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MVS-GCN: A prior brain structure learning-guided multi-view graph convolution network for autism spectrum disorder diagnosis

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ABSTRACT

Purpose: Recently, functional brain networks (FBN) have been used for the classification of neurological disorders, such as Autism Spectrum Disorders (ASD). Neurological disorder diagnosis with FBN is a challenging task due to the high heterogeneity in subjects and the noise correlations in brain networks. Meanwhile, it is challenging for the existing deep learning models to provide interpretable insights into the brain network. We propose a machine learning approach for the classification of neurological disorders while providing an interpretable framework.

Method: In this paper, we build upon graph neural network in order to learn effective representations for brain networks in an end-to-end fashion. Specifically, we present a prior brain structure learning-guided multi-view graph convolutional neural network (MVS-GCN), which collaborates the graph structure learning and multi-task graph embedding learning to improve the classification performance and identify the potential functional subnetworks.

Results: To demonstrate the effectiveness of our approach, we evaluate the performance of the proposed method on the Autism Brain Imaging Data Exchange (ABIDE) dataset and Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset. The experimental results indicate that our MVS-GCN can achieve enhanced performance compared with state-of-the-art methods. Notably, MVS-GCN achieves an average accuracy/AUC of 69.38%/69.01% on the ABIDE dataset. Moreover, the obtained results from our model show high consistency with the previous neuroimaging derived evidence of within and between-networks biomarkers for ASD. The discovered subnetworks are used as evidence for the proposed MVS-GCN model.

Conclusion: The proposed MVS-GCN method performs a graph embedding learning from the multi-views graph embedding learning perspective while considering eliminating the heterogeneity in brain networks and enhancing the feature representation of functional subnetworks, which can capture the essential embeddings to improve the classification performance of brain disorder diagnosis. The code is available at https://github.com/GuangqiWen/MVS-GCN.

1. Introduction

ASD is a neurodevelopmental disorder, with high variation in the severity of impairments in social communication and behaviors [1,2]. This disorder also involves a genetic influence via gene interactions or polymorphisms [3–5]. AD is a major and increasing global health challenge, with 40–50 million people currently living with it. There is no pathophysiological marker for ASD and AD diagnosis. Only relying on the psychological criteria [6] complicates the disease diagnosis, which could be biased by the subjective opinions of clinicians. There are no existing gold standards that can be used for definitive validation. Recently, machine learning methods have become an attractive and fundamental element of computer-aided diagnosis, and have been widely employed to analyze the neuropsychiatric disorders [7,8].

Resting-state functional magnetic resonance imaging (rs-fMRI) has become an essential tool for investigating neurophysiology [9]. Exploring the differences in brain activity for distinguishing ASD and normal control individuals facilitates the characterization of the underlying causes of ASD to an improved diagnosis and treatment. Hence, functional connectivity (FC) derived from rs-fMRI data has become a

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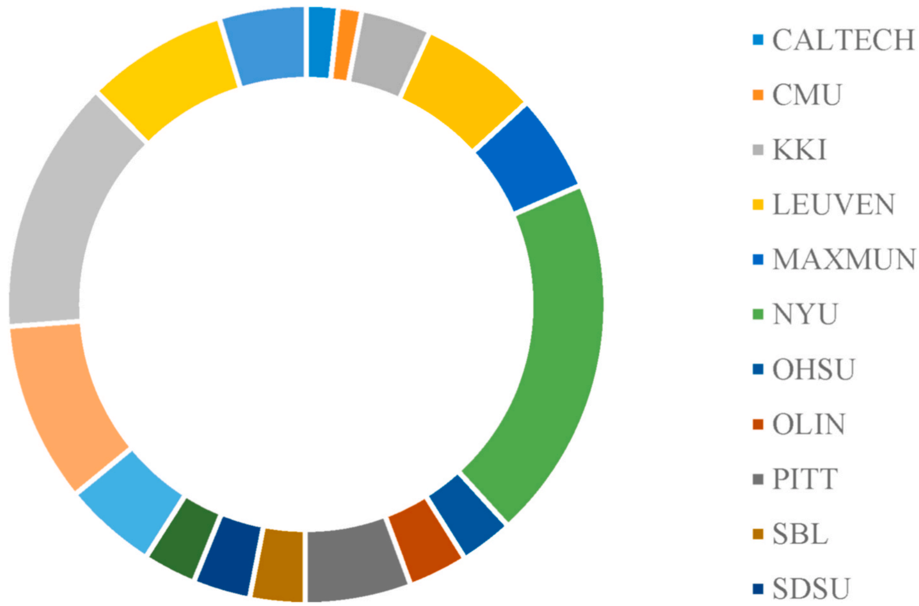


Fig. 1. The site distribution of the multi-center data in ABIDE.

powerful approach to measure and map brain activity [10]. The brain network has a complex structure, which is inherently represented as a graph with a set of nodes and edges [11,12]. The nodes in the graph denote the brain regions and the edges indicate the connection between regions. Currently, the graph is the most commonly used representation of brain networks in brain disease diagnosis. However, at the current stage, the graph classification for the ASD diagnosis faces many challenges as follow:

Challenge 1: How to overcome the heterogeneous data.

The ASD study involves multi-center data, introducing a great variety of different data distribution [13,14], shown in Fig. 1. The major challenge in multi-center research is data heterogeneity since the patients' populations and scanner protocol vary.

The heterogeneity in the multi-center data hinders the direct application of the traditional brain network embedding learning methods. Training a single predictive model on a multi-center dataset is more challenging to capture the heterogeneous data. More importantly, this inconsistency of brain network structures limits the exploration of the effective biomarkers.

Challenge 2: How to preserve the graph structures in graph embedding learning.

Considering all the correlations in the brain network may lead to the inclusion of noisy and spurious connections. The presence of noise in neuroimages is due technological limitations, operator performance, equipment, environment, and other factors [15]. Removing the weak (potentially noise) connections depends on a hard threshold without sufficient flexibility. Specifically, the brain networks constructed with large thresholds have few connections but more precise topological relationships between brain regions. However, the potentially important connections are inevitably lost. In contrast, the brain networks

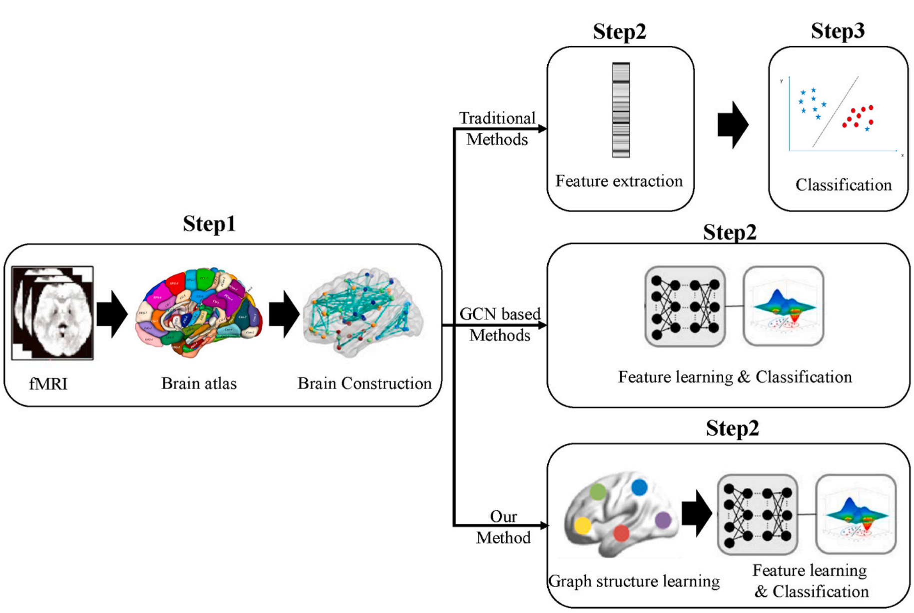


Fig. 2. Illustration of the traditional methods, GCNs methods and our unified method for brain network construction, graph embedding learning and classification. The first step for all the methods is constructing a connectivity matrix indicating the strength of interactions between the brain regions. For the traditional methods, the second and third steps are feature extraction and classification based on the constructed brain networks. Both of the two steps are conducted independently. They extract the hand-crafted features to represent the brain network, the main bottlenecks of which are the limited expressive power of the extracted features. Recently, the GCNs-based methods [8,21,22] have been proposed by jointly training the graph embedding learning and classification. However, the complex graph structure in the network limits the GCN's capacity for graph embedding learning. Our model improve the classification performance by the graph structure learning and graph embedding learning simultaneously.

constructed with small threshold values contain an amount of noisy connections, resulting in poor graph embedding of brain networks [16, 17].

Challenge 3: How to enable the GCN model to be interpretable.

In the medical domain, interpretability is essential as it can help decision-making during diagnosis and treatment planning. However, it is a challenge for the existing deep learning models to provide interpretable insights into the brain network. From the clinical perspective, identifying the subnetwork biomarkers [18–20] can help us understand the organization and alterations of brain networks in ASD. However, the complex structure of brain networks poses significant challenges to identify the biomarkers.

To overcome above challenges, we present a prior brain **S**tructure-guided **M**ulti-**V**iew **G**raph **C**onvolutional neural **N**etwork (MVS-GCN) which combines the graph structure learning and multi-task graph embedding learning to improve the classification performance and identify the potential functional subnetworks.

We formulate the disorder disease diagnosis as a graph classification. To solve the issue of complex structure in brain networks, we propose a graph structure learning algorithm to facilitate the construction of more common and cleaner brain networks. As illustrated in Fig. 2, we jointly train the graph structure learning and the graph embedding learning to obtain an appropriate brain network representation.

To alleviate the insufficient flexibility with a simple thresholding technique for binarizing the brain networks, we take full advantage of the multiple sparse level brain networks generated by multiple thresholds as a multi-view brain network for each subject. It is therefore intuitive to jointly learn the multi-view brain network embedding to boost the classification performance. Multi-task learning benefits from its ability to learn a shared representation across related tasks and to improve the generalization performance of each task. Identifying how the tasks are related and building commonality to capture such relatedness are critical issues in multi-task learning. Thus, we propose a new perspective of ASD classification with a multi-task learning paradigm. In our multi-task learning paradigm, we hypothesize that inherent correlations exist among the different views. With this assumption, we design a shared graph embedding learning layer and a view consistency regularization such that all the views can be trained jointly in an end-to-end manner, which is helpful for capturing the inherent correlations. Moreover, we propose a prior subnetwork structure regularization to guide the clustering procedure and ensure the accurate subnetwork identification.

Ultimately, we have conducted extensive experiments to investigate our proposed method on the public ABIDE dataset [23], and we also test our method on the ADNI dataset to evaluate the generalization of the model on the diagnosis of Alzheimer's disease. We also have provided comprehensive ablation experiments which can demonstrate the contribution of each key component in our proposed framework. Finally, our findings regarding the critical subnetwork identification align with the conclusion drawn from previous ASD studies.

To the best of our knowledge, this is the first work to address all the above challenges in the ASD diagnosis with brain networks and provide an interpretable framework. We summarize our main contributions as follows:

1 We propose a graph structure learning algorithm, which is able to adaptively construct a clean brain network by a supervised learning scheme. Compared with whole-brain networks, the coarsened graph representation is beneficial for the brain network embedding learning and disease diagnosis. Moreover, the graph structure learning removes the noisy correlations in the brain network by considering the group-level consistency in the subjects from multi-sites through highlighting the indicative edges.
2 We proposed a multi-view brain network embedding learning framework to improve the performance of disease diagnosis. The multi-view brain network embedding learning can obtain richer brain topological structure information, which is helpful for disease classification.
3 We introduce the prior knowledge (regarding the structure of the functional subnetworks related to ASD) to constrain the construction of brain networks. We propose a prior subnetwork structure regularization to obtain more potentially critical topological information.
4 Extensive experiments on two real medical clinical applications: diagnosis of Autism Spectrum Disorder (ASD) and diagnosis of Alzheimer's disease (AD), showing the effectiveness of the proposed framework. The experimental results demonstrate that network embedding learning from both correlations within individual brain networks and global population networks can improve prediction performance.

2. Preliminaries

2.1. Construction of the brain network

A brain network usually leverages a graph structure to describe interconnections between brain regions, which can be represented by a weighted graph $G=\{V,A\}$, where $V=\{v_i\}_{i=1}^{N_v}$ is the node set indicating brain regions, $A\in\mathbb{R}^{N_v\times N_v}$ is the adjacency matrix. In our work, the weighted graph G is binarized to an unweighted graph. More formally, it is constructed based on the edge weights on the graph, as shown in Eq. (2.1). In Eq (2.1), t is the threshold value utilized to separate the weighted graph to 1 or 0.

$$\widehat{a}_{i,j}=\begin{cases}1, & \text{if } |a_{i,j}|\geq t\\ 0, & \text{if } |a_{i,j}|<t\end{cases} \tag{2.1}$$

After constructing the brain network, the goal is to build and train a model to learn the graph embedding for subject classification.

2.2. Graph convolution networks

The power of deep learning models lies in enabling the automatic discovery of latent or the higher-level information from high dimensional neuroimaging data, which can be an important step to understand complex mental disorders. However, convolutional neural networks (CNNs) [24] do not generalize to irregular graphs since the discretized convolutions are only defined for the regular domains. Graph Convolutional Networks (GCNs) [25] aim to extend the data representation and classification capabilities of convolutional neural networks, which are highly effective for signals defined on regular Euclidean domains. Hence, following the idea of CNNs, GCNs are proposed to process problems with nonEuclidean data.

GCNs are stacked by several convolutional layers and each convolutional layer can be defined as:

$$\mathbf{H}^{(l+1)}=\sigma\left(\widetilde{\mathbf{D}}^{-\frac{1}{2}}\widetilde{\mathbf{A}}\widetilde{\mathbf{D}}^{-\frac{1}{2}}\mathbf{H}^{(l)}\mathbf{W}^{(l)}\right) \tag{2.2}$$

where $\widetilde{\mathbf{A}}=\mathbf{A}+\mathbf{I}_N$ is the adjacency matrix of the undirected graph G with self-connections $\mathbf{I}_N$. $\mathbf{W}^{(l)}$ is a layer-specific trainable weight matrix and $\sigma(\cdot)$ is the activation function. $\mathbf{H}^{(l)}$ is the feature matrix of the l-th layer. $\widetilde{\mathbf{D}_\mathbf{i}}=\sum_j\widetilde{\mathbf{A}_{\mathbf{ij}}}$. GCNs can be considered as a laplacian smoothing operator for the node features over graph structures [26]. The first hidden layer $\mathbf{H}^{(0)}$ is a set of the original input node features. All layers share the same adjacency matrix.

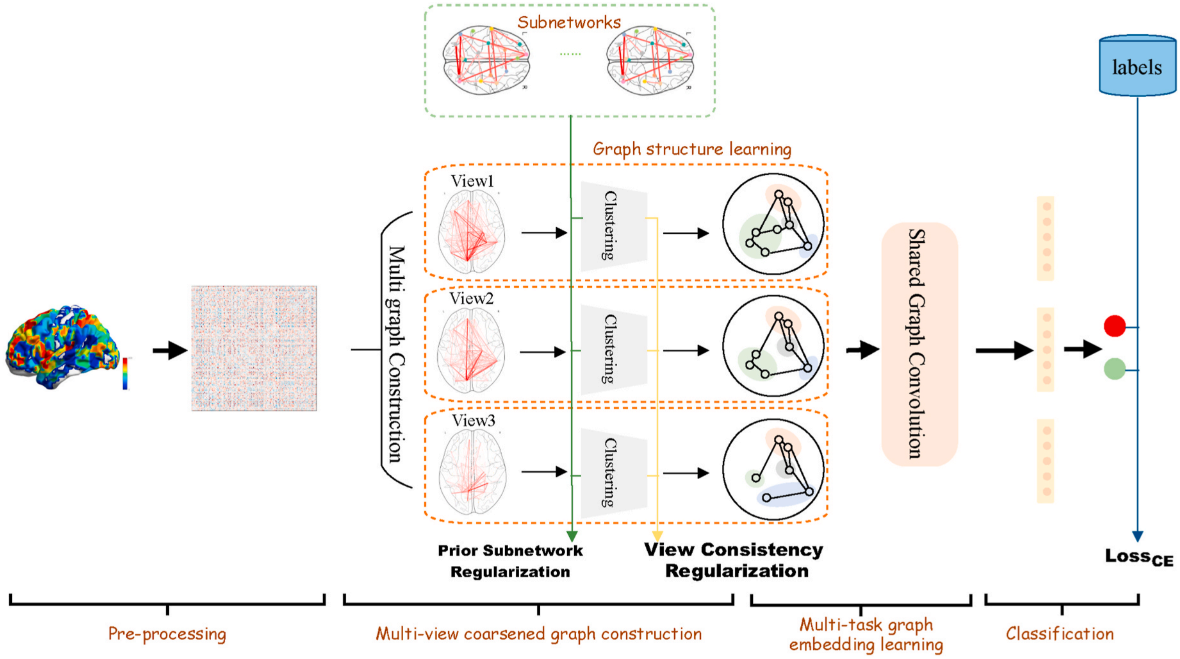


Fig. 3. The overall architecture of our proposed MVS-GCN. (1) Multi-view coarsened brain network construction contains two steps. The dense networks are binarized into multiple views of the brain network by different thresholds. Then, With the constructed graphs, we propose a graph structure learning to eliminate noisy connections in original graphs and achieve the coarsened graphs which are consistent for all the subjects by sharing the cluster indicator parameter. (2) Multi-task graph embedding learning: A shared graph embedding learning layer is proposed to capture the inherent correlations among the different views. (3) Two proposed regularizations: view consistency regularization and prior subnetwork structure regularization are incorporated into our model.

3. Methods

3.1. Overview

An illustration of the proposed MVS-GCN framework is shown in Fig. 3. It consists of three major components: 1) the graph structure learning (GSL), 2) the multi-task graph embedding learning for different views of brain networks (MVL), 3) the view consistency regularization (VCR) and the prior subnetwork structure regularization (SNR).

The original brain networks are enriched with topological connectivity, but these brain networks are highly heterogeneous because the subjects come from multiple sites. Meanwhile, the topological connections have a good deal of noise. Hence, the complex graph structure in the brain network hinders the graph embedding learning for GCN. To address this issue, we propose a graph structure learning to transform all heterogeneous brain networks into a unified graph space by highlighting the critical connections for classification. Through the graph structure learning, we obtain a more common and cleaner brain network.

To avoid the information loss and bias caused by a single view in this study, multiple views of brain networks are constructed to represent the original brain network with dense connections. Different thresholds determine different levels of topological structure. Specifically, the thresholded connectivity networks with larger threshold often preserve fewer connections and thus are sparser in connection while the networks with low threshold are more densely connected. We believe that the brain networks from the multiple views contain inherent correlations. Hence, we propose a multi-task graph embedding learning paradigm, which is able to capture the commonality between multiple views. Multi-task learning is an effective scheme for learning the association among the different tasks, and we establish a shared graph embedding layer for learning the features of each view. To ensure consistency between views, we propose a view consistency regularization so that the feature representation of different views is consistent.

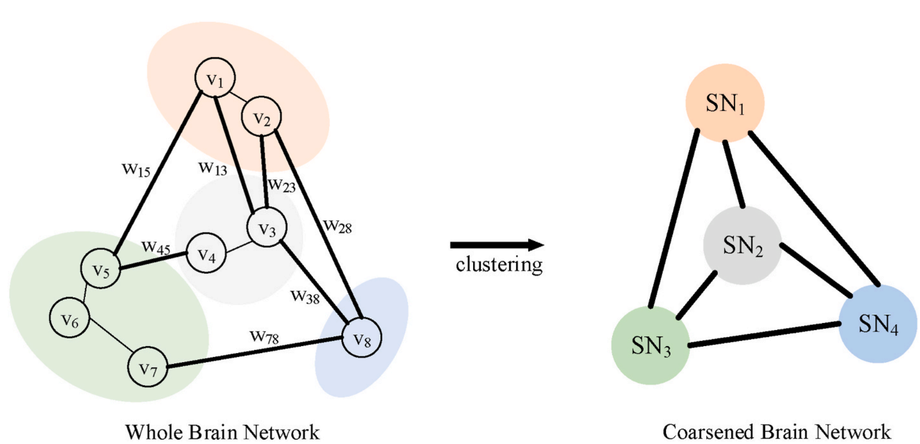


Fig. 4. The illustration of graph structure learning.

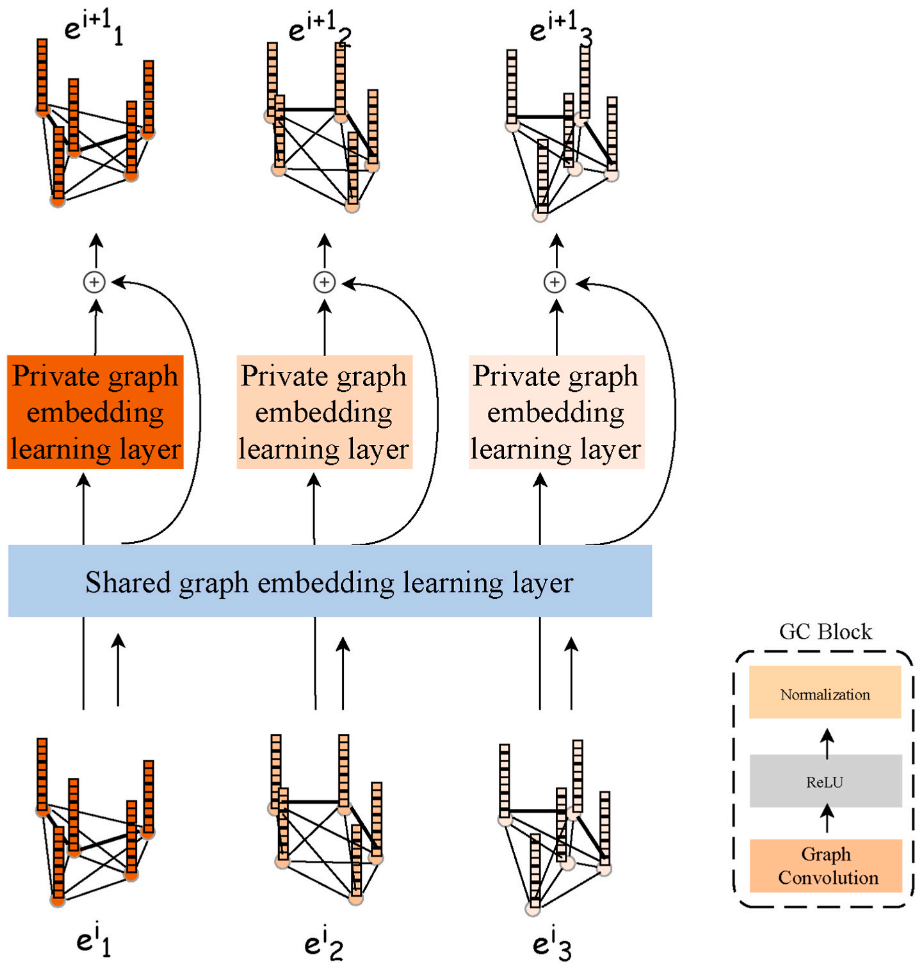


Fig. 5. Multi-view graph embedding learning with multi-task learning. It involves a shared graph convolution layer and a private graph convolution layer for each view.

3.2. GSL: graph structure learning

We convert fMRI time-series data into binarized graphs by computing the correlation between each pair of the brain regions by Eq. (2.1). However, simply binarizing the brain network in the above procedure still has two limitations. Firstly, the high dimensional connections in the original brain networks could be relatively large and thus not very discriminant, which causes an overfitting issue and increases computational complexity. Secondly, the brain networks from multiple sites are heterogeneous, which hinders the subsequent classification. In our work, we propose graph structure learning algorithm to remove the noisy connections in the brain network, and obtain consistent and clean graph structures simultaneously. However, the traditional clustering methods are unsupervised as independent procedures before the classification. Therefore, we propose a graph structure learning (GSL) for the heterogeneous and noisy brain networks, to remove the noisy connections in the brain network by considering the group-level consistency in the subjects from the multiple sites [27]. In other words, the weight of functional connections connecting the nodes crossing different clusters is enhanced whereas the nodes within clusters and their connections are removed. Moreover, we employ a unified framework to jointly train the proposed graph structure learning and graph embedding learning for classification in a supervision scheme, which leads to an improved classification performance.

The general idea of the method is to group the nodes of the whole graph into some clusters by hiding the non-indicative connections and highlighting the indicative connections, illustrated in Fig. 4. Our goal is to transform the whole brain graphs into the coarsened brain graphs. More specifically, $A \in \mathbb{R}^{N_n \times N_n}$ denotes the corresponding adjacency matrix which contains $\widehat{a}_{i,j} \in \{0,1\}, i,j \in \mathbb{R}^{N_n}$ of a whole brain network and $V = \{v_1, v_2, \ldots, v_n\}$. The graph structure learning can generate a coarsened brain graph, in which $\widehat{A} \in \mathbb{R}^{N_m \times N_m}$ is the corresponding adjacency matrix of the coarsened brain network, as shown in Fig. 4. We introduce a learnable parameter $F \in \mathbb{R}^{N_n \times N_m}$ which indicates the membership of a node to a cluster used for generating the coarsened brain: $\widehat{A} = F^T AF$. Given multiple graphs (brain networks), the underlying clustering F are shared among graphs. We assume each node v_i has its corresponding score s_i which represents its importance in G. Furthermore, with the node importance of s_i and s_j, we define the importance of edge between the i-th and j-th nodes as $s_i \widehat{a}_{i,j} s_j$, where $\widehat{a}_{i,j}$ denotes the weight of the edge. The learned edge weight helps identify the indicative edges. The weight of the superedge between supernodes SN_I and SN_J is then measured as:

$$W^{SN}_{I,J} = \sum_{i \in SN_I \wedge j \in SN_J} s_i * \widehat{a}_{i,j} * s_j \tag{3.1}$$

Briefly, the superedges between supernode SN_I and SN_J is the aggregation of edges multiplied with node importance. Then F can be formally defined as:

$$F_{ij} = \begin{cases} s_i, & v_i \in SN_j \\ 0, & v_i \notin SN_j \end{cases} \tag{3.2}$$

The graph clustering is able to remove the noisy connections and generate a consistent coarsened graph which is essential for the following graph representation learning and classification.

3.3. Multi-task graph embedding learning for multi-view brain networks

Removing weak (potential noise) connections depends on a hard threshold, which lacks flexibility. A critical issue is how to select an appropriate threshold to construct brain networks. To alleviate this issue, we apply multiple thresholds to generate multiple sparse level brain networks, which can reflect different topological structure levels of the original brain network. The brain network constructed by each threshold is considered as a different view and there exist inherent correlations among the multiple views of the brain networks. The integration of multi-view learning for graph embedding learning enables to achieve a more precise and complementary brain network representation. Therefore, the main aim in our study is to capture the inherent correlations between multiple views which is beneficial for the classification.

Multi-Task Learning (MTL) is a statistical learning framework that seeks to learn multiple models in a collaborative manner. It has been commonly used to obtain better generalization performance than learning each task individually. In our work, the graph embedding learning in each view can be considered as a separate classification task. More specifically, we select three threshold values to construct the three sparse level brain networks: large scale, medium scale and small scale. Different threshold values determine different topological structure levels. Then, we establish a multi-task graph embedding learning formulation, the aim of which is to train a unified model for modeling the view correlation. Our multi-task graph embedding learning module consists of a shared graph embedding learning layer (SGE) and view consistency regularization (VCR).

3.3.1. SGE: shared graph embedding learning

To obtain better generalization performance by exploiting the correlation among the different views in brain networks, we introduce a multi-task graph embedding learning which is able to fuse the graph embedding from the multi-view brain networks.

As shown in Fig. 5, we incorporate a shared graph embedding learning layer (SGE) for learning the association features between views in addition to the private graph embedding learning layers (PGE) which captures the unique embedding of each view. Then, each view embedding produced by the PGE is combined with the output from the SGE. We assume that the inherent correlations are also beneficial for graph embedding learning of each view.

For each view, our SGL is shown in Eq. (3.3):

$$Z = \left(\widehat{A}_k X_k^l W_k^l\right) + X_s^l \tag{3.3}$$

where X_k^l is l-th layer for k-th view in SGE, X_s^l denotes the l-th layer output of SGE. $W_k^l \in \mathbb{R}^{m\times m}$ is a learnable matrix in the l-th layer for k-th view. Therefore, the forward propagation of a graph can be regarded as jointly performing the following two operations: firstly executing graph embedding learning by its PGE, then capturing the shared features by the SGE.

We propose a shared graph embedding layer based on multi-task learning with parameter sharing to capture the associated features from different views at the sharing block which is essential for classification.

3.3.2. View consistency regularization

There exist complementary and inherent correlations between the different views of the brain network. It is desirable to exploit the consistent representation for the views. The multi-view graph embedding representation should be consistent due to the fact that the different views come from the same subjects.

To guarantee that different views are consistent during the graph embedding learning, we propose a view consistency regularization to enable the feature representations of the different views of the brain networks to be consistent. More specifically, $\widehat{A}_{view(i)}$ and $\widehat{A}_{view(j)}$ are graph structures of *view*(i) and *view*(j) of the brain networks, respectively. The aim of our view consistency regularization is to optimize the $\widehat{A}_{view(i)}$ and $\widehat{A}_{view(j)}$ to be similar.

The view consistency regularization is shown as follows:

$$L_{VCR} = -\sum_{(i,j)\in\mathcal{V}} \log \sigma\left(\mathbf{F}_i\left(\mathbf{F}_j\right)^T\right) \tag{3.4}$$

where F is the affiliation matrix in graph structure learning as mentioned before. $\mathcal{V}$ is the set of the different views in our model. By Eq. (3.4), the graph structure i-th view and one in j-th view tend to be consistent.

3.4. Prior subnetwork structure regularization

Some brain regions tend to work together to achieve a certain function, therefore it is desirable to incorporate the prior structure information into the proposed model to guide the process of graph structure learning.

Several works have demonstrated and found that certain functional subnetworks, such as salience network (SN) and default mode network (DMN), have a critical role in the pathogenesis of ASD. The aim is to design a model capable of incorporating the prior graph structures for improving classification performance. The graph structure learning may neglect the potentially important subnetworks. In order to address this, we consider the prior information of the subnetworks and incorporate the knowledge into the proposed model to encourage the connections within the important subnetworks with higher weights.

To incorporate the prior knowledge regarding the structure of the functional subnetworks, we propose a prior subnetwork structure regularization which enhances the feature representation of the functional subnetworks in training and improves the classification performance. At first, we identify all the brain regions within each functional subnetwork. Then, we highlight the connections between the regions by imposing larger weights on them. The prior subnetwork structure regularization enhances the confidence of the known structures, resulting in more accurate graph structure for the coarsened brain network construction.

$$L_{\mathrm{SNR}} = -\log\left(\frac{2}{\left|\mathcal{R}_p\right|^2}\sum_{i,j\in\mathcal{R}\ \text{and}\ c(i)\neq c(j)} s_i s_j + C\right) \tag{3.5}$$

where s_i in F can be interpreted as the membership of the node i to the cluster SN_j. With the optimized F, the function $c(\cdot)$ is the cluster mapping function which maps the nodes to the clusters according to the membership. $\mathcal{R}_p$ is the amount of the brain region of p-th subnetwork. To avoid the occurrence of log 0 during optimization, we add a constant C which is set to 0.000 01.

3.5. Learning

Based on the combination with view consistency regularization and prior subnetwork structure regularization. The overall loss is obtained by:

$$Loss = L_{CE} + \lambda_{VCR}L_{VCR} + \lambda_{SNR}L_{SNR} \tag{3.6}$$

The overall objective loss consists of three parts: the overall classification loss (Cross Entropy Loss), the view consistency regularization loss and the prior subnetwork structure regularization loss. λ_{VCR} and λ_{SNR} are weights of two regularizations, which are empirically set to 0.1 and 0.001.

Table 1
The parameter settings of the training of MVS-GCN.

Parameter name	Parameters
Optimizer	Adam
Learning rate	0.000 1
Dropout rate	0.2
Batch size	32
Max training epoch	200
Shared graph embedding learning layers	2
Private graph embedding learning layers	2

4. Experiment

In our experiments, we aim to answer the following five questions:

Q1: How does our proposed MVS-GCN perform compared with the state-of-the-art methods?
Q2: Does graph structure learning benefit the brain network classification?
Q3: Are the proposed view consistency regularization and prior subnetwork structure regularization effective for the brain network embedding learning?
Q4: How much is our proposed method influenced by the key hyperparameters including the number of supernodes and views?
Q5: Is the interpretability obtained by our model consistent with the previous findings?

4.1. Dataset

We evaluate our model on the Autism Brain Imaging Data Exchange (ABIDE) [23] and Alzheimer's Disease Neuroimaging Initiative (ADNI). The ABIDE aggregates data from 17 different acquisition sites [28] and openly shares rs-fMRI and phenotypic data of 1112 subjects. In this work, the images analyzed were preprocessed with the Connectome Computation System (CCS) [29]. We used the ABIDE preprocessed connectome project (PCP) data using the configurable pipeline, the Analysis of Connectomes (CPAC). The preprocessing step included slice timing correction, correction for motion, and normalization of voxel intensity. After the preprocessing, we obtained 871 quality MRI images with phenotypic information, comprising 403 individuals with ASD and 468 normal controls acquired at 17 different sites. We choose the functional preprocessed data based on AAL (Automated Anatomical Labeling dividing the brain into 116 regions) and CC200 (200 functionally homogeneous regions generated using spatially constrained spectral clustering algorithm) [30] functional parcellations to evaluate our model.

The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations, as a $60 million, 5-year public-private partnership. We focus on using rs-fMRI to discriminate individuals with Mild Cognitive Impairment (MCI) from individuals diagnosed with Alzheimer's Disease (AD). We select the same set of 133 subjects used in Ref. [31].

4.2. Implement details

In our experiment, we evaluated the effectiveness of MVS-GCN on both the ABIDE and the ADNI datasets. The parameters setting of our model is shown in Table 1.

In graph structure learning, the number of the supernodes in the coarsened graph is a very important hyperparameter, and it is empirically set to 8. Moreover, we further explore the performance varying with the number of supernodes in the discussion section.

4.3. Comparison with the state-of-the-art methods

To demonstrate the overall performance of the brain network diagnosis, we compare the proposed method with other state-of-the-art methods. For fair comparisons, all the comparable methods which were not tested on the ABIDE and ADNI in the original paper are evaluated in our experiments by the author's released source codes.

For a comprehensive comparison, we compare our MVS-GCN with the traditional methods, non-graph deep learning methods and the GCNs-based methods.

All the comparable methods are trained and tested on the same proportion of the dataset as ours. For all the compared methods, we set their division of data to be consistent with MVS-GCN. Moreover, we follow the same setting as the original papers to set the hyperparameters of the contenders. For the ones without the setting, we optimized the hyperparameters of each method to ensure that they are competitive in the comparison.

1. Traditional methods

In the flattened PC (person correlation) feature, there exists a large number of low level features (i.e., $\frac{M\times(M-1)}{2}$), where M is the total number of ROIs) that are extracted from the network as network features for the subsequent classification. Then, SVM with RBF kernel and random forest (RF) are employed as the base classifiers to learn the extracted features.

2. Non-graph deep learning methods

DAE: Denoising Autoencoders (DAE) [32] used two denoising auto-encoders to eliminate noise from the connectivity matrices. The weights used for denoising were further used to initialize the parameters for the classifier.

ASD-DiagNet: ASD-DiagNet[1] [33] is a joint learning method combining an autoencoder with a single layer perceptron (SLP) to improve the quality of the extracted features and classification performance. For ASD-DiagNet, we select the top 25% and bottom 25% of PC features as input features, which is consistent with the setting in the original paper.

CNN-EW: CNN-EW [34] is a convolutional neural network with element-wise filters for brain networks on the ABIDE dataset. Each element-wise filter gives a unique weight to each edge of the brain network which reflects the topological structure information.

DBN: The DBN [35] was employed to focus on the combination of resting-state fMRI (rs-fMRI), gray matter (GM), and white matter (WM) data. This was done based on the brain regions that were defined using the automated anatomical labeling (AAL), in order to classify autism spectrum disorders (ASDs) from typical controls (TCs).

LSTM-ASD: LSTM-ASD [36] is a long short-term memory (LSTM) based model for the classification of individuals with ASD and typical controls directly from the resting-state fMRI time-series.

3. GCN methods

ST-GCN: ST-GCN [22] is a spatio-temporal graph convolutional network[2] for predicting the subjects' age and gender by analyzing neuroimaging-based rs-fMRI data. Due to the limitation of ST-GCN to handle the equal-length signal data, we expanded and aligned the signal length of the data. Besides, since the ABIDE dataset contains less temporal information compared with the HCP dataset evaluated in the original paper, we reduced the layers in ST-GCN to 3 to prevent overfitting.

[1] https://github.com/pcdslab/ASD-DiagNet.
[2] https://github.com/ericksiavichay/cs230-final-project.

Table 2
Performance comparison of various methods. The average graph classification performance (accuracy (ACC), AUC, sensitivity (SEN) and Specificity (SPEC)) is reported. The best results are bold).

Category	Model	Atlas	SEN(%)	SPEC(%)	ACC(%)	AUC(%)	CV
Traditional Methods	PC feature + SVM	CC200	57.54	**68.73**	68.20	67.43	5-CV
	PC feature + RF	CC200	46.14	62.02	61.88	60.78	
Non-graph Methods	DAE [32]	CC200	**78.70**	53.20	67.61	63.51	
	ASD-DiagNet [33]	AAL	62.21	64.11	65.89	66.14	
	ASD-DiagNet [33]	CC200	60.31	67.76	68.31	67.76	
	CNN-EW [34]	AAL	70.40	66.44	66.88	–	
GCN Methods	GroupINN [8]	AAL	59.24	58.13	61.92	60.83	
	GroupINN [8]	CC200	61.52	57.36	63.60	63.17	
	ST-GCN [22]	CC200	54.78	48.91	57.29	51.73	
	Eigenpooling GCN [21]	CC200	58.81	59.94	57.50	58.16	
	sGCN [37]	CC200	64.73	60.12	67.54	64.33	
	BrainGNN [38]	CC200	61.65	60.79	61.84	60.79	
Our method	MVS-GCN	AAL	68.74	62.40	**67.14**	**66.91**	
	MVS-GCN	CC200	69.81	64.45	**69.38**	**69.01**	
Non-graph Methods	DBN [35]	AAL	84.00	32.96	65.56	–	10-CV
	LSTM-ASD [36]	CC200	–	–	68.50	–	
Our method	MVS-GCN	AAL	69.09	63.15	**68.92**	**66.44**	
	MVS-GCN	CC200	70.18	63.05	**69.89**	**69.11**	

Eigenpooling GCN: Eigenpooling GCN[3] [21] is an end-to-end trainable GCN with a pooling operator EigenPooling. The aim is to utilize the node features and local structures during the pooling process. For the Eigenpooling GCN, we set the number of clusters as 7. The model has two pooling layers that reduce the number of nodes in the graph to 20 and 1, respectively.

GroupINN: GroupINN[4] [8] jointly learns the node grouping and extracts graph features. GroupINN effectively combines node aggregation and classification, resulting in meaningful clustering results. We follow the same setting as GroupINN by setting the number of supernodes to 5 and the graph convolutional layer to 2.

s-GCN: s-GCN[5] [37] is a siamese GCN for identifying the patterns associated with the similarity between two graphs. The learned similarity metric can be properly captured with respect to the graph structure. We train the s-GCN with 2 convolutional layers and the number of neighbors for the graph structure is set to 10, which is under the same parameter settings as the original paper.

BrainGNN: BrainGNN[6] [38] is an end-to-end graph neural network-based framework for fMRI prediction that jointly learns ROI clustering and the downstream whole-brain fMRI classification. The hyperparameters employed in our comparison are consistent with the setting in the original paper.

Experimental results are reported in Table 2 where the best results are boldfaced. We highlight the following observations:

1) Compared with state-of-the-arts, the proposed MVS-GCN generally achieves the best performance on ABIDE dataset, as shown in Table 2. Firstly, we can see that compared with the traditional methods such as connectivity feature combined with SVM/RF, MVS-GCN observes an improvement of 1.1%/7.42% and 1.57%/8.22% in terms of ACC and AUC, respectively. Similarly, the performance of our MVS-GCN also outperforms non-graph deep learning methods. For example, compared with ASD-DiagNet, MVS-GCN achieves an additional improvement of 0.99% in ACC and 1.24% in AUC. To further highlight the advantages of MVS-GCN, we compare our MVS-GCN with the state-of-the-art GCNs-based methods. Our MVS-GCN achieves an average ACC/AUC of 69.3%/69.0% compared with GroupINN which achieves an average ACC/AUC of 63.6%/63.1%, resulting in a 5.7% and 5.9% increase in ACC and AUC, respectively. More importantly, compared with BrainGNN which is also developed for the ASD diagnosis, MVS-GCN observes an improvement of 7.46% and 8.21% in terms of ACC and AUC. These results indicate that our MVS-GCN is effective for the graph classification with the brain disorders diagnosis.
2) An interesting observation is that the non-graph methods, such as ASD-DiagNet, generally obtain better classification results than the GCN methods except our proposed MVS-GCN method. More specifically, compared with ST-GCN, Eigenpooling GCN and BrainGNN, ASD-DiagNet achieves 12.01%/16.03%, 10.70%/9.27% and 6.36%/6.64% improvements in terms of ACC/AUC, respectively. The results demonstrate that these GCN methods can not learn the potential representation of brain networks. The main reasons are that the complex graph structure and the multi-site heterogeneous data negatively influence the graph embedding learning of GCNs.
3) Altogether, our MVS-GCN outperforms not only the GCN methods but also the non-graph methods with respect to ACC and AUC. These results again support our conclusion that our proposed method can construct a more common and cleaner graph structure, which is beneficial for the graph embedding learning.

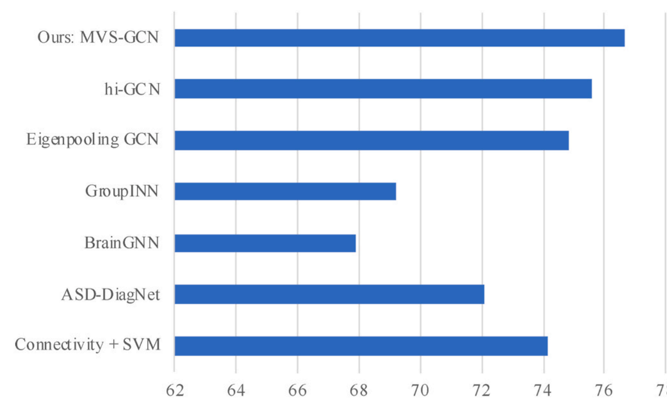


Fig. 6. The comparison of various methods on the ADNI dataset.

To thoroughly evaluate the proposed method, we test our model for the AD vs. MCI classification task on the ADNI dataset for Alzheimer

[3] https://github.com/alge24/eigenpooling.
[4] https://github.com/GemsLab/GroupINN.
[5] https://github.com/sk1712/gcn_metric_learning.
[6] https://github.com/LifangHe/BrainGNN_Pytorch.

Table 3
Effectiveness of the proposed components in MVS-GCN. The GSL indicates our graph structure learning. The SGE indicates the shared graph embedding learning layer. The VCR is our view consistency regularization and the SNR is prior subnetwork structure regularization.

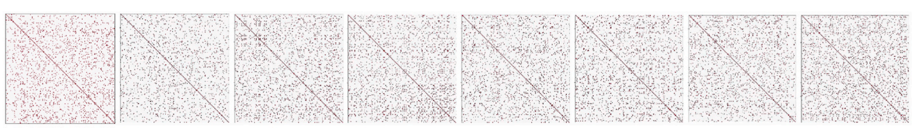
Model	GSL	SGE	VCR	SNR	SEN(%)	SPEC(%)	ACC(%)	AUC(%)
GCN					57.14	54.31	58.47	57.93
GS-GCN	✓				61.52	57.36	63.60	63.17
GSS-GCN	✓	✓			65.36	62.54	67.05	66.72
MVS-GCN -w/o SNR	✓	✓	✓		68.52	60.61	68.40	67.86
MVS-GCN -w/o VCR	✓	✓		✓	68.98	63.81	68.21	68.05
MVS-GCN	✓	✓	✓	✓	**69.81**	**64.45**	**69.38**	**69.01**

Disease. As can be seen in Fig. 6. We can see that the proposed method achieves better classification performance than the competing methods on the ADNI dataset of accuracy, which demonstrates the generalization of our MVS-GCN method.

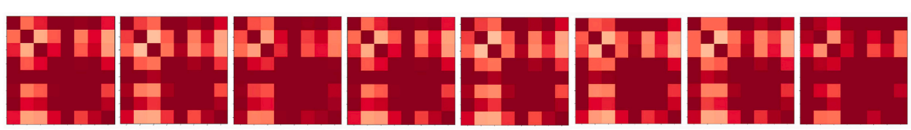
4.4. Ablation study

In addition to the above-mentioned results, we are also interested in the effectiveness of each component in the proposed model. Accordingly, we conduct an ablation study for the MVS-GCN to investigate how the components affect the classification performance. Experimental results are reported in Table 3 where the best results are boldfaced.

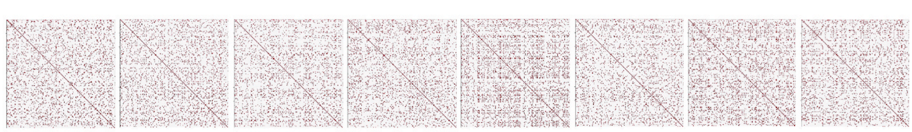
1. We find that GS-GCN outperforms the GCN by 5.2%/5.2% in terms of ACC/AUC, which demonstrates the effectiveness of the graph structure learning. The graph structure learning has a clear impact on the performance of the classification by constructing common and clean brain networks which proves our hypothesis that the complex graph structure in brain network hinders the graph embedding learning by GCN.
2. Compared with GS-GCN, MVS-GCN -w/o SNR (GS-GCN with multi-task graph embedding learning) achieves an average ACC/AUC of 68.3%/67.8%, resulting in a 4.7% and 4.7% increase in ACC and AUC, respectively. The observation implies the effectiveness of the proposed scheme of the multi-view brain network embedding learning, for capturing the inherent correlations of different views.
3. With the prior subnetwork structure regularization, MVS-GCN -w/o VCR outperforms GSS-GCN by 1.2%/1.3% in terms of ACC/AUC, respectively. The improvement is benefited from the constructed brain networks by capturing the prior structure of the critical functional subnetworks. The prior structure information contains more significant topological information, which is helpful for classification.
4. Additionally, by integrating view consistency regularization and prior subnetwork structure regularization into MVS-GCN, we can see that better results can be achieved. It demonstrates that the two proposed regularization are complementary.
5. To investigate the effective of two regularizations, we compared MVS-GCN -w/o VCR and MVS-GCN -w/o SNR with GSS-GCN, respectively. It can be clearly observed that the MVS-GCN -w/o



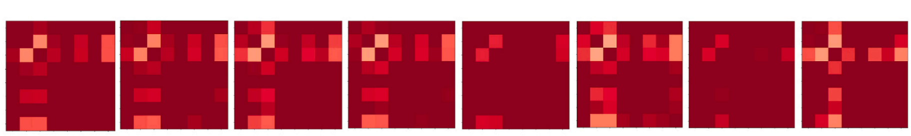
(a) Original graphs of ASD subjects



(b) Coarsened graphs of ASD subjects

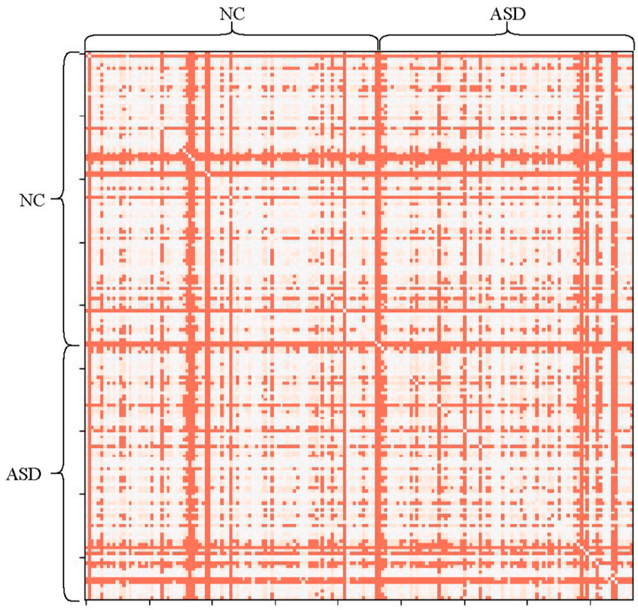


(c) Original graphs of the normal control subjects

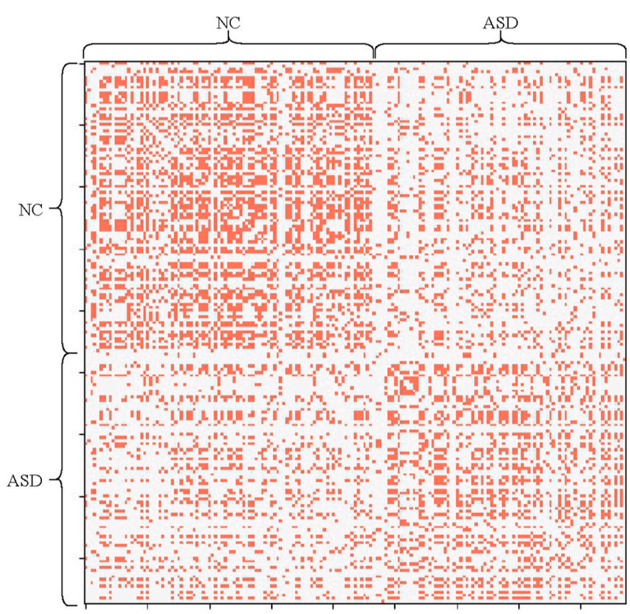


(d) Coarsened graphs of the normal control subjects

Fig. 7. Visualization of the ASD and normal control examples with respect to the connectivity matrix of the original graphs and the coarsened graphs.



(a) Similarity matrix of the original brain networks



(b) Similarity matrix of the coarsened brain networks obtained by the proposed graph structure learning

Fig. 8. Visualization of similarity matrices of original graph and coarsened graph for subjects.

Table 4
The influence of positive functional connectives and negative functional connectives. The GS-GCN with Pos + Neg_split indicates that the positive and negative functional connections are learned separately and concatenated before classification. The GS-GCN with Pos + Neg_nosplit indicates that the two type connections are not split to be learned and classified positive and negative functional connections together.

Model	Positive/Negative	SEN(%)	SPEC(%)	ACC(%)	AUC(%)
GS-GCN	Positive	60.01	**62.54**	62.91	62.89
	Negative	51.73	49.14	55.22	54.81
	Pos + Neg_split	**61.52**	57.36	**63.60**	**63.17**
	Pos + Neg_nosplit	57.25	54.56	59.70	59.15

VCR achieves an additional improvement of 3.2% in terms of specificity compared with MVS-GCN -w/o SNR, which denotes that the classification of MVS-GCN -w/o VCR is more effective due to the guidance of the prior subnetwork structure regularization. This result suggests that the prior subnetwork structure regularization is more essential for constructing brain networks.

4.5. Discussion

4.5.1. The effectiveness of the proposed graph structure learning

To further evaluate the effective of the graph structure learning, we visually explore the coarsened graphs generated by the graph structure learning and compare them with the original graphs. Sixteen samples (eight ASD patients and eight NC subjects) of the results are presented in Fig. 7. By observing them individually, the original graphs of each subject showed high inconsistency. However, the inconsistency of each subject is alleviated with the process of the graph structure learning. Therefore, our results seem to yield a solid evidence that imposing the graph structure learning method during training the network is a viable method for improving GCN's performances. Through the graph structure learning, the indicative connections are highlighted. We can also find that the most of the connections in the brain network are non-indicative of the final classification task. Furthermore, by observing the results in Fig. 7, it is apparent that the difference of ASD individuals and normal controls with respect to the original connectivity matrix is difficult to be discriminated. By contrast, the discrimination between ASD individuals and normal controls with respect to the coarsened graphs is strengthened by the graph structure learning. By comparing Fig. 7 (a) and (b), we can also see that the graph structure learning alleviates the heterogeneity in the brain networks between subjects. By strengthening the difference between the two classes, the graph structure learning further improves the performance of our classification. In addition, we visualized the similarities of all the subjects in Fig. 8. By comparing Fig. 8(a) and (b), we can see that the samples belonging to the same class become more similar after the graph structure learning, and the samples in different become smaller. The results demonstrate that two classes of subjects are more discriminative after the graph structure learning. More specifically, with the guidance of the supervision, the graph structure learning enables the gaps between samples of different classes to be larger and the distances of the within-class samples to be smaller. Our results indicate the importance of graph structure learning on the complex brain networks for improving the classification performance.

4.5.2. The effectiveness of positive and negative functional connectivity

In this section, we investigate the influence of positive and negative functional connectivity for classification. The results are shown in Table 4.

1. We find that GS-GCN with the positive connectives outperforms the model with the negative ones, resulting in a 7.69%/8.08% increase in terms of ACC/AUC. The result demonstrates that the positive

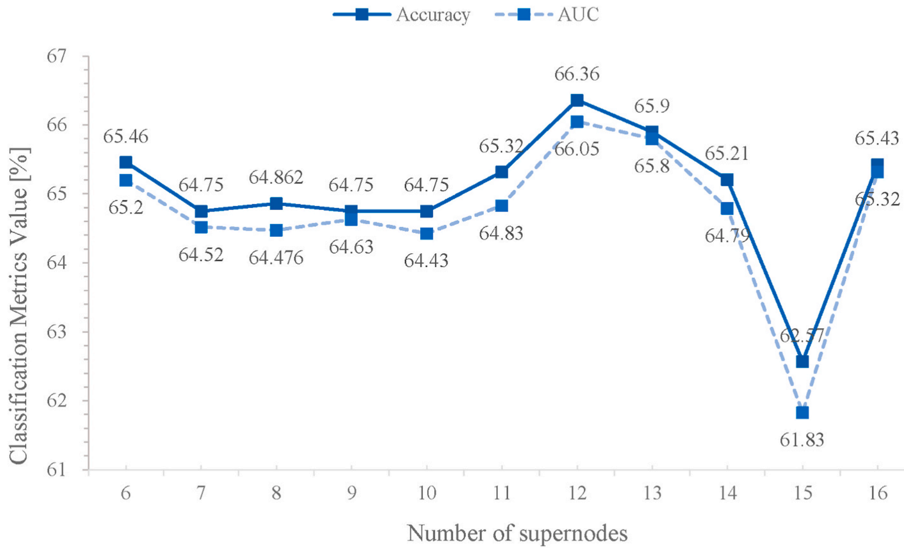


Fig. 9. Performance for different number of supernodes of coarsened graphs.

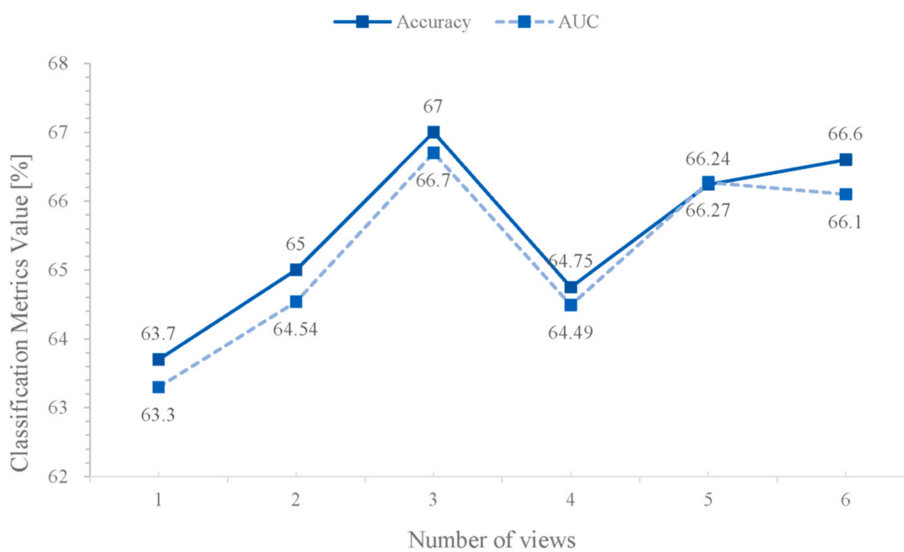


Fig. 10. Performance variation as the number of views increases.

functional connectives are more essential for classification, which is consistent with the conclusion of [39]. Furthermore, the performance of the model is further improved when combining positive and negative functional connectives together. It indicates that the negative connectives provide limited contribution for the classification as a supplement to the positive connectives.

2. Additionally, we compare the model where the positive and negative connectives are not split with the model with two separate branches for modeling individual connectivities. We find that the performance of classification of the latter model is better, which suggests that the positive and negative connectives should be considered individually. Due to the different contributions of the two connectivity, it is inappropriate that the node embedding is updated by aggregating information from both positively and negatively correlated neighbors during the training of GCN.

4.5.3. The influence of the hyperparameters of MVS-GCN

In the MVS-GCN model, two important hyperparameters are the number of supernodes in graph structure learning and the number of views. In order to evaluate the impact of these parameters on the performance of MVS-GCN, we conducted two experiments with varied values for the number of supernodes and the number of views, respectively.

We vary the values of the supernode number for the graph structure learning, and show the results in Fig. 9. From Fig. 9, it can be found that the number of the nodes in coarsen graph has a significant impact on the classification performance, which demonstrates that the coarsening level in the brain network is an important factor for the graph structure learning. More specifically, if the number of supernodes is small, the topology information of the coarsened graph is condensed whilst if the number of supernodes is large, the information would be richer in the coarsened graph.

To explore the influence of the variability across the number of views, we varied the value of the view $\mathcal{V} \in \{1, 2, 3, 4, 5, 6\}$ and investigated the variation of performance with multiple values. From Fig. 10, it can be found that the performance improves with the number of views increasing until the number is 3, demonstrating that different views contain inherent correlations which are beneficial for capturing topology information. In addition, we can find that as the number of views increases, the performance of the model tends to stabilize, verifying that

Table 5
The top 3 subnetworks as well as the top 6 cross inter-subnetworks selected and the corresponding weights optimized by our model.

Subnetwork Name	Weights	Inter-subnetwork Name	Weights
CEN	0.003 7	CEN-SN	0.002 74
SN	0.003 5	CEN-AN	0.002 60
DMN	0.003 4	CEN-VN	0.002 58
–	–	SN-VN	0.002 52
–	–	DMN-SN	0.002 50
–	–	SN-AN	0.002 48

increased views will inevitably introduce redundant information to the model, leading to a decreased classification performance.

The results further demonstrate that graph structure and multi-views graph embedding learning are important for network embedding learning.

4.5.4. Interpretability

In our work, we attempt to improve the explainability by identifying the critical subnetworks through the learned indicative connections. To better understand the cortical circuitry in the functional connectivity, we evaluate our model to investigate the intrinsic subnetworks from a data-driven perspective. The score of the p-th subnetwork SN_p is calculated as:

$$Score_{SN_p} = \frac{2}{|\mathcal{R}_p|^2} \sum_{i,j \in \mathcal{R}_p \wedge c(i) \neq c(j)} s_i s_j \tag{4.1}$$

where the R_p is the amount of the brain region of p-th subnetwork. Each item $s_{i,j}$ can be interpreted as the membership of the node i to the cluster SN_j. Moreover, we calculate the scores of the sub-networks under each view, and calculate the average of the sub-network scores of all the views as their final scores.

Moreover, the inter-network connections in this system have also been proven to play essential roles. In addition to the analysis of independent sub-networks, we also analyze the interaction between subnetworks. To explore the important cross-subnetwork correlation, the correlation score of two subnetworks SN_p and SN_q is calculated as:

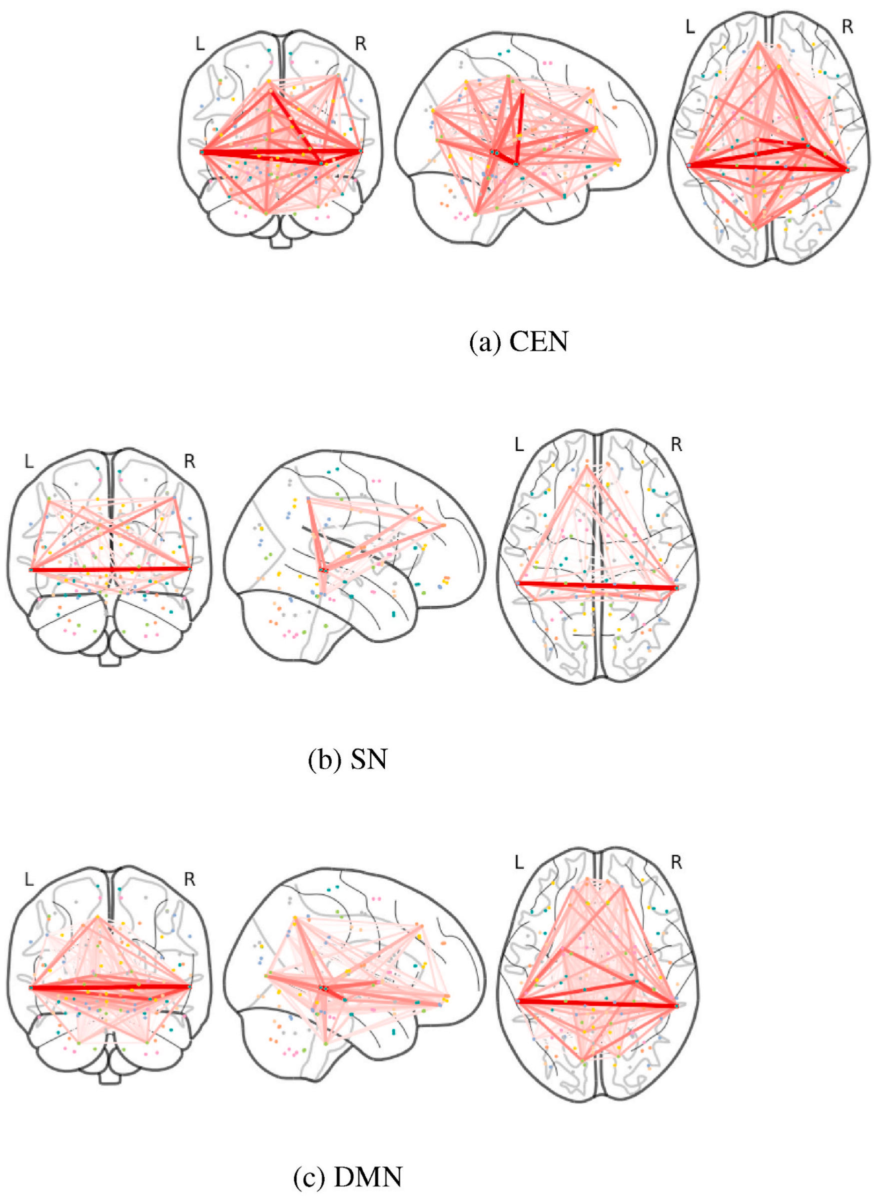
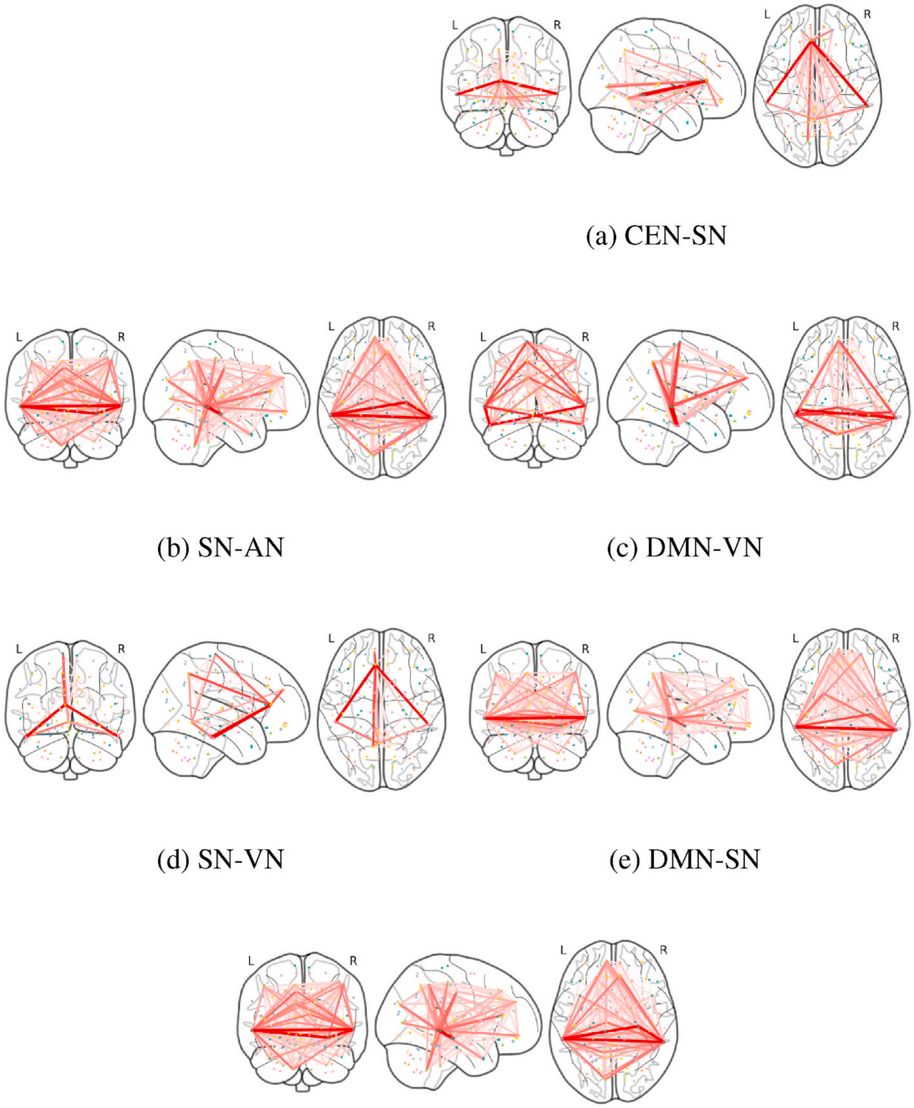


Fig. 11. The top 3 subnetworks identified by our model.



(a) CEN-SN

(b) SN-AN

(c) DMN-VN

(d) SN-VN

(e) DMN-SN

(f) SN-AN

Fig. 12. The top 6 inter-subnetworks identified by our model.

$$Score_{SN_{p,q}} = \frac{2}{\mathcal{R}_p \mathcal{R}_q} \sum_{i \in \mathcal{R}_p, j \in \mathcal{R}_q \wedge c(i) \neq c(j)} s_i s_j \tag{4.2}$$

where $Score_{SN_{p,q}}$ can also be interpreted as the sum of the importance of any two nodes belonging to subnetwork p and subnetwork q, respectively.

The brain network studies in neurotypical individuals have identified several major intrinsically connected networks related to visual, motor, auditory, memory and executive processes. In our work, we empirically investigate the effectiveness of the identified subnetworks and inter-subnetworks. From Table 5, we find the top 3 subnetworks are CEN, SN and DMN, and the top six sub-network connection strengths are (SN, CEN), (SN, AN), (DMN, VN), (SN, VN), (DMN, SN), (SN, AN).

The critical subnetworks and inter subnetworks are visularized in Figs. 11 and 12. This is also consistent with previous discoveries about ASD in the medical field [40,41]. Neuroimaging research indicates that ASD has a great relationship with the dysfunction of the triple network including CEN, SN and DMN [42]. It is worth noting that , CEN, and DMN are often activated or deactivated together in attention-demanding tasks, which indicates that the network works synergistically to support attention and cognition. In particular, the triple network model assumes that SN plays a central role in initiating the transition between CEN and DMN, which is a necessary process for attention and flexible cognitive control. Moreover, from a clinical standpoint, anti correlated contributions from regions of the default mode network (DMN) and somato motor network (SMN) have been previously reported in ASD [43]. Besides, the cross subnetwork connections including DMN-VN keep their sign of relation to diagnosis variable at different frequency bands in the diagnosis of ASD [44].

5. Conclusion

Although graph convolution neural networks have made a massive breakthrough in the field of brain network analysis, the graph embedding learning on brain networks faces several challenges, including heterogeneity in subjects and the noisy connections in brain networks. In this paper, we proposed a prior brain structure learning-guided multi-view graph convolutional neural network (MVS-GCN) which combines the graph structure learning with multi-task graph embedding learning to improve the classification performance and identify the potential functional subnetworks. We conduct extensive experiments on the public ABIDE dataset and ADNI dataset to verify the effectiveness of our model, which indicates that our MVS-GCN achieves promising performance compared with the state-of-the-art methods, including the alternative traditional methods, GCNs-based methods and non-graph deep learning methods.

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