Proceedings of the 6th International Conference on Biological Engineering and Medical Science
DOI: 10.54254/2753-8818/2026.37490

Graph-Based Analysis of Functional Brain Connectivity from fMRI Data

Tengyue Pan

Stevenson School, Pebble Beach, USA
tpan28@stevensonschool.org

Abstract. Functional magnetic resonance imaging (fMRI) provides whole-brain measurements that can be converted into functional connectivity networks for quantitative analysis. Graph-based methods represent brain regions as nodes and statistical relationships among regional blood oxygen level-dependent signals as edges in this review. The above are the main steps in the analytical pipeline: preprocessing, brain parcellation, connectivity estimation, graph construction and calculation of nodal, global and community-level indicators. Representative studies are compared in terms of healthy brain organisation, neurological and psychiatric disorders, dynamic functional connectivity, and graph neural network applications. According to the above analysis, graph theory provides intuitive indicators of segregation, integration, efficiency, hub organisation and modularity, and graph learning methods can learn more complex patterns for prediction. However, the results are still sensitive to motion correction, atlas selection, connectivity measures, thresholding strategies, sample size, scanner differences and model interpretability. Future work will focus on building standardised and open pipelines, cross-site validation, multimodal data fusion, dynamic network models, and explainable graph neural networks. The above developments may enhance the reproducibility and clinical applicability of functional brain connectivity analysis.

Keywords: functional brain connectivity, functional magnetic resonance imaging, graph theory, brain networks, graph neural networks

1. Introduction

At present, neuroscience is investigating how all the parts of the brain in the human body are connected. Instead of working independently, the areas of the brain continuously communicate through large-scale neural networks that support perception, memory, language, emotion and executive functions [1, 2]. Consequently, researchers increasingly investigate the brain from a network perspective, in which cognition emerges from interactions among distributed brain regions rather than isolated anatomical structures [1].

Functional magnetic resonance imaging (fMRI) is now one of the most frequently used neuroimaging methods for research on these interactions, and it can detect changes in the blood oxygen-level-dependent (BOLD) signal in the brain non-invasively [3]. Biswal and his colleagues were the first to show spontaneous functional connectivity in resting-state fMRI, and since then,

© 2026 The Authors. This is an open access article distributed under the terms of the Creative Commons Attribution License 4.0 (https://creativecommons.org/licenses/by/4.0/).

DOI: 10.54254/2753-8818/2026.37490

functional connectivity analysis has been widely used to study brain organisation in healthy people and patients with neurological diseases [4]. Large public datasets, such as the Human Connectome Project, have also provided standardised neuroimaging data for large-scale studies to advance research [5].

Among all the methods for studying functional connectivity, graph theory has gradually become one of the more popular ones. A graph can be constructed with brain regions as nodes and functional connections as edges to calculate several attributes of the network, such as integration, segregation, efficiency and modularity [1, 2]. The above methods have extended understanding of the healthy organisation of the brain and shown characteristic network alterations in diseases such as Alzheimer's disease, schizophrenia and epilepsy [2, 6].

Recently, with the development of machine learning, graph neural networks (GNNs) have been introduced to learn directly from graph-structured neuroimaging data and have extended the scope of graph-based analysis [6]. At the same time, problems of data preprocessing, methodological differences and model interpretability have also reduced reproducibility and clinical applicability [6].

This paper reviews graph-based functional brain connectivity analysis using fMRI data. Section 2 presents the general ideas of fMRI, functional connectivity and brain networks. Section 3 presents general graph construction methods and graph-theoretic indicators. Section 4 shows some representative research results and recent developments in graph learning approaches, and Section 5 introduces existing deficiencies and prospects for future research. Based on the above analysis, graph theory and other modern computational methods have been applied to study the functional organisation of the human brain.

2. Basic concepts of fMRI, functional connectivity, and brain networks

2.1. Functional magnetic resonance imaging

Functional magnetic resonance imaging (fMRI) is a relatively widely used method of neuroimaging to study changes in brain function in living subjects, and it can be performed non-invasively at a relatively high spatial resolution [3]. Structural magnetic resonance imaging (MRI) shows the anatomy of the brain, and functional magnetic resonance imaging (fMRI) detects changes in the blood oxygen level-dependent (BOLD) signal that occur locally in the brain after neuronal activation [3]. When a group of neurons is activated, the resulting increase in metabolic demand of that area leads to the dilation of cerebral blood vessels. This haemodynamic response reduces the concentration of deoxyhaemoglobin, and thus changes in the magnetic resonance signal can be observed indirectly.

As the BOLD signal reflects a haemodynamic response rather than electrical activity, fMRI has relatively low temporal resolution compared with electrophysiological methods such as electroencephalography (EEG) and magnetoencephalography (MEG). However, because it can monitor whole-brain activity simultaneously, it is also suitable for studying large-scale functional connections among various areas in the brain [1, 2]. Therefore, fMRI has been widely used in recent years to study cognition, memory, attention, language, emotion and neurological disorders [1, 2].

Most contemporary fMRI experiments fall into two categories: task-based fMRI and resting-state fMRI. Task-based fMRI measures BOLD responses in the brain to particular cognitive or behavioural tasks to find brain areas involved in these functions. Resting-state fMRI records spontaneous low-frequency BOLD fluctuations in the brain when individuals are not engaged in explicit tasks [3]. Biswal and his colleagues first showed that these spontaneous fluctuations are

DOI: 10.54254/2753-8818/2026.37490

highly correlated in homologous motor cortices, providing the earliest evidence of intrinsic functional networks in the absence of external stimulation [4]. Since then, resting-state fMRI has become one of the most popular methods for studying large-scale brain organisation due to its simplicity, reproducibility and suitability for clinical populations unable to complete complex experimental tasks [1, 2].

2.2. Functional connectivity

Functional connectivity is the statistical dependence of neurophysiological signals recorded at different locations in the brain [7]. Functional connectivity in fMRI studies is generally expressed as the Pearson correlation coefficient between regional BOLD time series, and a connectivity matrix is obtained to quantify pairwise relationships across the brain [2]. Strong positive correlations indicate similar BOLD fluctuations; near-zero correlations indicate weak statistical dependence, and negative correlations indicate anti-correlated fluctuations after the preprocessing pipeline [2].

Functional connectivity refers to statistical dependence and should be distinguished from structural and effective connectivity. Structural connectivity describes the physical anatomical pathways of white matter fibres connecting different brain areas, which can be measured by diffusion MRI [1]. By contrast, effective connectivity aims to estimate directional or causal influences between brain areas through computational models, such as dynamic causal modelling or Granger causality analysis [7]. Functional connectivity shows that signals are statistically related, but it does not reveal the underlying anatomical path or cause [7].

Early functional connectivity studies generally assumed that these correlations remained unchanged during an fMRI scan, a method now known as static functional connectivity [8]. Recently, some studies have shown that functional connections change over time and thus have introduced the idea of dynamic functional connectivity [8]. Sliding-window analysis and other computational methods have been used by researchers to show that brain networks change their connectivity patterns under different conditions of rest and cognition, and that network organisation is dynamic [8]. Dynamic functional connectivity has thus become a research topic to explore attention, consciousness, ageing and neurological diseases [8].

2.3. Brain networks and graph theory

At the macroscopic scale examined by fMRI, the brain can be viewed as a network of interconnected areas that work together to process information [1]. The above represents the network of functional connections among brain regions [2]. Nodes are anatomically or functionally defined regions of the brain, and edges are functional connections based on correlations in regional BOLD signals [1, 2].

Graph theory offers a way to quantify both functional segregation and functional integration in the brain, and these two principles work together [2]. Functional segregation is specialised information processing within densely connected local subnetworks, and functional integration is efficient communication among distant brain areas [2]. Therefore, some graph metrics have been used to study large-scale brain networks.

Node degree in a binary graph is the number of connections a brain region has, and node strength in a weighted graph is the sum of the weights of its connections [2]. The clustering coefficient indicates the degree to which neighbouring nodes are clustered in a dense manner and thus locally process information [2]. The characteristic path length is the average of the shortest communication distances between all pairs of nodes and is a measure of overall communication efficiency [2]. Other

DOI: 10.54254/2753-8818/2026.37490

measures that provide supplementary information on the organisation of networks, information transmission and community structure are betweenness centrality, global efficiency, local efficiency and modularity [2].

Many structural and functional neuroimaging studies have reported small-world-like brain-network organisation, characterised by relatively high clustering and short path lengths compared with appropriate reference networks [2]. A small-world organisation is generally regarded as having good global communication capabilities and specialised local processing [1, 2]. This organisation has been repeatedly observed in many structural and functional neuroimaging studies and is considered a fundamental characteristic of healthy brain organisation [1, 2].

Graph theory can be used to build a network model of complex neuroimaging data for computational analysis in neuroscience. These graphs can be used to compare healthy and diseased groups, and advanced computational methods such as graph machine learning and graph neural networks have also been developed based on them [6].

3. Graph-based methods for functional brain connectivity analysis

Graph-based analysis is now one of the most popular computational methods for studying functional brain connectivity because it can convert complex neuroimaging data into mathematically analyzable networks [2, 9]. Graph theory can be used to study the brain as a large-scale network of connections, and both local and global organisation characteristics of this network can be quantified. Generally speaking, the steps are data collection and preprocessing, brain parcellation, connectivity estimation, graph construction, graph-theoretical analysis, and applications [2, 9]. Each step changes the structure of the final network; therefore, it must be done carefully.

3.1. fMRI data preprocessing

Before constructing a functional brain network, the raw fMRI data needs to be preprocessed to reduce noise and improve the consistency of different subjects [9]. Although the preprocessing pipelines of popular neuroimaging software packages are slightly different, most studies use several common steps.

The first is slice timing correction, which addresses the time difference resulting from sequential image slice acquisition [9]. Head motion correction is performed next, and all brain volumes are spatially aligned with a reference image. Motion correction is required to prevent systematic correlations in the data caused by small-scale head movements from affecting functional connectivity results [10]. Power and others have shown that subject motion causes many false-positive functional connections and may even create false group differences if not properly controlled [10]. Therefore, motion regression and frame censoring are now frequently used preprocessing steps in recent functional connectivity studies.

Generally speaking, the added preprocessing steps include spatial normalisation to a standard anatomical template, such as the Montreal Neurological Institute space; spatial smoothing to improve the signal-to-noise ratio; temporal filtering to keep physiologically relevant low-frequency BOLD fluctuations (typically 0.01-0.1 Hz); and removal of nuisance signals caused by white matter, cerebrospinal fluid or physiological noise [9, 11]. The above pre-processing steps will enhance the reliability and reproducibility of the network analysis.

DOI: 10.54254/2753-8818/2026.37490

3.2. Brain parcellation and network construction

After preprocessing, the continuous brain volume needs to be divided into discrete regions called nodes; this is known as brain parcellation [2, 12]. The selection of a parcellation atlas is a relatively high-level choice that directly affects the spatial resolution and topology of the network.

Many anatomical and functional atlases have been released. Anatomical atlases, such as the Automated Anatomical Labeling atlas, divide the brain according to anatomical landmarks and are still widely used due to their simplicity and interpretability [12]. Functional atlases—including those developed by Schaefer and Yeo—partition the cortex according to intrinsic functional organization derived from resting-state fMRI data, often providing improved correspondence with functional networks [12]. High-resolution atlases have increased the spatial resolution but have also raised the computational cost and noise sensitivity; therefore, a trade-off has been made between anatomical detail and statistical robustness.

After the nodes are defined, edges are added to represent functional connections between pairs of brain areas. A typical index of the degree of temporal correlation among regional BOLD signals is the Pearson correlation coefficient [2]. Pearson correlation is computationally simple and easy to interpret, so it has been used to study resting-state fMRI connectivity [2]. Correlation measures only linear statistical associations and cannot distinguish between direct and indirect effects.

Alternative connection methods have therefore been proposed. Partial correlation estimates conditional statistical associations between pairs of regions after accounting for other signals, and often yields sparser networks than Pearson correlation [2]. Mutual information is used to measure non-linear relationships among brain areas, and coherence and wavelet coherence quantify frequency-specific functional connections. Connectivity measures capture different aspects of neural communication, and currently, no single optimal method has been found [2].

The resulting connectivity matrix is often thresholded to eliminate weak or possibly spurious connections before graph construction [2]. No universally accepted threshold has been established, and different thresholds can result in different network topologies and graph metrics. Some research has set a fixed correlation threshold; others have used proportional thresholding to maintain a constant network density across participants. Recently, weighted graph analysis has been applied to retain continuous connectivity strengths without losing potentially significant information [2].

3.3. Graph-theoretical metrics

After building the functional connectivity graph, graph-theoretical metrics can be used to quantify network organisation [2-4]. Generally speaking, the above measures fall into three categories: node-level, global and community-level.

Degree centrality at the node level refers to the number of connections a particular brain region has; thus, highly connected hubs that are likely to integrate information are identified [2]. Betweenness centrality measures the number of shortest paths a node belongs to in a network and thus its role in transmitting information between different modules [2]. Brain regions exhibiting both high degree and high betweenness are frequently considered network hubs because they coordinate communication among distributed functional systems [1, 2].

Global graph metrics can be used to characterise the overall organisation of the whole-brain network. Characteristic path length is the average shortest communication distance between nodes, and it shows how well a network can transmit information globally [2]. Global efficiency is another index that measures how efficiently information can be transmitted throughout the network [2].

DOI: 10.54254/2753-8818/2026.37490

Many studies have reported relatively short path lengths and high global efficiency for healthy functional brain networks under matched graph density and network-construction conditions [2].

Measures of functional segregation describe local information processing. Clustering coefficient measures the degree of local density in a neighbourhood of nodes, and local efficiency indicates the fault-tolerance capability of a subnetwork [2]. Together, these measures show how specialised functional communities support distributed cognition.

Community detection algorithms further partition the network into modules with strong internal connections and weak external connections [2]. Functional modules generally correspond to well-known intrinsic brain systems, such as the default mode network, frontoparietal control network, salience network, visual network and sensorimotor network [1, 2]. A module is a relatively independent system that can perform specific functions in cognition.

3.4. Emerging graph learning approaches

Graph-theoretic analysis has traditionally used manually designed network indicators to describe connectivity patterns. Although these measures are highly interpretable, they may not reveal complex nonlinear relationships in high-dimensional brain networks [6]. Therefore, recently, graph machine learning techniques have been applied to functional connectivity analysis.

Among the above methods, Graph Neural Networks (GNNs) have gained attention because they can directly process graph-structured data and retain topological information [6]. Unlike previous machine learning methods that require manual construction of graph features, GNNs automatically learn hierarchical representations of nodes through iterative neighbourhood information aggregation [6]. They can also model local and global network features simultaneously.

BrainGNN is a typical framework that introduces biologically interpretable graph pooling mechanisms to identify brain regions more relevant to neurological disease classification [13]. Instead of treating all nodes equally, BrainGNN learns task-specific subnetworks related to disease-associated functional changes to enhance both the predictive performance and interpretability [13]. Ktena and others have also proposed spectral graph convolution methods that can learn similarity metrics directly from functional connectivity graphs for subject classification [14].

Graph learning methods can perform well but are not without flaws. Deep neural networks generally require much larger datasets than traditional graph analysis methods, and thus are more prone to overfitting in neuroimaging studies with relatively small sample sizes [6]. In addition, many deep learning models are "black boxes" and thus harder to interpret biologically than traditional graph-theoretical metrics [6, 13]. Therefore, recent studies have begun to focus on explainable artificial intelligence and interpretable graph neural networks to balance predictive performance with neuroscientific interpretability.

In short, graph-based functional connectivity analysis is a new application of graph theory to high-dimensional fMRI data for constructing an organised model of the brain. These methods have become the basic tools for studying healthy cognition, neurological disorders and machine learning-based brain network analysis, providing the methodological foundation for the representative studies introduced in the following section.

4. State-of-the-art studies of graph-based functional brain connectivity

In the past 20 years, graph-based analysis has developed from a theoretical system into a general method for studying large-scale functional organisation of the brain. Recently, there have been advancements in neuroimaging acquisition and computational modelling and machine learning to

DOI: 10.54254/2753-8818/2026.37490

enable high-fidelity, interpretable studies of complex brain networks. At present, the three main directions of research are to characterise the normal organisation of the brain, identify disease-related network changes, and develop graph learning methods for clinical prediction and personalised medicine [1, 2, 5, 6].

4.1. Characterizing healthy brain networks

One of the first and most well-known applications of graph theory in neuroscience is the characterisation of healthy functional brain networks. Network neuroscience studies have shown that structural and functional brain networks exhibit small-world topology, with high local clustering and short average path lengths [2]. The network structure can support efficient information transfer and maintain a good balance between functional segregation and global integration [1, 2]. This line of research has provided a quantitative system for studying large-scale organisation of the brain and continues to be applied in network neuroscience.

Based on the above work, the network neuroscience framework proposes that cognition arises from the cooperation of multiple dynamic brain systems rather than from activity in isolated cortical areas [1]. This framework supports graph-theoretical analysis of how brain networks are organised during learning, development, ageing and cognitive tasks [1, 2]. Network neuroscience does not divide the brain into several independent functional areas but studies the interconnected operation of distributed functional networks, such as the default mode network, salience network and frontoparietal control network [1].

Large-scale cooperative projects have further expanded these results. The Human Connectome Project has released standardised multimodal neuroimaging datasets with high spatial and temporal resolution for large-scale graph-theoretical analysis of populations [5]. The availability of these high-quality datasets has improved the reproducibility of research and enabled the examination of network organisation in different age groups, cognitive abilities and behavioural phenotypes [5]. Human Connectome Project-based research has a larger sample size than previous studies with relatively small participant groups and can help validate graph-theoretical results in independent populations.

4.2. Graph-based analysis of neurological and psychiatric disorders

Graph theory has been used in the study of neurological and psychiatric disorders because many brain diseases involve disruptions in large-scale functional communication rather than isolated regional abnormalities [2]. In recent years, some studies have begun to investigate changes in the overall network structure of the brain to better understand cognitive decline and other diseases.

Alzheimer's disease is now a relatively well-known neurodegenerative disorder. Many studies have shown that patients with Alzheimer's disease have reduced global efficiency, a disrupted small-world organisation, and weakened long-range functional connectivity compared to healthy older adults [15]. These findings suggest that neurodegeneration may reduce the brain's capacity for integration across distributed functional systems. Efficiency and modularity of the graph are also measures of how much disease affects a network [2, 15]. Recently, some studies have combined graph analysis and machine learning to classify diseases based on functional connectivity features [6, 13].

Graph-based methods have also been applied to psychiatric disorders, and altered functional-network organisation has been reported in conditions such as schizophrenia, major depressive disorder and autism spectrum disorder [2, 6]. Although the particular network modifications differ in

DOI: 10.54254/2753-8818/2026.37490

various disorders, graph-theoretical indices can be used to detect large-scale abnormalities that are not evident in traditional region-based analysis [2].

Epilepsy is a typical case, and graph analysis has also been employed to study network abnormalities in seizure activity [2]. Collectively, the above results show that graph-based methods have been applied to study many different diseases of the nervous system and mental disorders.

4.3. Integration of machine learning and graph neural networks

Recently, new graph-based analysis methods have been developed in the field of artificial intelligence for direct learning from functional brain networks. Traditional graph-theoretical studies generally use manually selected network metrics, such as clustering coefficient or global efficiency, as the input features for statistical analysis [2]. Although these indicators are highly intuitive, they may not reflect complex nonlinear relationships in the high-dimensional connectivity data.

Graph Neural Networks (GNNs) address this problem by learning hierarchical feature representations directly from graph-structured brain networks [13]. Unlike conventional machine learning algorithms that do not explicitly operate on graphs, GNNs retain both node attributes and topological information during training to obtain a more complete description of functional connectivity patterns. BrainGNN, proposed by Li et al., introduced biologically informed graph pooling strategies to automatically identify disease-relevant brain regions and maintain model interpretability [13]. Li and others have reported in their evaluations that BrainGNN improved the classification performance and identified the brain regions that contributed to the prediction [13].

Ktena and others have also proposed spectral graph convolution methods to learn similarity measures of individual brain connectivity graphs [14]. Their framework has shown that graph convolutional networks can effectively distinguish subjects based on functional brain organisation without the need for manually engineered graph features [14]. In short, all these studies show that graph learning techniques are an extension of traditional graph theory.

Although they have shown good results, graph neural networks still have some deficiencies. Most deep learning models require significantly larger datasets than traditional statistical methods and are thus more prone to overfitting in neuroimaging studies with relatively small sample sizes [6]. Many graph learning algorithms are also computationally expensive and less interpretable than traditional graph metrics, thus limiting their clinical application [6, 13]. Therefore, recently, more research has focused on explainable artificial intelligence to enhance transparency without sacrificing predictive performance [6, 13].

4.4. Comparison of current research trends

Graph-based functional connectivity analysis has shown good results, but the methods in the current studies are not consistent. Different preprocessing pipelines, brain parcellation schemes, connectivity estimation methods, graph thresholding strategies and network metrics often result in different outcomes for the same dataset [2, 9, 11]. Therefore, the results of these studies cannot be directly compared, and methodological uniformity and open-science practices are needed.

Another new trend is the shift from static functional connectivity to dynamic functional connectivity; that is, functional brain organisation is not fixed but changes continuously over time during an fMRI scan [8]. Dynamic network analysis has found transient brain states associated with attention, learning, consciousness and cognitive flexibility, and offered new perspectives not available through traditional static connectivity measures [8]. At the same time, multimodal

DOI: 10.54254/2753-8818/2026.37490

neuroimaging studies are increasingly combining fMRI with diffusion MRI, EEG, MEG and genetic information to obtain more comprehensive information on brain organisation [1, 6].

Recently, research in graph-based functional connectivity has increasingly moved from describing network features to predicting behaviour. Graph theory, large-scale neuroimaging databases and machine learning have been combined to advance research on the organisation of the brain and explore new clinical applications for network neuroscience. However, many of the applications of these methods in daily clinical practice still have issues with reproducibility, interpretability and methodological uniformity; these problems will be discussed in the following section.

5. Limitations and future prospects

Substantial progress has been made in graph-based functional connectivity analysis, but some methodological and practical problems still limit its reliability, reproducibility and clinical applicability. All stages of the analysis pipeline, from data collection and preparation to network construction, graph analysis and machine learning, introduce challenges. These deficiencies must be addressed before graph-based brain network analysis can be applied to routine clinical practice.

5.1. Limitations of fMRI-based functional connectivity

The first limitation is that the BOLD signal does not directly measure neuronal activity. fMRI has good spatial resolution and whole-brain coverage, but it measures changes in the BOLD signal rather than neuronal activity directly. Thus, the functional connectivity estimates are indirect measures of neural communication and may be influenced by vascular physiology, age-related changes in the cerebrovasculature, medication or disease-induced alterations in neurovascular coupling. The above factors complicate the biological interpretation of functional connectivity and should be carefully considered in cross-population comparisons.

Another problem is that the temporal resolution of fMRI is relatively low. Typical fMRI repetition times are about 0.5-2 seconds, whereas EEG and MEG can capture electrical or magnetic activity at the millisecond scale. As a result, rapid neuronal interactions cannot be directly observed by conventional fMRI, and thus fast-changing cognitive processes or transient network dynamics are difficult to study.

5.2. Methodological variability and reproducibility

A typical problem of graph-based functional connectivity analysis is the considerable methodological variability introduced by these analytical choices. Functional brain networks are not directly observed but are constructed by several analytical choices, such as preprocessing strategies, brain parcellation, connectivity estimation, threshold selection, and graph metric calculation [2, 9, 11]. Each decision will change the resulting network structure and the meaning of graph-theoretical indicators significantly.

For example, different brain atlases define nodes based on different anatomical or functional criteria, and thus have varying network resolutions and connectivity patterns [12]. Pearson correlation, partial correlation, mutual information and coherence are all choices for the connectivity measure in fMRI data analysis, and they can result in different functional networks [2]. Thresholding strategies further complicate the comparison by removing weak connections and thus

DOI: 10.54254/2753-8818/2026.37490

changing the topology of the graph; weighted networks keep more information but may also contain noisy connections [2].

Different preprocessing pipelines have also led to inconsistent results in the studies. Motion correction, nuisance signal regression, temporal filtering and spatial smoothing are carried out differently by the various neuroimaging software packages [9, 11]. Although standardised preprocessing frameworks have improved reproducibility, no universal pipeline has been established yet [9, 11]. Therefore, the previous studies are not directly comparable.

5.3. Limitations of graph neural networks

Graph neural networks (GNNs) are now one of the most promising new developments in functional brain connectivity analysis, but they also present new problems. Deep learning models generally need a much larger amount of data than traditional graph-theoretical methods for good generalisation [6, 13]. Unfortunately, many neuroimaging studies still have a relatively small sample size because MRI acquisition is expensive and time-consuming [6]. Models trained on small datasets are prone to overfitting and may not perform well on an independent group.

Model interpretability is another important concern. The well-known graph indicators of clustering coefficient, global efficiency and modularity have clear neuroscientific interpretations because they directly reflect the organisation of networks [2]. In contrast, many deep neural networks are complex nonlinear models whose internal representations are not easily interpreted biologically [6, 13]. This "black-box" characteristic can reduce clinician confidence and limit the use of such models in healthcare applications that require transparent decision-making.

Generalisation of graph learning models is also an unsolved problem in research. Models trained on a single dataset may show reduced performance when applied to data obtained from different MRI scanners, different acquisition protocols or different patient groups [6]. Therefore, enhancing the robustness of cross-site application is still required for future machine learning studies in neuroimaging.

5.4. Future research directions

In the future, research will probably aim to improve the accuracy, reproducibility and clinical applicability of graph-based functional connectivity analysis. One important direction is dynamic functional connectivity, which can show how brain networks change over time during an fMRI scan without assuming that connectivity is fixed [8]. Thus, a supplementary indicator of time-varying functional connectivity has been obtained for research on attention, memory and other neurological disorders.

Another promising direction is multimodal neuroimaging; that is, fMRI is combined with other methods such as diffusion MRI, EEG or MEG to obtain joint structural and functional information [6]. Combining several imaging methods may provide a more comprehensive understanding of brain organisation and improve the accuracy of network-based biomarkers.

Recent developments in graph neural networks (GNNs) and explainable artificial intelligence are also expected to advance graph-based brain network analysis. Although GNNs have achieved good results in disease classification, enhancing their interpretability for clinical application is still required [6, 13]. Therefore, future models should balance predictive accuracy with biological interpretability.

Finally, with the increasing availability of large public neuroimaging datasets, standardised preprocessing pipelines and open-science initiatives have been introduced to improve reproducibility

DOI: 10.54254/2753-8818/2026.37490

and promote the development of personalised brain network models [5, 9]. The above developments will help to apply graph-based functional connectivity analysis in research and practice.

6. Conclusion

Graph-based analysis of functional brain connectivity offers an organised system for converting fMRI time series into quantitative descriptions of large-scale brain organisation. First, there is preprocessing and brain parcellation for analysis; then, connectivity estimation and graph construction are carried out to calculate nodal, global and community-level indicators. The above selections are not random; motion correction, atlas resolution, connectivity measures and thresholding strategies can all significantly change the resulting network and the interpretation of graph metrics. Traditional measures of network structure still include degree, clustering coefficient, path length, efficiency, centrality and modularity; these are all intuitively understandable indicators of network integration, segregation, hub organisation and functional modules. Dynamic functional connectivity extends the above framework to study changes in network structure over time, and graph neural networks can learn complex patterns directly from connectivity graphs for prediction or classification. Their potential, however, is limited by small sample sizes, scanner and site differences, computational cost, and insufficient biological interpretability. Reliable future studies should thus report the preprocessing and graph-construction decisions transparently, evaluate the sensitivity to alternative pipelines, use independent and cross-site validation, and distinguish exploratory findings from clinically robust biomarkers. Multi-modal integration of diffusion MRI, EEG or MEG can provide complementary structural and temporal information, and explainable graph-learning methods can be used to link predictive features with neuroscientific mechanisms. In short, graph theory and modern graph learning are complementary rather than in opposition. Advancements in reproducible and clinically applicable brain-network analysis will need to combine interpretable network indicators, scalable computational techniques, standardised evaluation criteria, and careful consideration of the physiological limits of BOLD signals. Modeling functional connections as mathematical networks allows graph theory to provide quantitative indicators of information integration, functional segregation and communication efficiency that supplement traditional region-based analysis. Graph theory has been used to study the organisation of the healthy brain and network alterations associated with neuropsychiatric disorders based on fMRI data.

Recently, with the development of dynamic functional connectivity, graph neural networks and large-scale neuroimaging databases, graph-based analysis of brain networks and disease classification has been extended. However, there are still some problems: methodological differences, a lack of reproducibility, indirectness in BOLD signals, and the interpretability of artificial intelligence models. To address the above problems, standardised analytical pipelines, multimodal neuroimaging integration, explainable artificial intelligence and personalised brain network modelling will be required in the future.

In short, graph-based functional connectivity analysis is a type of interdisciplinary system that integrates neuroscience, graph theory, statistics and machine learning to study large-scale brain organisation. With the continuous progress of computational methods and neuroimaging technology, graph-based approaches are expected to be employed increasingly frequently in basic neuroscience research and in the development of clinically applicable biomarkers for personalised medicine.

DOI: 10.54254/2753-8818/2026.37490

References

[1] Seguin, C., Sporns, O., & Zalesky, A. (2023). Brain network communication: Concepts, models and applications. *Nature Reviews Neuroscience, 24*(9), 557–574. https://doi.org/10.1038/s41583-023-00718-5

[2] Bahrami, M., Laurienti, P. J., Shappell, H. M., & Simpson, S. L. (2023). Brain network analysis: A review on multivariate analytical methods. *Brain Connectivity, 13*(2), 64–79. https://doi.org/10.1089/brain.2022.0007

[3] Hillman, E. M. C. (2014). Coupling mechanism and significance of the BOLD signal: A status report. *Annual Review of Neuroscience, 37*, 161–181. https://doi.org/10.1146/annurev-neuro-071013-014111

[4] Biswal, B., Yetkin, F. Z., Haughton, V. M., & Hyde, J. S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magnetic Resonance in Medicine, 34*(4), 537–541. https://doi.org/10.1002/mrm.1910340409

[5] Elam, J. S., Glasser, M. F., Harms, M. P., Sotiropoulos, S. N., Andersson, J. L. R., Burgess, G. C., Curtiss, S. W., Oostenveld, R., Larson-Prior, L. J., Schoffelen, J.-M., Hodge, M. R., Cler, E. A., Marcus, D. M., Barch, D. M., Yacoub, E., Smith, S. M., Ugurbil, K., & Van Essen, D. C. (2021). The Human Connectome Project: A retrospective. *NeuroImage, 244*, 118543. https://doi.org/10.1016/j.neuroimage.2021.118543

[6] Bessadok, A., Mahjoub, M. A., & Rekik, I. (2023). Graph neural networks in network neuroscience. *IEEE Transactions on Pattern Analysis and Machine Intelligence, 45*(5), 5833–5848. https://doi.org/10.1109/TPAMI.2022.3209686

[7] Friston, K. J. (2011). Functional and effective connectivity: A review. *Brain Connectivity, 1*(1), 13–36. https://doi.org/10.1089/brain.2011.0008

[8] O'Connor, D., Chang, C., & Mitsis, G. D. (2023). Editorial: Advancing the measurement, interpretation, and validation of dynamic functional connectivity. *Frontiers in Human Neuroscience, 17*, 1206098. https://doi.org/10.3389/fnhum.2023.1206098

[9] Notter, M. P., Herholz, P., Da Costa, S., Gulban, O. F., Isik, A. I., Gaglianese, A., & Murray, M. M. (2023). fMRIflows: A consortium of fully automatic univariate and multivariate fMRI processing pipelines. *Brain Topography, 36*(2), 172–191. https://doi.org/10.1007/s10548-022-00935-8

[10] Power, J. D., Barnes, K. A., Snyder, A. Z., Schlaggar, B. L., & Petersen, S. E. (2012). Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *NeuroImage, 59*(3), 2142–2154. https://doi.org/10.1016/j.neuroimage.2011.10.018

[11] Birn, R. M. (2023). Quality control procedures and metrics for resting-state functional MRI. *Frontiers in Neuroimaging, 2*, 1072927. https://doi.org/10.3389/fnimg.2023.1072927

[12] Peng, L., Luo, Z., Zeng, L.-L., Hou, C., Shen, H., Zhou, Z., & Hu, D. (2023). Parcellating the human brain using resting-state dynamic functional connectivity. *Cerebral Cortex, 33*(7), 3575–3590. https://doi.org/10.1093/cercor/bhac293

[13] Li, X., Zhou, Y., Dvornek, N., Zhang, M., Gao, S., Zhuang, J., Scheinost, D., Staib, L. H., Ventola, P., & Duncan, J. S. (2021). BrainGNN: Interpretable brain graph neural network for fMRI analysis. *Medical Image Analysis, 74*, 102233. https://doi.org/10.1016/j.media.2021.102233

[14] Ktena, S. I., Parisot, S., Ferrante, E., Rajchl, M., Lee, M., Glocker, B., & Rueckert, D. (2018). Metric learning with spectral graph convolutions on brain connectivity networks. *NeuroImage, 169*, 431–442. https://doi.org/10.1016/j.neuroimage.2017.12.052

[15] Yang, Z., Chen, Y., Hou, X., Xu, Y., & Bai, F. (2023). Topologically convergent and divergent large scale complex networks among Alzheimer's disease spectrum patients: A systematic review. *Heliyon, 9*(4), e15389. https://doi.org/10.1016/j.heliyon.2023.e15389