Review

Applications of hypergraph-based methods in classifying and subtyping psychiatric disorders: a survey

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Abstract

Psychiatric disorders exhibit extremely high heterogeneity, thus making accurate diagnosis and timely treatment challenging. Numerous neuroimaging studies have revealed abnormal changes in brain functional connectivity among patients with psychiatric disorders. To better understand the complexity of these disorders, researchers have explored hypergraph-based methods. Using functional magnetic resonance imaging data and hypergraph theory, studies have modeled and analyzed brain functional connectivity hypernetworks to classify psychiatric disorders and identify associated biomarkers. Furthermore, modeling a subjects-level hypergraph aids in estimating potential higher-order relationships among individuals; thus, hypergraphs can be used for classifying psychiatric disorders and identifying biomarkers. Recent neuroimaging studies have revealed specific subtypes of psychiatric disorders with biological importance. Hypergraph-based clustering methods have been used to investigate subtypes of psychiatric disorders. However, limited work has surveyed the applications of hypergraph-based methods in classifying and subtyping psychiatric disorders. To address this gap, this article provides a thorough survey, and discusses current challenges and potential future research directions in this field.

Keywords: Psychiatric disorders, brain functional connectivity hypernetworks, hypergraph, classification, clustering, biomarkers, subtypes

1. INTRODUCTION

Psychiatric disorders substantially affect patients' quality of life, comorbid medical conditions, suicide risk, and utilization of medical resources. Traditional methods of diagnosing and treating psychiatric disorders heavily rely on diagnostic criteria (e.g., DSM-5), medical history collection, and clinicians' subjective judgment and experience. However, several challenges can lead to misdiagnosis, including variability in clinical manifestations of the same disorder, overlapping phenomenology and genetics among different disorders, comorbidities, and high heterogeneity in patient longitudinal trajectories. Moreover, traditional methods are not supported by objective biological evidence, and do not provide accurate information on physiological indicators and pathological mechanisms. Consequently, understanding of the etiology of psychiatric disorders and the development of treatments is limited. Therefore, developing objective

and accurate diagnostic methods is imperative to enhance the diagnosis and treatment of psychiatric disorders.

Brain functional connectivity, revealed by functional magnetic resonance imaging (fMRI) data, exhibits significantly abnormal patterns in patients with psychiatric disorders compared with normal controls (NCs) [1-11]. These abnormal patterns involve multiple brain regions and can affect cognition, emotion, attention, and behavior. Among various neuroimaging techniques, fMRI offers a non-invasive means of studying brain function with high spatial resolution, and has been widely used to detect and characterize the connectivity between brain networks or regions that are functionally interconnected. Functional connectivity [12-15] refers to the temporal dependency of neuronal patterns across anatomically separated brain regions. Analysis of differences in functional connectivity patterns between patients with psychiatric disorders and NCs through machine learning methods may enable subjects classification and

provide new insights into disease mechanisms [16-18]. Researchers have attempted to integrate machine learning and data analysis techniques to uncover the global alterations and disrupted patterns of brain functional connectivity in psychiatric disorders. A major aim has been to identify robust biomarkers facilitating comprehensive understanding of the neural mechanisms underlying these diseases [19-24].

Graph theory has gained substantial attention in the field of neuroimaging [25], particularly in the construction of brain functional connectivity networks (FCNs) and a subjects-level graph based on functional connectivity features for classifying psychiatric diseases and identifying biomarkers. The brain is considered a complex network comprising dynamically interacting neurons or brain regions, wherein network connectivity signifies the mutual influence between these elements. Using fMRI data to construct FCNs can reveal the functional connections and interactions within the brain. Analyzing the network properties and topological features aids in comprehensive understanding of the pathological mechanisms underlying psychiatric diseases [26, 27]. In FCNs, brain regions are represented as nodes, and pairwise connections represent interactions between regions. Previous studies have demonstrated the universality and analytical value of graph theory in investigating brain FCNs [28-30]. The features extracted from FCNs have been used to classify the subjects. The subjects-level graph is a useful tool for measuring relationships between subjects and improving classification performance. However, both FCNs and subjects-level graph are limited in their ability to fully describe the complexity of the brain and the underlying relationships between subjects, because they can only quantify relationships between pairs of vertices. In contrast, a hyperedge of the hypergraph can connect more than two vertices, thereby enabling capture of more complex data correlations. Hypergraphs have been extensively studied and applied in network analysis, including in node classification [31], community detection [32], and link prediction [33]. Constructing functional connectivity hypernetworks (FCHNs) through hypergraphs enables high-order relationships among multiple brain regions to be effectively represented, thus providing valuable insights into the complexity of the brain. The construction of a subjects-level hypergraph enables accurate identification of potential high-order relationships among multiple subjects. Thus, hypergraph-based classification methods have contributed to deeper understanding of individual differences and characteristics of psychiatric diseases, enhanced classification accuracy, and facilitated the extraction of biological evidence.

The availability of neuroimaging techniques has revolutionized the study of brain mechanisms by allowing researchers to use clustering methods to explore biologically defined subtypes of psychiatric disorders. These capabilities have aided in addressing the heterogeneity of psychiatric diseases and advancing the development of precision medicine in psychiatry. Many studies have demonstrated the existence of consistent functional connectivity patterns across subgroups, thus providing further support for the subdivision of psychiatric disorders into specific subtypes [34-41]. Additionally, graph theory approaches have been used to detect transdiagnostic biotypes of psychiatric disorders. Du et al. have proposed a graph kernel based clustering method for this purpose [42]. On the basis of the functional connectivity features of resting-state fMRI (rs-fMRI), the method uses the graph-based substructure pattern mining (gSpan) technique [43] to uncover topological information regarding functional connectivity. The graph kernel similarity measure [44] has been used to measure relationships between subjects. The hierarchical clustering [45] and normalized cut (Ncut) [46] algorithms have also been applied to explore different subgroups within schizophrenia (SZ) and autism spectrum disorder (ASD). In a study investigating early onset SZ, Yang et al. have surveyed 15 intrinsic connectivity networks (ICNs). The authors used a graph-based community detection method to identify subgroups within this dataset and subsequently identified two ICN-based communities with substantial heterogeneity, which were associated with the clinical diagnosis, or the relative severity of positive and negative symptoms [47]. Despite growing interest in using data-driven approaches to identify subtypes of psychiatric disorders, the current findings exhibit inconsistencies, and there are few graph-based or hypergraph-based clustering methods for subtyping psychiatric disorders. In contrast to graph-based clustering methods, hypergraph-based clustering methods have greater potential to uncover the underlying data structure. Consequently, the latter have garnered considerable attention and are being extensively applied, thus presenting a valuable opportunity for uncovering subtypes of psychiatric disorders through hypergraph-based clustering methods.

Although hypergraph theory is not new, few articles have investigated its applications in classifying and subtyping psychiatric diseases. This article has three aims: (1) to provide an overview of hypergraph theory; (2) to review current studies using hypergraphs for classifying psychiatric diseases and detecting biotypes; and (3) to discuss current challenges and possible future research directions in this field. Although covering all peer-reviewed studies is impossible, this review provides unique perspectives contributing to a more comprehensive understanding of the current state of the field.

2. HYPERGRAPH THEORY

This section introduces hypergraph theory, including the basic definitions of the hypergraph, hypergraph construction methods, and hypergraph learning methods.

2.1 Preliminary
An ordinary graph $G(V, E; W)$ consists of a set of vertices V and a set of edges E. V contains n vertices, where

Review

$V = \{v_1, v_2, \ldots, v_n\}$. Each edge $e_{ij} \in E$ connects two vertices from V. The element W_{ij} of the adjacency matrix W represents the weight of the edge e_{ij}, indicating the relationship between vertex v_i and v_j. However, the graph is limited in describing the complex structure of data in most applications, because it captures only second-order relationships.

Hypergraphs, developed as an extension of ordinary graphs, capture valuable high-order relationships in data. The hypergraph $\mathcal{G}(V, \mathcal{E}, \mathcal{W})$ consists of a vertex set V, a hyperedge set $\mathcal{E}$, and a weight matrix $\mathcal{W}$. Each hyperedge $e_j \in \mathcal{E}$ contains more than two vertices from V. The weight matrix $\mathcal{W} = diag\{w(e_1), w(e_2), \ldots, w(e_{|\mathcal{E}|})\}$, $\mathcal{W} \in \mathbb{R}^{|\mathcal{E}| \times |\mathcal{E}|}$, preserves the weights of all hyperedges in the diagonal positions of the matrix. $|\mathcal{E}|$ denotes the number of hyperedges. The weight $w(e_j)$ of hyperedge e_j indicates its importance in the hypergraph. Generally, the hypergraph $\mathcal{G}$ can be represented by an incidence matrix $H = [H_{ij}] \in \mathbb{R}^{|V| \times |\mathcal{E}|}$, where $|V|$ denotes the number of vertices. The (0,1)-incidence matrix illustrates the associations between vertices and hyperedges. **Figure 1** displays an example of a hypergraph represented by a (0,1)-incidence matrix. H can also be a continuous matrix with elements ranging from 0 to 1, which provides a more detailed representation than the (0,1)-incidence matrix. In this case, H represents the probability that each vertex belongs to each hyperedge. Correspondingly, such a hypergraph is called a probabilistic hypergraph. Assigning weights to hyperedges is crucial in constructing a hypergraph. A commonly used approach for weighting a hyperedge is calculating the sum of Gaussian kernel-based similarities for all paired vertices within the hyperedge. Additionally, a study has explored methods for learning the weights of hyperedges [48]. On the basis of H and $\mathcal{W}$, the vertex degree of v_i and hyperedge degree of e_j are defined as $d(v_i) = \sum_{e_j \in \mathcal{E}} w(e_j) H_{ij}$ and $\delta(e_j) = \sum_{v_i \in V} H_{ij}$, respectively. A hypergraph containing all hyperedges with the same hyperedge degree d is known as a d-uniform hypergraph. Let D_v and D_e represent the diagonal matrices containing the vertex degrees and hyperedge degrees, respectively. The hypergraph adjacency matrix, calculated as $A = H\mathcal{W}D_e^{-1}H^T$, is used to represent the high-order relationship between vertices of the hypergraph. The element A_{ij} denotes the sum of the proportional weight of each hyperedge containing v_i and v_j. Similarly to the graph Laplacian matrix, the normalized hypergraph Laplacian matrix is defined as $L = I - D_v^{-\frac{1}{2}} H\mathcal{W}D_e^{-1}H^T D_v^{-\frac{1}{2}}$, where I is an identity matrix.

2.2 Hypergraph construction

Constructing a high-quality hypergraph is a complex task, because of several factors. First, high-dimensional data are subject to the "curse of dimensionality". Second, the data may come from different distributions; thus, combining them into a hypergraph is challenging. Third, the data may contain varying levels of noise, thereby further complicating the construction process. To address these problems, many methods for hypergraph construction have been proposed. In different application scenarios, carefully choosing the hypergraph construction strategy, optimization algorithm, and parameters is crucial to ensure that the resulting hypergraph accurately captures the high-order correlations among samples. The main hypergraph construction methods are implicit methods and explicit methods.

Explicit methods of hypergraph construction are designed for data with explicit attribute information, such as the color, shape, and texture of visual objects in images, or data with network information (e.g., social network, reaction network, cellular network, and brain network). Because such data might not be available in some cases, the scope of application for these methods is relatively limited.
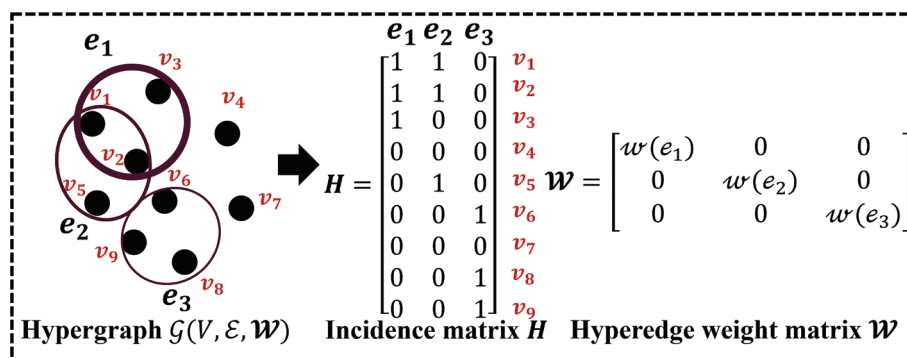

Figure 1 | Example of a hypergraph represented by a (0,1)-incidence matrix.
The hypergraph $\mathcal{G}$ contains a vertex set $V = \{v_1, v_2, \ldots, v_9\}$, a hyperedge set $\mathcal{E} = \{e_1, e_2, e_3\}$, and a weight matrix $\mathcal{W}$. Each hyperedge in $\mathcal{E}$ contains more than two vertices. The hypergraph structure is represented by a (0,1)-incidence matrix, wherein rows and columns correspond to vertices and hyperedges, respectively. The weight matrix $\mathcal{W}$ indicates the importance of all hyperedges in the hypergraph. The weight of each hyperedge is located at the corresponding diagonal position of $\mathcal{W}$.

In contrast, implicit methods of hypergraph construction are based on the features of samples. Herein, we focus on the implicit methods, which can be further categorized into distance-based methods and representation-based methods. A detailed review of hypergraph construction methods can be found in reference [49].

2.2.1 Distance-based methods for constructing hypergraphs.

The distance-based methods [50, 51] rely primarily on neighborhood information within a specific feature space to form hyperedges. Two frequently used strategies for hyperedge generation are the nearest neighbor-based strategy [50] and the clustering-based strategy [51]. In the nearest neighbor-based strategy, the distances between all paired vertices in the feature space are initially computed. Subsequently, the nearest neighbors for each vertex (referred to as the center vertex) are identified on the basis of either the k-nearest neighbors or ϵ-ball neighborhood criterion to form a hyperedge. In the clustering-based strategy, a hyperedge is formed by grouping vertices from the same cluster with a clustering algorithm (e.g., K-means).

In various applications, distance-based methods are often considered simple and efficient. However, their main limitation is the lack of accuracy in measuring the distances between the paired vertices in a certain feature space, owing to the presence of noise and data outliers. The hyperparameters (i.e., k and ϵ) significantly affect the structure of the hypergraph and consequently the performance of hypergraph learning when the nearest neighbor-based strategy is used. However, no general principle is currently available to guide the selection of hyperparameters. Additionally, finding the k nearest neighbors of each center vertex is costly for large-scale data. A major drawback with the clustering-based strategy is the difficulty in determining the appropriate number of clusters, which directly influences the structure of the hypergraph.

2.2.2 Representation-based methods for constructing hypergraphs.

Representation-based methods use data reconstruction to construct the hypergraph through two steps: representation learning and hypergraph construction. Representation learning is first performed to map the data to a low-dimensional feature space. Subsequently, a hypergraph is constructed according to the correlations between samples in the feature space. Representative hypergraphs include l_1-hypergraph [52], elastic net hypergraph [53], and l_2-hypergraph [54]. The l_1-hypergraph is constructed by using a linear regression model with l_1 regularization term. Specifically, for each vertex, the feature vector is linearly combined with the feature vectors of the nearest neighbors. The vertices corresponding to the non-zero coefficients in the reconstructed coefficient vector of the vertex, along with the vertex itself, form a hyperedge. In contrast to the l_1-hypergraph, the elastic net hypergraph is constructed on the basis of the elastic net model, which combines l_1-regularization and l_2-regularization. The models used for constructing the aforementioned hypergraphs use the l_2-norm to quantify the reconstruction error. Therefore, they are both susceptible to the effects of sparse reconstruction errors. Additionally, neither linear model described above can effectively handle nonlinear data. In contrast, the l_2-hypergraph model addresses these limitations by eliminating sparse noise components present in the original data, integrating locality, and maintaining constraints within the linear regression framework.

Compared with distance-based methods, representation-based methods are more flexible and adaptive and are particularly suitable for datasets with clear clustering structures in lower-dimensional feature space. However, a major drawback of representation-based methods is their vulnerability to data noise and outliers. Furthermore, on the one hand, if the center vertex is represented by all vertices except itself, the computational cost becomes high. On the other hand, if the center vertex is represented by only its nearest neighbors, the resulting hypergraph may not accurately capture the correlation among samples in the entire data distribution.

2.3 Hypergraph learning

Clustering and label propagation of vertices are two typical tasks in hypergraph learning. In this section, we introduce the hypergraph-based spectral clustering method for clustering vertices, as well as the hypergraph-based classification method for label propagation of vertices. A detailed introduction can be found in reference [55].

2.3.1 Hypergraph-based spectral clustering.

The hypergraph-based spectral clustering method is the most commonly used approach for clustering vertices. This method partitions vertices into distinct clusters by capturing the complex relationships among the vertices in the hypergraph, by using the hypergraph Laplacian regularizer. Consequently, the connections among vertices in the same cluster are dense, whereas the connections among different clusters are sparse. The hypergraph Laplacian regularization term, denoted

$$\Omega(\boldsymbol{f}) = \frac{1}{2}\sum_{e \in \mathcal{E}}\sum_{\{u,v\} \subseteq e} \frac{w(e)}{\delta(e)}\left(\frac{\boldsymbol{f}(u)}{\sqrt{d(u)}} - \frac{\boldsymbol{f}(v)}{\sqrt{d(v)}}\right)^2 = \boldsymbol{f}^T \boldsymbol{L} \boldsymbol{f},$$ reflects

that vertices belonging to the same hyperedge are likely to share the same labels. The hypergraph-based spectral clustering method can be transformed into a real-valued optimization problem by relaxing the original hypergraph normalized cut, and it is a generalized eigenvalue problem of the hypergraph Laplacian matrix. Specifically, when vertices are clustered into C clusters, the optimization problem is transformed into finding a C-way partition using multiple eigenvectors simultaneously. Currently, the most commonly used approach is construction of a matrix using C

eigenvectors that correspond to the C smallest eigenvalues of the hypergraph Laplacian matrix. Each column of the matrix is an eigenvector, and each row is considered the representation of the graph vertices in a C-dimensional Euclidean space. Subsequently, the K-means is applied to the matrix to assign cluster labels to the vertices.

2.3.2 Hypergraph label propagation. The process of hypergraph label propagation involves propagating label information from labeled vertices to unlabeled vertices in a hypergraph. The main objective of hypergraph label propagation (i.e., hypergraph-based classification) is to minimize the hypergraph Laplacian regularization term and the empirical loss term. The hypergraph Laplacian regularization term is based on the assumption that vertices within the same hyperedge are likely to have the same labels. The empirical loss term represents the sum of the squared errors between the predicted label vectors and the initial label vectors for all vertices.

Hypergraph label propagation includes transductive hypergraph learning and inductive hypergraph learning. In transductive hypergraph learning, hypergraph construction and learning consider both training and testing data. However, this method has drawbacks including high computational cost and limited scalability for new data. Inductive hypergraph learning uses only labeled data for constructing a hypergraph and acquiring a projection matrix. Specifically, the projection matrix is obtained by projection of the original feature vectors of the labeled data onto the label vectors during training. Subsequently, the projection matrix is used to project the original feature vectors of unlabelled data to the subspace spanned by it to obtain the label vectors of unlabeled data during testing. Either l_2-regularization or $l_{2,1}$-regularization can be imposed to enforce the constraint on the projection matrix. In comparison to transductive hypergraph learning, inductive hypergraph learning is more efficient and effective in processing emerging data, and thus is suitable for large-scale data. Nevertheless, it poses a challenge of low classification accuracy due to insufficient training data.

3. APPLICATION OF HYPERGRAPHS IN CLASSIFYING PSYCHIATRIC DISORDERS

The applications of hypergraphs in the classification of psychiatric disorders and biomarker identification are based on neuroimaging features and hypergraph-based classification methods, thus providing clinicians with valuable aids to improve diagnostic accuracy and personalize treatment. Hypergraph-based classification methods include FCHNs-based classification methods and subjects-level hypergraph-based classification methods.

In FCHNs-based classification methods, the FCHN of each subject represents the brain FCHN in the form of a hypergraph. This hypernetwork consists of nodes representing specific brain regions and hyperedges containing multiple nodes representing interactions among related brain regions. The construction of discriminative FCHNs is crucial for classification. With the aid of pattern recognition and machine learning techniques, such as support vector machine (SVM) and deep learning models, the subjects can be effectively classified according to the higher-order features extracted from constructed FCHNs. In addition, the biomarkers associated with psychiatric disorders can be identified.

In subjects-level hypergraph-based classification methods, a subjects-level hypergraph is used to capture high-order relationships among subjects. In the hypergraph, each node represents an individual subject, and each hyperedge contains multiple subjects with high correlation among them. The subjects-level hypergraph can uncover the underlying relationships among subjects for performing the classification of subjects. These methods have the potential to enhance classification performance and enable more accurate identification of relevant biomarkers of psychiatric disorders. These two types of methods are described in detail below.

3.1 Functional connectivity hypernetworks-based classification
3.1.1 Node definition in a functional connectivity hypernetwork. The definition of nodes substantially affects the construction and subsequent analysis of FCHNs. Previous node definition methods in FCNs are divided primarily into three categories: structural prior template information-based methods, functional template information-based methods, and data-driven-based methods. All these methods can be used for defining the nodes in FCHNs.

Among the structural prior template information-based methods, the automatic anatomical labeling template [56] is the most prevalent. This method uses brain imaging data from a specific population and defines structurally connected regions as nodes. Each node is characterized by an average time series of the relevant brain region. Because structurally close regions might not necessarily share the same function, these methods may not be appropriate for analytical tasks regarding brain function.

Functional template information-based methods are focused on accurately identifying and locating functional regions in the brain. Fan et al. have introduced a novel functional template [57] that combines data from various imaging techniques; considers spatial structural and functional heterogeneity information; and repartitions the brain into 210 cortical and 36 subcortical subregions. Similarly to the structural prior template information-based methods, each node of FCHNs constructed with these methods is characterized by the average time series of the corresponding brain region. Using these methods in FCHNs improves the performance in examining brain disorders characterized by functional changes.

Data-driven methods define nodes in terms of the data itself. Among them, independent component analysis (ICA) [58], group ICA (GICA) [59-61], and group information-guided ICA (GIG-ICA) [62] are widely used. On the basis of the assumption that the spatial information of brain functional networks is independent, these methods take the activation area in each network and the extracted time series corresponding to each network as a node and its feature vectors, respectively. Notably, GIG-ICA, proposed by Du and Fan, uses multi-objective function optimization to emphasize the independence of subject-specific independent components and the correspondence of independent components across different subjects, thus increasing the accuracy of the obtained independent components and time series [63-65]. Many researchers have used GIG-ICA to extract network features in their work and have achieved high disease classification accuracy [66-79]. In addition, the method performs well in removing artifacts [80, 81]. Du et al. have also proposed a framework called NeuroMark [82], which provides a common node definition for big data analysis and has been widely applied to explore the association between symptom severity and functional connectivity in patients with schizophrenia [83], to investigate sex-specific differences in brain functional network connectivity by using ICNs [72, 84], and to evaluate the association between dynamic functional network connectivity and the risk of Alzheimer's disease (AD) [85-87]. More recently, Du et al. have proposed a splitting-merging assisted reliable ICA (SMART ICA) method [88, 89] that obtains more reliable nodes by clustering the multi-order ICA results. The method automatically performs clustering on the independent components obtained under different parameter settings (i.e., the number of components), thereby resulting in functional networks with high reliability under different settings. A MATLAB toolbox called Intelligent Analysis of Brain Connectivity integrates GIG-ICA, NeuroMark, and SMART ICA [90], and can be downloaded at www.yuhuidu.com. Using these methods to define the nodes of FCHNs helps researchers mine more abundant and accurate features from FCHNs, thereby improving the classification performance of psychiatric diseases.

3.1.2 Connectivity estimation in functional connectivity hypernetworks.

Compared with traditional FCNs, FCHNs allow capture of more complex interactions between brain regions, thus enhancing understanding of psychiatric disorders. In FCHNs, the degree of synchronization of functional activities among multiple nodes from the same hyperedge is high. As described in Subsection 2.2, the two main types of methods for constructing FCHNs are distance-based methods and representation-based methods. Distance-based methods construct FCHNs by calculating the distances or correlations of the time series of all paired nodes and finding the nearest neighbors of each center vertex for forming hyperedges. The representation-based methods extensively use sparse representation models to uncover the relationships among nodes within the latent feature space to form hyperedges. These methods help provide accurate FCHNs and eliminate insignificant and spurious connectivity. Therefore, more accurate features can be extracted from FCHNs for subsequent analysis. Specific hypergraph construction methods are described in Subsection 2.2.

3.1.3 Classification.

Recent studies have used hypergraphs to develop FCHNs for improving the classification accuracy of psychiatric disorders and identifying biomarkers associated with disease pathology. Specifically, these studies have used original time series from rs-fMRI or time series derived from data-driven methods. FCHNs are constructed by using either the k-nearest neighbor strategy or sparse linear representation models (e.g., LASSO and its extensions). Features extracted from these FCHNs are fed into a classifier (typically SVM) to classify the subjects. For example, studies have constructed FCHNs and used a multi-task feature selection method to jointly identify the most informative features for classifying mild cognitive impairment (MCI) and attention deficit hyperactivity disorder (ADHD) [91, 92]. Another study has constructed FCHNs by using a sparse linear regression model combining brain region features and subgraph features. Multi-kernel SVM has been used to classify patients with AD and NCs [93]. Subsequent studies have improved these methods and proposed multimodal hypernetwork modeling techniques that leverage the richer information present in multimodal data [94-96]. Moreover, hypergraphs have been used to identify connectivity relationships and optimize the weights of hyperedges, to better represent the relationships among brain regions [97, 98]. To address the limitation of the LASSO model in explaining the grouping effect of FCHNs, Guo et al. have used the elastic net and GroupLASSO model to construct hypernetworks, then applied them to classify patients with depression and NCs [99].

Recently, progress has been made in analyzing FCNs by using hypergraphs combined with deep learning models. Ji et al. have introduced a hypergraph attention network called FC-HAT and successfully applied it to classify functional brain networks [100]. By optimizing the dynamic hypergraph generation and attention aggregation stages, FC-HAT can be used to dynamically construct FCHNs, update the hypernetworks and node embeddings, and extract abnormal connectivity patterns and brain regions, thus aiding in identifying biomarkers for ASD and ADHD. Additionally, Bi et al. have proposed a generative adversarial network called HSIA-GAN, which aggregates hypergraph structural information for automatic classification of subjects and feature extraction [101]. Furthermore, Banka et al. have incorporated hypergraph theory into adversarial deep learning to propose a hyperconnectome autoencoder framework to jointly learn the deep latent embeddings

Review

of subject-specific multi-view brain graphs. This method can uncover differences in brain states between AD and MCI [102]. In addition, Pan et al. have proposed a novel hypergraph generative adversarial network to exploit the complementary information between rs-fMRI and diffusion tensor imaging, thereby improving classification performance and identifying discriminative brain regions for AD [103]. Zuo et al. have proposed a multimodal representation learning and adversarial hypergraph fusion framework, and successfully used it to diagnose AD from complete trimodal images [104].

These studies have demonstrated the potential of FCHN-based classification methods in the classification of psychiatric diseases and the identification of biomarkers, thereby providing useful directions and inspiration for future research.

3.2 Subjects-level hypergraph-based classification

The subjects-level hypergraph-based classification methods explore the potential high-order relationship among subjects by using the hypergraph learning model to classify psychiatric diseases. Zu et al. have proposed an approach using hypergraph learning to identify subnetwork biomarkers in two different populations: patients with ASD or ADHD. In that study, the vertices in the hypergraph are represented as subjects, and the subnetworks with similar functional connectivity patterns among subjects are encoded by using hyperedges. Additionally, the weights of the hyperedges are jointly optimized. This approach overcomes the limitations of previous simple pairwise connectivity models, which are unable to capture complex connectivity patterns among more than two brain regions that form connected subnetworks [105]. Moreover, studies have introduced the hypergraph Laplacian regularizer in multi-task feature selection models to offer more complementary information by using multiple imaging data. The k-nearest neighbor strategy has been used to construct a hypergraph, and a multi-kernel SVM has subsequently been applied to combine multi-modal features for the automatic classification of AD and MC [106, 107]. Gao et al. have constructed a hypergraph through a star expansion method for four MRI sequences, and estimated the correlations among subjects through a semi-supervised centralized learning approach. In that study, MCI diagnosis was considered a binary classification task within a hypergraph structure [108]. Liu et al. have proposed a view-aligned hypergraph learning method that explicitly models the coherence between views, and applied it to three data modalities for the classification of AD/MCI. The method can achieve feature integration in each view space by constructing hypergraphs based on sparse representation [109]. Zhang et al. have also proposed a multimodal data fusion algorithm based on hypergraph manifold regularization, which considers similarity relationships within and across modalities to integrate imaging and genetics datasets from SZ [110]. That study not only has enhanced the accuracy of classification but also

has discovered notable correlations among risk genes, environmental factors, and abnormal brain regions.

The combination of deep learning models and hypergraph learning has been widely used in the classification of psychiatric disorders. Lostar et al. have introduced the hypergraph U-Net to acquire a low-dimensional representation with high-order subjects information by using the hypergraph structure, and have validated the method on brain network data from patients with autism and dementia [111]. In that study, brain maps of the subjects, rather than brain regions, were used as the nodes of the subjects-level hypergraph. In another study, Madine et al. have proposed a hypergraph neural network approach for ASD diagnosis, by using unsupervised multi-kernel learning to uncover latent relationships among subjects, thus facilitating the learning process. The study revealed that the right hemisphere consistently leads to enhanced classification accuracy between ASD and NCs [112]. Zhu et al. have proposed a novel approach for identifying subjects with MCI and fine-grained MCI by using dynamic hypergraph reasoning [113, 114]. The method is supported by a semi-supervised framework and is aimed at overcoming the problem of inconsistency between the constructed hypergraph structure and clinical labels/scores. This method incorporates the complex and complementary relationships of multimodal imaging data into the hypergraph inference processes. Aviles-Rivero et al. have proposed a semi-supervised hypergraph framework specifically for diagnosing AD [115]. The framework constructs a robust hypergraph that preserves the semantics of the data through a dual embedding strategy, thereby increasing prediction accuracy by using a dynamically tuned hypergraph diffusion model. However, the above methods based on deep learning currently rely heavily on large datasets, thus presenting a challenge when limited brain imaging data are available. Additionally, most brain imaging datasets are sourced from various sites and exhibit heterogeneity, which can affect the accuracy of deep learning models in classification tasks. Furthermore, although deep learning models demonstrate excellent feature learning abilities, the interpretation of the learned features remains limited, thus restricting analysis and understanding of brain diseases.

Currently, two major challenges persist in hypergraph-based classification: model reproducibility and interpretability. Addressing these challenges is crucial to ensure the confidence of identified biomarkers. An ideal model consistently produces similar results and offers explanations. Therefore, in our future research, we aim to design reproducible and interpretable models to gain a better understanding of psychiatric disorders.

4. APPLICATION OF HYPERGRAPHS IN SUBTYPING PSYCHIATRIC DISORDERS

Traditional classification studies of psychiatric disorders have often overlooked the heterogeneity in psychiatric

disorders. Thus, novel imaging-based methods that transcend traditional classifications in identifying biologically homogeneous subgroups of psychiatric disorders must be developed. This subtyping analysis approach not only enhances the understanding of the neurobiological heterogeneity of psychiatric disorders but also facilitates the advancement of personalized medicine. Clustering methods using brain functional connectivity features have been extensively used to uncover subtypes of disorders. However, previous studies have focused on examining the relationships between pairs of subjects and have neglected the potentially complex relationships among multiple subjects.

Because hypergraphs can effectively model high-order relationships in data, hypergraph-based clustering methods are important in studies of transdiagnostic biotype identification, and can aid in exploring more reliable biotypes for psychiatric disorders. Specifically, the functional connectivity features of fMRI data can be used to construct a subjects-level hypergraph by using distance-based or representation-based methods. In the hypergraph, each vertex represents a subject, thus enabling exploration of high-order relationships among subjects. Du et al. have proposed a hypergraph clustering approach to explore subtypes of bipolar disorder with psychosis and SZ [116]. In that study, a hyperedge sampling method was used to extract high-order similarities among subjects, and community detection was used to regroup subjects; subsequently, two reliable biotypes were identified between subjects with bipolar disorder with psychosis and subjects with SZ. The hypergraph clustering-based method has provided a new research avenue for transdiagnostic biotype detection.

Although hypergraph-based clustering methods have been extensively studied in various fields, their application to transdiagnostic biotype detection has been relatively limited. In the future, by using hypergraph-based clustering methods, previously hidden evidence of new biotypes may be uncovered in complex data.

5. DISCUSSION AND OUTLOOK

Functional connectivity plays a crucial role in understanding psychiatric disorders. Numerous studies have identified abnormal brain functional connectivity patterns in psychiatric disorders. Hypergraphs are increasingly used to classify psychiatric diseases and identify biotypes. However, substantial challenges remain in translating these findings into clinical practice. Below we discuss insights into future issues worthy of exploration in this area.

Constructing more precise and flexible hypergraphs and effectively applying them to neuroimaging data is a promising area of future research. Neuroimaging data are often high-dimensional and noisy, thus posing challenges in capturing the underlying relationships within the data. Existing hypergraphs often remain fixed throughout the learning process, and the initial hypergraph may contain numerous noisy connections that hinder the learning process. Developing hypergraphs tailored to the data and specific downstream tasks can potentially enhance hypergraph performance for effective analysis and understanding of neuroimaging data.

Hypergraph models face challenges regarding reproducibility. The primary aim of using hypergraph models in clinical settings is to ensure that these models can consistently detect clinically relevant biomarkers. However, current models are highly sensitive to parameters, and the validation process lacks robustness, thus potentially explaining why the reproducibility has been poor. To address these shortcomings, a possible future strategy is developing parameter-free models based on data-driven approaches. Additionally, models learned from multiple datasets exhibit poor reproducibility. A potential solution is to enhance model performance and to detect more powerful biomarkers by using multi-view fusion technology to provide the model with valuable complementary information. Additionally, increasing the sample size would also contribute to improving the reproducibility of the model.

Multimodal brain imaging data provide valuable complementary information for hypergraphs applied to classifying psychiatric disorders and identifying subtypes. These data can reveal complex changes that occur across different modalities and are associated with the underlying pathology of psychiatric disorders. By incorporating multimodal data from neuroimaging, genetics, and behavioral responses, recent studies have improved the accuracy of classifying psychiatric disorders and identifying robust diagnostic markers. However, research using multimodal data for hypergraph-based classification of psychiatric disorders and subtype identification remains limited. By developing a unified framework that jointly learns an optimal hypergraph based on multimodal data, the unique and complementary information provided by different modalities can be fully exploited.

A deeper understanding of the dynamics and true evolution of brain FCHNs will be beneficial in the study of psychiatric disorders. The successful application of hypergraphs in FCHNs is advantageous, owing to its natural compatibility with the architecture of brain networks. However, brain connectivity is often disrupted by various factors, such as experience, aging, and disease, thus leading to incomplete or uncertain construction of brain FCHNs. Dynamic connectivity of brain FCHNs could help better understand the changes of brain functional connectivity in psychiatric disorders, allowing for precise biomarkers.

The combination of deep learning models and hypergraph learning holds promise in the classification of psychiatric disorders. Deep learning models have advantages over traditional machine learning methods, because they can automatically learn features from data in a data-driven manner and represent learned decision

rules through multi-layer nonlinear structures [17, 117]. However, deep learning methods currently encounter challenges, such as overfitting due to limited sample size and interpretability, inadequate feature learning, and noise interference. In future research, addressing these issues will be a primary focus to advance the field of psychiatric diagnosis.

The use of hypergraph-based clustering methods in accurately mining potential relationships among subjects and identifying biotypes of psychiatric disorders is an area that has yet to be thoroughly investigated. In the field of machine learning, hypergraph models have been shown to be effective in modeling structures and relationships in real-world data. Despite extensive research on hypergraph-based clustering methods, their application in identifying subtypes of psychiatric diseases remains limited. This scarcity presents ample opportunities for future research and development.

6. CONCLUSION

Hypergraphs have the advantage of accurately mining potential high-order relationships among brain regions or subjects for the construction of FCHNs or a subjects-level hypergraph. Hypergraphs enable comprehensive understanding of the individual differences and characteristics of psychiatric disorders, and exploring the underlying biological basis. Despite the development and application of numerous classification and clustering methods for the diagnosis of psychiatric diseases, studies based on hypergraphs, particularly regarding transdiagnostic biotype detection of psychiatric diseases, remain limited. Herein, we reviewed hypergraph theory, investigated its applications in the classification of psychiatric diseases and biotype identification, and discussed current challenges and potential future research directions in the field. In the future, in-depth research in this field is expected to offer more universal, accurate, and reliable methods and insights.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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