2014). For example, the discriminating sub-graph can not only analyze the connection patterns around nodes, but also capture the changes of connection patterns and properties in the region more easily than the topological statistics (Cao et al. 2015a). In the study of uncertain brain functional networks, discriminating graph can effectively describe the difference of different brain functional networks between Alzheimer's disease and normal people. It has become more and more valuable to use discriminating sub-graph as an important feature of brain functional networks for the analysis of diseases (Kong and Yu 2014; Cao et al. 2015a; Fei et al. 2014; Pu et al. 2015; Cao et al. 2015b). The brain functional network analyses based on fMRI data have already been a great significance in the diagnosis of neuropsychiatric diseases (Cao et al. 2015a, b).

Therefore, the effective use of complex network analyses in the study of brain functional networks has been demonstrated. However, most of the methods by current research are still dominated by static networks. Many physical and biological system studies have shown that the pattern of brain connections will develop over time. Different reactions will occur in different environments or under different external demands (Bassett and Sporns 2017). Therefore, more and more research turn their attention to the study of brain functional networks based on dynamic graphs. The dynamic functional networks are an important field in brain neuroscience research. It can not only study the general brain state, but also study the transition between different brain states (Pillai and Jirsa 2017; Ciric et al. 2017). The combination of voxel scale brain function networks and dynamic networks will form the voxel-scale brain function temporal networks. With the continuous development of research, a large number of fMRI data for various populations have been accumulated in various brain function studies. Using these data, voxel-scale timing diagrams of dynamic brain function networks for different groups of people can be constructed (Pillai and Jirsa 2017; Ciric et al. 2017; Allen et al. 2014; Kucyi et al. 2016; Griffa et al. 2017). If the management and query of these data can be implemented, research on computer-aided diagnosis, brain function network analysis, and the like can be conducted. Looking at these data, we will find that the data in the brain function networks has the characteristics of network complexity, temporal correlation, and computation complexity.

Network complexity In the study of brain functional networks, as the nerve center of human body, the brain has more complex information transmission structure than other systems. Collaborative cooperation and mutual transmission of information enable people to address complete complex tasks and cognitive functions. The structure of brain functional networks contains a variety of topological properties (small world, scale-free, etc.), which are complex and variable. There are different manifestations in different tasks, functions or brain diseases and the topological properties of different subgraphs are also different.

Temporal correlation When the brain is working, the nodes and regions in the brain functional network show a high degree of correlation with time under different tasks and behavior patterns. Under the same cognitive tasks or diseases, there are consistent patterns in the sequence of brain functional network changes among different groups of people. Therefore, it can be seen that temporal correlation is an important feature in the study of brain functional networks.

Computation complexity With the expanded research, the brain functional network research has gradually developed to the voxel level. In the study of the voxel-wise brain functional network, the definition of the graph vertex has exceeded 20, 000, and the resolution of the fMRI device gradually increases (Bressler and Menon 2010). Those values will continue increasing. The increase of the number of nodes will lead to a significant increase in computational difficulty and computational complexity. All of these require innovative methods based on the existing hardware.

Brain functional network construction

There are clear differences in the construction between brain functional networks and traditional networks (i.e., communication networks and social networks). In the traditional networks, the nodes (vertex) and edges are usually pre-defined. However, it is difficult to accurately define the location and properties of nodes in functional networks based on fMRI (Margulies et al. 2010). The brain functional networks mainly derive from the analysis of neuroimaging data (Margulies et al. 2010). At present, in the study of brain functional networks, the way of extracting network data is defined in two categories. The first category is called hypothesis-driven brain functional network construction methods (Margulies et al. 2010), which is based on anatomical or medical brain regions as region of interest (ROI), ROI is used as node of the networks. It is used to construct a brain network by studying the connectivity between ROIs or nodes. The other type is data-driven brain functional network construction methods (Li et al. 2009). Data-driven analysis of observational data and separation of observational data enable the construction of brain networks. Such methods are usually based on data decomposition and clustering.

In the hypothesis-driven method, the predefined nodes are usually divided into certain disjoint regions based on the cerebral cortex, and these brain regions (i.e., cerebral cortex) are the nodes of the brain networks. According to different scale levels, these nodes are represented by specific brain regions (Tian 2010; Liang et al. 2010). The structure of the brain networks depend on the definition of the nodes. Different division methods will lead to different network structures.

In the data-driven method, the voxels with similar space or voxels with similar functions are divided into the same regions mainly through decomposition or clustering (Pruttiakaravanich and Songsiri 2016; Bullmore and Sporns 2009; Kong and Yu 2014) or extracting voxels of the same or similar working mode. The decomposition or clustering approaches usually use principal component analysis (PCA) (Zhou et al. 2010), singular value decomposition (SVD) (Lukic et al. 1999), independent component analysis (ICA) (Du et al. 2017) and so on.

However, whether hypothesis driven or data driven, the construction of the network is mainly done through two steps, which are node definition and edge establishment.

Node definition

It is a challenging task to analyze the data of a brain network to define the nodes (Craddock et al. 2013). The reasons are as follows. First, a key issue is the contained noise and uncertainty in the data. In brain, similar regions usually have similar physiological characteristics and noise will weaken the discrimination among these similar regions. On the other hand, if these areas are merged to form a larger area, the utility of the constructed network will be reduced. The second challenge is the response of multi-domain connectivity of neurobiological properties. That is, nerve activity is the joint reaction of multiple physiological systems or physiological activities. These areas may include spatial neighbors, functional connections, structural connections, etc. Different areas correspond to different measures and analysis approaches, the definition of brain area directly affects the cognition of brain network. If the regions that map different physiological activities are defined as a single brain region, it may lead to noise interference. When constructing a brain network, it is necessary to integrate data in each area to reduce noise interference. Also it is needed to integrate the connection between each area to reduce the uncertainty of the connection. Ideally, each brain area should maintain an evenly partitioned connection pattern to maintain the usefulness on the networks.

For example, as shown in Fig. 1, 1, 2, 3, 4 represent four brain regions,. It can be seen from Fig. 1a that 1, 2 are in the same connection mode, 3, 4 are in the same connection mode. A merge of similar pattern areas can obtain a larger area, which are shown in Fig. 1b. Its connection mode is well preserved and the constructed network can accurately represent the connection mode of the area (Power et al. 2011).

For functional connectivity analysis of resting state fMRI, different criteria have been used to assess the quality of a set of regions as node definitions, which include function uniformity and spatial interpretability, (1) Function uniformity: The defined area shall have uniformity of function distributions. The regions of the voxels should have similar time domain characteristics or similar functional connectivity patterns. (2) Spatial interpretability: The contiguous segmented regions adjacent to each other have the interpretability of continuous space. Spatial proximity may also help to identify regions of uniform anatomy, thereby maintaining the interpretability of the connection results (Yoldemir et al. 2016; Ma et al. 2016).

At present, there are three most common methods to define graph nodes: 90 brain partition structures based on AAL brain templates (Salvador et al. 2005), 264 brain template partition structures given by Power264 (Power et al. 2011) and the voxel-based network structures (Power et al. 2010; Cecchi et al. 2007; Pruttiakaravanich and Songsiri 2016; Bullmore and Sporns 2009). Each of them has its own advantages in brain network analyses.

Of the three methods, AAL (Salvador et al. 2005) is the most widely used brain partition method. It is mainly based on the prior anatomical structure of the brain. This method has more corresponding anatomical structures and belongs to a hypothesis-based method in brain function analysis. And it effectively represents the connection of functional areas in brain structures. However, due to the fact that functions and structures are not one-to-one correspondence, this method has received certain limitations.

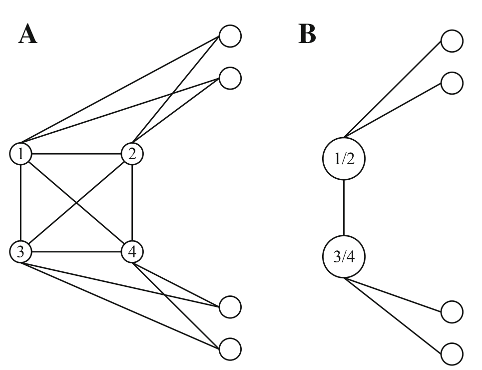

Fig. 1 Connection-based network partitioning **a** Division based on sub-regions, **b** division based on block

Power264 (Power et al. 2011) yielded 264 putative areas spanning the cerebral cortex, subcortical structures and the cerebellum, The definition of Power264 brain region is a brain region mode obtained by data analysis, giving certain stimulation to the brain and analyzing the changes and composition of regions activated by stimulation. This method is based on the data-driven method, which has more detailed brain regions compared with AAL.

The voxel-based method is also a data-driven method (Power et al. 2010; Cecchi et al. 2007; Pruttiakaravanich and Songsiri 2016; Bullmore and Sporns 2009; Wang et al. 2018b). It directly analyzes the collected voxel data, which is the latest and most comprehensive method covering brain data. The voxel-based method can not only reflect the transmission of information in brain functional regions, but also reflect the working mode in brain regions. However, due to the large number of voxels, this method results in a large network scale, which makes it difficult for the original calculation methods to be applied to such a large network analyses. However, with the development of graph theory technology and data calculation capability, there are more possibilities in the analysis using this method.

Edge establishment

The "network" is a collection of nodes and edges. If two node pair (i, j) and (m, n) corresponds to the same edge, the network is an undirected network, otherwise, it is a directed network. If each edge is given a corresponding weight, the networks are weighted networks, otherwise, it is unweighted networks, as shown in Fig. 2.

Connections with different specificities can be extracted from fMRI data. At present, the research of connection establishment mainly focuses on functional connections (i.e., undirected connections) (Du et al. 2017; Wang et al. 2018b; Ide et al. 2014) and effective connections (i.e., directed connections) (Huang et al. 2011). In functional connectivity research, sparse learning methods are used in many research efforts to achieve a sparse network from functional neuroimaging data. Sparse network can keep the network connection state to the greatest extent and reduce useless connections. By simplifying the structure of the network, it is convenient to reduce the complexity and computation of the network. The relevance of BOLD signal changes in the two regions is usually calculated using the similarity calculations such as Pearson correlation

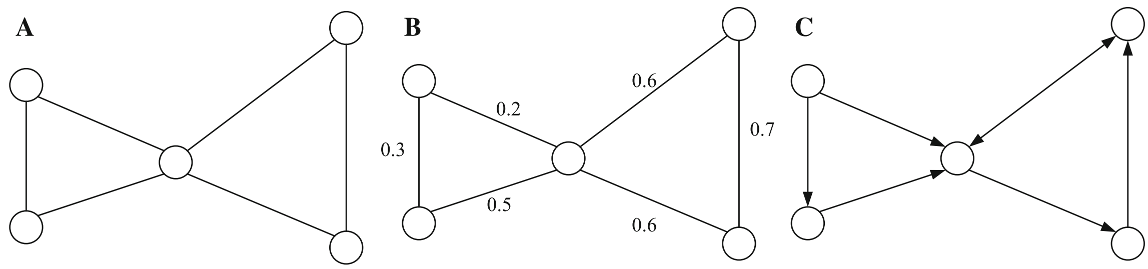

Fig. 2 Brain function network analysis process. **a** undirected and unweight network; **b** undirected and weighted network; **c** directed and unweight network

coefficients, Euclidean distances or mutual information (Lord et al. 2013; John et al. 2017; Margulies et al. 2010; Li et al. 2009; Zhou et al. 2010; Lukic et al. 1999; Du et al. 2017; Wang et al. 2018b; Ide et al. 2014).

In effective connections research, connections can be established from (i, j) and (m, n), If the two brain regions to be analyzed are named source area and target area, the source area to the target area and the connections are usually undirected and weighted. The weight of the edge can be positive or negative. The structural networks can be considered as physical paths for information transfer. It is assumed that there are connected areas and they need to work together to perform certain tasks. The effective connection corresponds to a causal relationship between activities in different brain regions. Some effective brain functional network research define the network as a Bayesian network, so as to transform the problem of brain network extraction into the learning problem of Bayesian network (Ide et al. 2014; Huang et al. 2011). Bayesian network also defines the brain networks sparsely. The calculation methods are summaried in the Table 1.

In Pearson correlation and Euclidean distances, x_i and y_i are the two vertices of the brain network. In mutual information, the joint distribution of the two random variables X and Y is $p(x, y)$, the edge distribution is $p(x)$, $p(y)$, mutual information $I(X; Y)$ is the relative entropy of the joint distribution $p(x, y)$ and the marginal distribution $p(x)$, $p(y)$.

Table 1 Edge establishment calculation methods

Methods	Formulas
Euclidean distances	$r = \sqrt{\sum_{i=1}^{n}(x_i - y_i)^2}$
Pearson correlation	$r = \frac{N\sum x_i y_i - \sum x_i \sum y_i}{\sqrt{N\sum x_i^2 - (\sum x_i)^2}\sqrt{N\sum y_i^2 - (\sum y_i)^2}}$
Mutual information	$I(X;Y) = \sum_{y\in Y}\sum_{x\in X} p(x,y)\log(\frac{p(x,y)}{p(x)p(y)})$
Bayesian network	$P(B_i\|A) = \frac{P(B_i)P(A\|B_i)}{\sum_{j=1}^{n} P(B_j)P(A\|B_j)}$

Euclidean distance is the distance between two nodes calculated in Euclidean space, which is used to describe the similarity of two nodes. Pearson correlation coefficient can be used to measure the linear relationship between the connection between two nodes, which can show the strength of the connection.

Mutual information can be regarded as the amount of information contained in a random variable about another random variable or the uncertainty of a random variable reduced by knowing another random variable. Mutual information can show the interaction between nodes.

Bayesian network is composed of representative variable nodes and directed edges connecting these nodes. Bayesian network is a directed graph without loops. If there is a non directed acyclic graph, and point A starts from B and returns to A through C, forming a ring. If we change the edge direction from C to A to a from A to C, it will become a directed acyclic graph. Nodes represent random variables and the directed edge between nodes represents the relationship between nodes (from the parent node to its child node, such as A-C, A is the parent node of B, B is the parent node of C, B is the child node of A, and C is the child node of B). A conditional probability is used to express the relationship strength, while prior probability is used to express the information if there is no parent node.

After calculating the connection information between all nodes in the brain function network, in order to describe the network more clearly and reduce the computational complexity, we need to keep the sparse connection according to a certain threshold. The network is transformed into a sparse network. The connection between 10% and 70% would be reserved according to the analysis requirements (Power et al. 2011; Yoldemir et al. 2016; Ma et al. 2016), such as disease diagnosis, connection change, activation area detection, etc.

Brain functional network analyses

After the establishment of brain functional networks based on fMRI, the next step is to analyze the brain networks. The analysis of the brain functional networks helps researchers to further understand the brain function. By comparing the changes in the network structure for different diseases, different ages and different groups of people, it is possible to provide new ideas and directions for the study of brain.

At present, the analyses of brain functional networks can be divided into two categories. One is statistical analysis of brain functional networks. Generally, it includes two parts: the study of network topologies and the study of network subgraph patterns (Kong and Yu 2014; Cao et al. 2015a; Fei et al. 2014; Pu et al. 2015; Cao et al. 2015b). The other is the disease classification, which is based on a computer-aided diagnosis (CAD) system by extracting the features of different networks and comparing them to realize the division of different populations. At present, this kind of methods are mainly machine learning method (Hojjati et al. 2017; Jie and Zhang 2016).

The main analysis process is shown in Fig. 3. First, the input image is preprocessed. The most commonly used method in the current study is to use the statistical parametric mapping (SPM) toolkit (Eickhoff et al. 2005) for preprocessing and extract the available BOLD signals in the brain network nodes. Based on this signal, a connection network is established, that is, a connection matrix. Then the extracted connection matrix is used for analysis to calculate the topological measures of the network and the features of the nodes. Finally, according to these features, statistical analyses of brain functions or CAD research are performed.

Statistical analyses of brain functional networks

Statistical analyses are to study the graph invariants, such as topology features, subgraph attributes, etc, based on graph theory. An important advantage of graph theory is that it provides a unified framework for comparing different types of graph data, which include medical and functional data comparisons (Mp and Hulshoff Pol 2010; Wang et al. 2010; Tian 2010). It also includes sample data comparisons. The graph invariants, such as centrality or modularity, can be computed for obtaining brain connection patterns. For example, Martijn and Sporns (2013) found that the center of the brain's functional networks can be used as a hub, hub is the nerve center in the functional network. Information transmission takes hub as the center and radiates to the periphery, and can be calculated according to the graph theory. Through the research, they found that the hub is the center of neural transmission, when the dysfunction occurs, there is a phenomenon that the hubs can miss. However, this type of methods are insensitive to changes in local connectivity (Liang et al. 2010; Martijn and Sporns 2013).

At present, some research found subgraphs can not only retain the original topological informations of samples, but also effectively retain the original discriminant informations. Therefore, the data mining methods based on regional molecular graphs or subgraphs are more

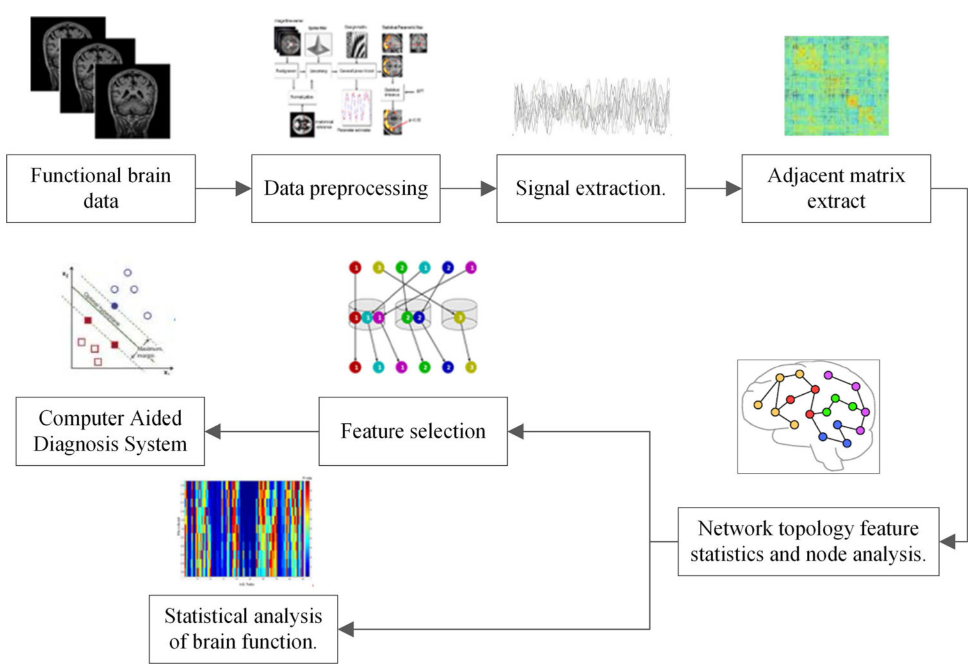

Fig. 3 Brain function network analysis process Including network data analysis and diagnosis of diseases

suitable to meet the needs of complex brain network data analysis (Kong and Yu 2014; Cao et al. 2015b). The functional subgraphs of brain functional networks can be used as new network features of brain diseases. In different brain diseases, subgraphs may show different structures. Using data mining methods to analyze brain network data is very challenging (Cao et al. 2015b). Moreover, some research also apply a neural energy coding theory to the analyses and statistics of brain network models (Zhu et al. 2018; Wang and Wang 2014; Wang et al. 2017).

CAD for brain diseases based on machine learning

The classification of brain networks provides methods for diagnosis of brain diseases. At present, most of the research on brain networks consider the function of a single brain region or the correlation between brain regions as the classification features. Jie and Zhang (2016) calculated the similarity map kernel between patients with mild cognitive impairment, Alzheimer's disease and healthy control group, and combined the graph kernels with kernel support vector machine (SVM) to implement the computer aided diagnosis of patients with functional cognitive impairment. Graph kernel is an effective approximate measure of graph structure similarity. There are different graph kernels for different graph structures (labeled graphs, weighted graphs, directed graphs, etc.). Therefore, a graph kernel can be used as a feature of a graph. As a common machine learning classification method, SVM can use the features to classify. Finally, the method achieves good diagnostic performance. Vergara et al. (2017) used a combination of leave-one-out verification and SVM to achieve detection of patients with traumatic brain injury. However, machine learning methods depend on the features extracted manually and can not effectively reflect the changes of brain topologies (Pereira et al. 2009; Zhao et al. 2015; Katwal et al. 2013; Kong and Yu 2010; Vergara et al. 2017).

Combination of machine learning and statistical analyses

Therefore, the ideal models are the combinations the above two kind of methods. Khazaee et al. (2017) used functional local topological features and global topological features on SVM to identify patients with mild cognitive impairment and Alzheimer's disease and obtained better accuracy. Guo et al. (2013) calculated three node metrics based on graph theory and then the topological metrics are compared in groups by nonparametric permutation tests. The topological statistics found have different effects on the classification results. It can be seen that the combination of the two methods is able to take advantage of the network connection mode changes between nodes and be used for diagnosis.

In addition, the correlation analysis between feature importance and statistical significance shows that there is a strong positive correlation between topological values. It can improve the accuracy of feature selection and diagnosis. In other words, the brain regions corresponding to the features that can improve the diagnostic accuracy are important in the network topology statistical analysis. The features of brain regions which are more concerned in the statistical topological change information may also be important in diagnosis.

Application of brain functional networks for brain diseases research

Brain function networks have shown important applications in brain disease analyses. The functional connection models provide an important description tool for the correlation and analysis of the main functions of human brain at work (Enzhong et al. 2015; Bassett and Sporns 2017; Wang et al. 2010; Tian 2010). Moreover, in the clinical research of brain function networks, it has been shown that the network structure of brains changed to different degrees after the occurrence of brain diseases (Power et al. 2010; Bullmore and Sporns 2012; Yao et al. 2015). Many studies have shown that most neurological and psychiatric disorders have such disconnection between nodes, such as the neurodegenerative diseases (Alzheimer's disease, Parkinson's disease, mild cognitive impairment, etc.) and the mental disorders (depression, anxiety, schizophrenia, etc.).

It is known that brain functional networks have the attribute of "small world" and optimized topologies such as modular distribution structures (Buckner et al. 2008; Sheline et al. 2010). Combined with the research in the above chapters, it can be concluded that brain function network provides reference information for the diagnosis of nervous system diseases, and has become an important content of disease brain function network research. All kinds of nervous system diseases will affect these topological properties of brain functional networks. When brain diseases occur, they will lead to changes in the topological structure of brain functional networks.(Bressler and Menon 2010; Zhou et al. 2010; Pereira et al. 2009). At present, there are a lot of research using the brain network analysis methods based on graph theory to discuss the above issues.

Neurodegenerative diseases

Some achievements have been made in the diagnoses and research of neurodegenerative diseases. Hojjati et al. (2017) combined graph theory with machine learning to classify patients and normal controls by recognizing mild cognitive impairment and the features of brain functional network changes in Alzheimer's disease. Lopes et al. (2017) believe that the diseased functional areas in the brain functional networks is one of the causes of Parkinson's syndrome and they proposed to study the changes of functional connectivity in the brain functional networks by studying the differences of cognitive features in patients with Parkinson's syndrome. The study found that with the deterioration of Parkinson, the connection between brain regions will gradually break. Tomše et al. (2017) demonstrated that the brain network analysis can identify Parkinson's disease and depression.

Mental disorders

Brain functional network has been widely used in mental disorders. Mental disorders generally study anxiety, depression, schizophrenia. Drysdale et al. (2017) analyzed the changes of brain functional network connectivity patterns in different depression patients. Depression can be divided into four subtypes. And they believe that targeted treatment of the four subtypes can effectively improve the treatment effect. Liao et al. (2012) studied anxiety disorder by establishing resting brain network and directed effective connection, and found that the core of functional network in patients with anxiety disorder was abnormal. Mwansisya et al. (2017) reviewed the research results of brain functional networks in schizophrenia in the past two decades and summarized the future development of schizophrenia research, It can be seen from the content of the review that the nature of brain functional network of schizophrenia has changed greatly compared with normal people.

Other brain diseases

In addition, there are related studies on other brain diseases (Wei et al. 2015; Vergara et al. 2017). Currently, although most of the research and database development are focused on these diseases, the brain functional network has important implications for the physiological changes and abnormalities of the brain. Therefore, the brain function network has also been used for the diagnosis and research of other brain diseases. Kaushal et al. (2016) studied resting state reorganization patterns in patients with traumatic complete spinal cord injury (TSCI) using graph theory. By describing the brain as a large-scale complex network, it was found that the connectivities of its subgraph structures in patients' functional networks were reduced compared with that in normal controls.

Currently, the research on brain function networks for brain diseases are still in the initial exploration stage. The imaging examination technology and network analysis method are not perfect and whether the changes of topological parameters of patients with brain disease can fully explain the changes of brain function are still problems to be studied in depth. The future studies need to improve the image scanning techniques to lead to better results in analyses of brain functional networks. The imaging research can more accurately reflect the brain function activities and find sensitive and specific brain functional network imaging signs for the early diagnosis of brain diseases. Moreover, it needs to further study the relationship between the changes of topological parameters and cognitive functions of patients with brain diseases in order to further explain the pathophysiological mechanism of brain diseases.

Summary of related brain functional network research

As shown in Table 2, the representative references for relevant part of this paper are summarized according to each research subjects. As can be seen from the table, the research on brain functional networks can be divided into three categories and eight subcategories. The research results reviewed in this paper cover both the basic methods of research and their applications.

Problems and possible research directions in brain functional network research

Although some important discoveries have been made in the research of complex brain networks, due to the fact that the applications of network analysis technologies in brain networks are not mature, there are still many problems to be solved.

Brain network size

At present, the network construction methods can not completely follow the working mechanism of the brain functions. However, with the development of complex network research and the progress of understanding of brain networks, the definition of the brain network nodes is constantly changing. A more detailed brain function network will be helpful to understand the brain function patterns. The more complex model can use more complex and large-scale brain networks to explore the brain functions and physiological problems that cannot be described in the current research stage (Wang et al. 2018b; Kourosh et al. 2018). It can be seen that the change of the brain network scales affect the understanding of the brain functional networks, which will be a very important and challenging

Table 2 Summary of related research

Contents	Tasks	Descriptions	Representative References
Network construction	Node definition	Brain region (i.e., ROI)	Atluri et al. (2016)
			Mp and Hulshoff Pol (2010)
			Wei et al. (2015)
			Tian (2010)
			Wang et al. (2015)
			Bullmore and Sporns (2012)
			Fei et al. (2014)
			Cao et al. (2015b)
			Huang et al. (2011)
		Voxel size	Wang et al. (2010)
			Power et al. (2010)
			Cecchi et al. (2007)
			Pruttiakaravanich and Songsiri (2016)
			Bullmore and Sporns (2009)
			Bressler and Menon (2010)
			Wang et al. (2018b)
			Kourosh et al. (2018)
			Li et al. (2019)
	Edge establishment	Static network	Lord et al. (2013)
			John et al. (2017)
			Margulies et al. (2010)
			Li et al. (2009)
			Zhou et al. (2010)
			Lukic et al. (1999)
			Du et al. (2017)
			Ide et al. (2014)
		Dynamic network	Pillai and Jirsa (2017)
			Ciric et al. (2017)
			Allen et al. (2014)
			Kucyi et al. (2016)
			Power et al. (2011)
			Yoldemir et al. (2016)
			Thompson and Fransson (2018)
			Xu et al. (2018)
			Figueroa et al. (2019)
Network analysis	Statistical analyses	Topological approach	Wang et al. (2010)
			Zhu et al. (2018)
			Wang and Wang (2014)
			Tian (2010)
			John et al. (2017)
			Bullmore and Sporns (2012)
			Bullmore and Sporns (2009)
			Wang et al. (2017)
			Yao et al. (2015)
			Craddock et al. (2013)
			Liao et al. (2011)
			Jiang et al. (2010)

Table 2 continued

Contents	Tasks	Descriptions	Representative References
Data mining	Khalili et al. (2017)		
	Drysdale et al. (2017)		
	Kong and Yu (2014)		
	Cao et al. (2015a)		
	Fei et al. (2014)		
	Pu et al. (2015)		
	Cao et al. (2015b)		
	Ma et al. (2016)		
	Martijn and Sporns (2013)		
Machine learning	CAD	Hojjati et al. (2017)	
		Jie and Zhang (2016)	
		Pereira et al. (2009)	
		Zhao et al. (2015)	
		Katwal et al. (2013)	
		Kong and Yu (2010)	
		Vergara et al. (2017)	
Combination methods	Statistical and classification	Khazaee et al. (2017)	
		Guo et al. (2013)	
Brain diseases	Neurodegenerative diseases	Alzheimer, Parkinson, MCI, etc.	John et al. (2017)
			Fei et al. (2014)
			Huang et al. (2011)
			Hojjati et al. (2017)
			Jie and Zhang (2016)
			Khazaee et al. (2017)
			Lopes et al. (2017)
			Tomše et al. (2017)
	Mental disorders	Depression, anxiety, schizophrenia, etc	Mwansisya et al. (2017)
			Salvador et al. (2005)
			Drysdale et al. (2017)
			Liao et al. (2012)
			Lefort-Besnard et al. (2018)
	Other diseases	Brain injury, etc.	Vergara et al. (2017)
			Kaushal et al. (2016)

direction. With the development of the research into the voxel level, the computing time and complexity will increase greatly, and the existing methods based on topological statistical features will be significantly restricted (Li et al. 2019).

Dynamic brain networks

As mentioned above, the brain is a temporal correlation structure, and information transmission is also changing. Therefore, the brain network should also be a dynamic structure. Therefore, how to build a dynamic brain function networks across different time scales and different time points to understand the changes of brain function topological structure with time, so as to further explore the mechanism of brain real-time function activity, is also one of the directions of future research in brain function networks (Thompson and Fransson 2018). At present, some researchers have applied data mining methods to the analysis of brain function network subgraph data mining, but these methods are mostly based on the static brain area level brain network, such as AAL, in which structure is relatively simple (Xu et al. 2018; Figueroa et al. 2019). When a brain network is analyzed as a dynamic structure, the difficulty of analysis increases. Therefore, with the change of the definition of brain nodes, how to analyze the more complex dynamic brain network has become an issue to be addressed.

Directed brain networks

Most of the brain network research focused on the undirected networks. The research of the undirected network omit the important 'direction' information in the brain function network (Liao et al. 2011). There is interaction in the time domain between the nodes of the brain function network. This type of directed continuous function integration constructs the overall function of the brain. Therefore, it is necessary to construct a directed functional network to describe the causal relationship between neural activities in order to understand the organization mode and functional activity law of the brain more deeply and carefully. There are larger complexities in directed network analyses. As brain function networks are complex wholes, its network characterizations are particularly difficult (Dickten et al. 2016). Therefore, with the deepening of research, the analysis of brain function directed networks will become an important part in the field of brain network analyses. How to use more effective technologies and methods to solve the problems of high complexity of data and heavy workload in directed network computing is also a key problem in brain network research (Adkinson et al. 2019).

Task state brain networks

Up to now, the research of the brain network mainly focuses on a resting brain function network. In the research of the resting brain function network, many important network properties of brain in spontaneous activities have been reflected (Jiang et al. 2010). However, the brain is a complex organic structure, which implies various advanced cognitive activities in the deep part of brain networks (Shi et al. 2018). Therefore, when research focuses change from resting state to task state, especially when the brain enters advanced cognitive activities such as thinking, it is not clear what changes will happen to the organizational structure of the functional networks. In different cognitive states, what kind of changes will appear in the organizational structure of brain functional networks. What kind of influence will these changes have. These problems have become the research directions (Ide and CsR 2018). When the structure changes, which form the network changes will take, whether its sub network will produce different combinations due to the change of cognitive state is also one of the development directions of the research. The introduction of task state will be more significant to the research of brain function diseases.

Structure and function combination networks

The research of the brain function networks focused on the functional changes of brain in different time and cognitive activities to realize brain functional networks on physiology and cognition. However, the generation of function is based on structure, that is, the function of brain is based on the relationship between neurons. Structure and function are inseparable. Structures provide the basis for functions. Functions are actually the representation of structures. Many studies have shown that the structure and function of human brain are closely related. The study of many neuropsychiatric diseases also shows that the abnormality of brain structures are often accompanied by corresponding functional changes. Because fMRI is functional imaging, when we link function and structure, we need to integrate different data together and there is a multimodal brain function network. With the development of brain information data acquisition technology, more and more structures and functions will be integrated (Bansal et al. 2018; Lefort-Besnard et al. 2018). Therefore, how to effectively use the structure and function data to realize the multimodal networks data integration analyses has become one of the research issues. However, the data obtained by different methods are totally different in structure and function. Its integration, registration and analysis will be the problems in the research. In the research, how to integrate the nodes under different definitions of structure and function, and how to build the brain network that can be used for diseases diagnosis and physiological analyses will be the challenge in the new research.

Brain function databases

Currently, many databases have been established on the basis of the studies (Eickhoff et al. 2016). These databases often use open models to provide researchers with important research foundations. However, these data do not follow a uniform standard and the results produced when different methods are used to establish different models for these data studies cannot be completely unified. Furthermore, the scale of the data is constantly increasing. Therefore, a unified standard needs to be established in the research to integrate these data in order to improve the efficiency of data storage and retrieval.

Brain network hubs

In the current research, the brain network hubs, as the central nodes of neural information transmission, are important components of brain function network information integration and transmission in the cooperative working mode of neuron clusters in complex cognitive tasks (Wang et al. 2018a). When these central nodes are used for analyses, the computational complexity can be effectively reduced and the accuracy of detection of mechanism changes such as brain diseases can be enhanced (Li et al. 2018). In the past, interventional methods such as stimulation were used to cause network changes, hubs were obtained through data analysis. However, with the in depth research on brain networks and the deepening of the understanding of the role of brain hubs in neural networks, more and more methods for analyzing network hubs through computational models have been adopted (Liang et al. 2018). With the development of big data and other disciplines and the constant change of the brain network analysis scale, it is expected that the study of brain network hubs is one of the hot topics in the study of brain network complex functions.

Conclusion

The development of fMRI technology enables us to understand the functional connections of human brain from the perspective of networks. The complex network theory reveals many important topological properties hidden in the structure and function networks of human brains. On one hand, the research of complex brain function networks will promote the construction of brain function networks. On the other hand, it will enhance our understanding of the brains processing modes information and the working mechanism of various cognitive functions. Researchers found that the complex network analyses can reveal the topological structure of brain function networks. In brain diseases, these topological structures will have different degrees of abnormal changes. Therefore, fMRI based brain function network research can not only provide a new perspective for understanding the pathological mechanism of neuropsychiatric diseases, but also provide methods for early diagnosis and treatment evaluation of diseases.

Acknowledgements Not applicable.

Author contributions ZYW and JCX collected the background information. ZYW, JCX and ZQW analyzed and compared the current research situation. ZW, JX had the major responsibility for preparing the paper, ZYW, ZQW and YDY wrote part of the paper. JCX, YZ and WQ. supervised the project. All authors read and approved the final manuscript.

Funding This work was supported by the National Natural Science Foundation of China (61472069, 61402089, U1401256, 61672146), and the Fundamental Research Funds for the Central Universities (N2019007, N180101028, N180408019), and the China Postdoctoral Science Foundation (2019T120216 and 2018M641705), and the CETC Joint Fund, and the Recruitment Program of Global Experts under Grant (01270021814101/022).

Data availability statement Not applicable.

Compliance with ethical standards

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

Competing interests The authors declare that they have no competing interests.

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