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Network-based artificial intelligence approaches for advancing personalized psychiatry

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Abstract

Psychiatric disorders have a complex biological underpinning likely involving an interplay of genetic and environmental risk contributions. Substantial efforts are being made to use artificial intelligence approaches to integrate features within and across data types to increase our etiological understanding and advance personalized psychiatry. Network science offers a conceptual framework for exploring the often complex relationships across different levels of biological organization, from cellular mechanistic to brain-functional and phenotypic networks. Utilizing such network information effectively as part of artificial intelligence approaches is a promising route toward a more in-depth understanding of illness biology, the deciphering of patient heterogeneity, and the identification of signatures that may be sufficiently predictive to be clinically useful. Here, we present examples of how network information has been used as part of artificial intelligence within psychiatry and beyond and outline future perspectives on how personalized psychiatry approaches may profit from a closer integration of psychiatric research, artificial intelligence development, and network science.

KEYWORDS
artificial intelligence, machine learning, mental disorders, networks, network science, psychiatry

1 | INTRODUCTION

Psychiatric disorders, including schizophrenia, major depressive disorder, or bipolar disorder, contribute to 21% of the global disease burden (Eaton et al., 2008). Psychiatric research has made tremendous advancements in characterizing factors involved in the pathophysiology of these conditions, but a detailed understanding of the mechanisms that lead to illness onset is still elusive. Across different data types, perhaps with the exception of rare genetic variants, the effect sizes of biological changes found in patients are generally low (Szucs & Ioannidis, 2017). They are also broadly distributed across different data types, including structural and functional neuroimaging, genetic association, gene expression, epigenetic, proteomics, or metabolomics data. This has raised substantial interest in the application of machine learning (ML) tools that can integrate features with individually small effect sizes into modes that are more predictive, thus giving deeper insights into affected biological mechanisms, and may serve as the basis for the development of clinically useful applications (Calhoun & Sui, 2016; Durstewitz et al., 2019). The development of such ML models has, however, also highlighted the challenge of selecting informative features from high-dimensional data and accurately capturing their relationship with respect to pathophysiology. Biological research has been successful in capturing relationships between biological entities, and these are frequently conceptualized

in the form of networks (Dehmer et al., 2010). Prominent examples include genetic co-expression (Zhao et al., 2010), gene regulatory (Davidson & Levin, 2005) or protein–protein interaction networks (Cho et al., 2004; Colizza et al., 2005), or networks of brain-functional connectivity (Wu et al., 2008). The field of "network medicine" aims to explore human illness in the context of such complex network relationships and offers a conceptual framework for the integration of different data modalities into a coherent representation that is amenable to computational analysis (Barabási et al., 2011). Besides improving the etiological understanding of complex illness, notable applications of network medicine frameworks include the potential advancements of personalized medicine through the integration of molecular interaction networks in predictive frameworks for diagnosis, prognosis, and treatment, the prediction of drug combinations, the artificial-intelligence based re-purposing of drugs (Benincasa et al., 2020; Cheng et al., 2019; Lee & Loscalzo, 2019; Morselli Gysi et al., 2021; Silverman et al., 2020; Sonawane et al., 2019), or the network-based stratification of patients (Sarno et al., 2021). As network approaches offer an intuitive framework for integrating data across different phenotypes, they also offer a promising approach for exploring the respective relationships and potentially shared biological underpinnings of different diseases (Huang et al., 2022). This illustrates that network science amalgamates the investigation of network relationships at different levels of biological organization, for example, from cellular molecular and gene regulatory to brain-functional and phenotypic networks. In particular in neuroscience, where network analysis has already substantially contributed to our understanding of neural circuitry and its involvement in psychiatric disorders, a more in-depth integration of network science methods has been proposed as a promising future perspective (Barabási et al., 2023).

An interesting question, in particular from the perspective of personalized medicine applications in psychiatry, is how networks can be effectively used for the prediction of clinical phenotypes. This is interesting since conventional ML tools use individual-level data as input and do not naturally incorporate network information. Therefore, we focus here on approaches that have already been used successfully in this context and explore two principal strategies (Figure 1). In the first, important structural properties of graphs are extracted and used as input for ML. In the second, the graphs are directly used as part of ML approaches and used for prediction or to support the predictive value of another ML model. We discuss interesting examples for each of these approaches and explore future perspectives for artificial intelligence-based network science in psychiatry. It should be noted that the stated performance estimates may not reflect the true generalization performance of the underlying models due to methodological and sample size effects or effects related to publication bias.

2 | UTILIZING GRAPH TOPOLOGY MEASURES IN MACHINE LEARNING

Network structures are commonly represented by nodes that are connected by edges that can be weighted and directed (directed graphs) or undirected (undirected graphs), depending on the application. For instance, symptom networks can be represented as directed graphs (Belvederi Murri et al., 2020). The structure of a given graph and its topological properties can be of biological relevance. For example, in protein–protein interaction (PPI) networks, nodes (i.e., proteins) with high numbers of connections are more likely to have important cellular functions (Costanzo et al., 2019; Piñero et al., 2016). Also, densely interconnected proteins tend to be related to each other functionally and such proteins serve an important function in the structure of the network (Barabási et al., 2011). Accordingly, proteins that have been associated with the same illnesses tend to appear in similar modules

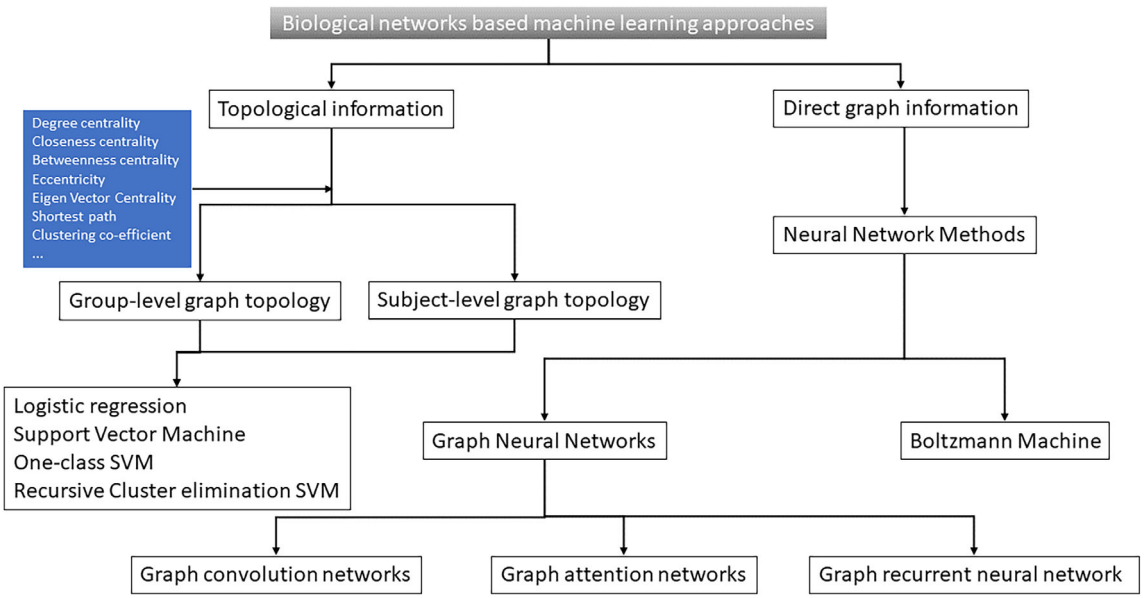

FIGURE 1 Overview of the graph-based machine learning strategies discussed in this article.

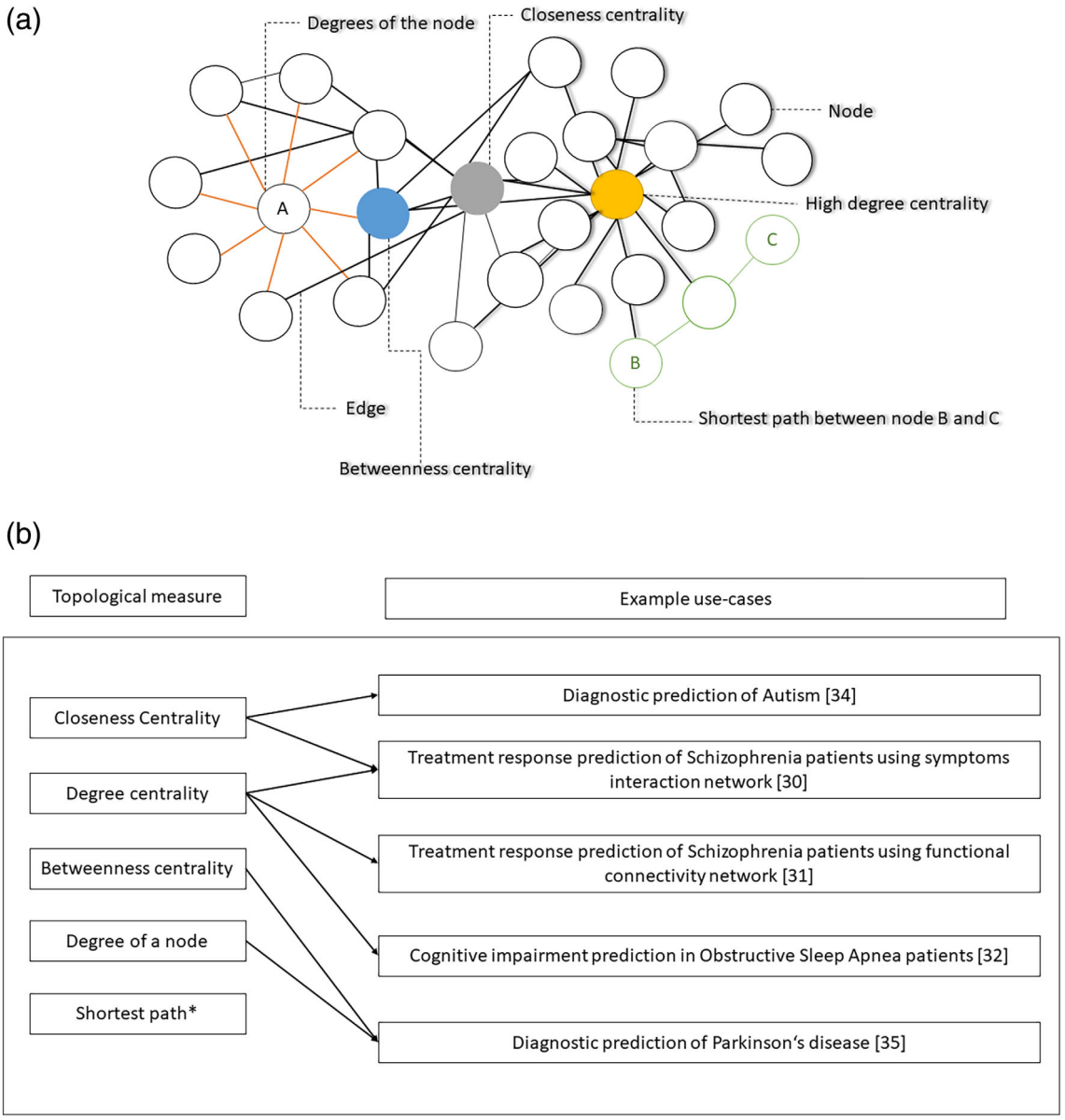

FIGURE 2 (a) Examples of topological properties of a graph that can be used in ML approaches. For example, a node is an element in a graph, and the edge connects the two nodes. Degree (marked orange) of a node A is the number of connections a node has. The node (marked yellow) with high degree centrality has the highest number of connections, as shown in the figure. The shortest path between two given nodes (B and C) is shown in green. The node marked in blue is positioned on the shortest path between other nodes, which denotes control over the information passing among others (i.e., high betweenness centrality). The gray node has the smallest average shortest path length among all the nodes across the network (i.e., high closeness centrality). (b) Example use-cases of the highlighted topological properties. *While the shortest path as a topology measure was not directly used in the referenced papers, it is used to compute betweenness centrality, a topological measure that is relevant in the diagnostic prediction of autism (Kazeminejad & Sotero, 2019) and Parkinson's disease (Kazeminejad et al., 2017).

within biological networks (Ghiassian et al., 2015; Menche et al., 2015). Figure 2a illustrates the examples of commonly investigated topological graph properties.

2.1 | Group-level information

Graph structural properties may encode information that could be mechanistically important and useful in a precision medicine context, but may not be easily accessible by artificial intelligence methods applied to the underlying raw data. Therefore, utilizing such structural properties for ML constitutes a type of "feature engineering" where data are processed so that the resulting features may be more powerful predictors. However, there is an intrinsic difficulty in using such structural properties for ML as they are, depending on the data modality, often computed at the group and not the individual subject level. For example, genetic co-expression networks are computed based on the similarity of gene expression across subjects, resulting in

structural network estimates for the entire cohort that are not straightforward to use for individual-level prediction. Thus, in previous studies, topological network properties have often been used as feature selection methods prior to the application of ML to individual-level data. For example, the shortest-path between the nodes of a PPI network was investigated by Li et al. (2020) to select the most relevant genes for the prediction of high-risk malignancy in tumor samples. Similarly, Abbas et al. (2019) utilized topological properties such as betweenness centrality, closeness centrality, average neighbor node, clustering coefficient, and node resilience clustering measures to prioritize biomarker candidates of inflammatory bowel diseases and determine their utility for classification using random forest (RF) ML. Netzer et al. (2012) used topological measures such as node degree, local clustering coefficient, eccentricity (i.e., the maximum distance between the node and any other node), distance vertex deviation, and vertex entropy in a metabolic network to select the top metabolites as features to classify and differentiate individuals with obesity from controls using a support vector machine (SVM) algorithm. Similarly, Esfahlani et al. (2018) used the topological information of a symptom network to classify patients with schizophrenia with respect to therapeutic response. Specifically, the authors used the degree centrality (DC, the number of edges a given node has), as well as the closeness centrality, of the symptom network to select the symptoms to be used as features for classification. The authors compared two feature selection methods, one using network-based feature selection and the other using non-network-based feature selection such as ReliefF, SVMweight, and Information Gain, and found that network-based feature selection resulted in better classification accuracy.

2.2 | Individual-level graph information

Some data modalities allow the quantification of network properties directly at the individual subject level. MRI data, for example, have been frequently used for the determination of brain-structural and brain-functional network parameters, and several studies have utilized these properties as input for ML analysis. For example, Liu, Fang, et al. (2022) used DC, a topological measure of the functional connectivity of the brain network, to classify schizophrenia patients from healthy controls using an SVM classifier. The authors observed a classification accuracy of 84.2% and identified several brain regions including the bilateral putamen, left inferior frontal gyrus, left middle occipital cortex, bilateral middle frontal gyrus, left cerebellum, left medial frontal gyrus, left inferior temporal gyrus, and left angular as contributing the most to this classification task. Liu, Shu, et al. (2022) performed a similar analysis using DC measures as features to predict cognitive impairment in patients with obstructive sleep apnea. The authors also performed the analysis using several ML approaches including RF, logistic regression, and SVM, and found that SVM was most predictive with an area under curve of 0.78.

In addition to DC and CC, there are other topological properties that have been used as input features for ML approaches. For example, eigenvector centrality (EVC) measures the influence of a node in a given network. All the nodes are given relative scores based on whether they are connected to highly scored vectors. A high eigenvector score of a node denotes that the node is connected to many other nodes with high eigenvector scores. Sato et al. (2018) utilized EVC information from an fMRI-derived functional connectivity network to classify the brain networks into "typical" and "atypical" using one class support vector machines. It was found that an atypical brain functional network was related to higher levels of psychopathology.

Other topological properties frequently used in graph-based ML approaches are the shortest and the global characteristic path length, efficiency, small-worldness, and the clustering coefficient. The average length of the shortest path between two given nodes is called the global characteristic path length. Efficiency is a measure of how efficiently nodes are connected with each other. Small-worldness of a graph is described by a high modularity and efficiency. Kazeminejad and Sotero (2019) utilized these graph measures obtained from a brain connectivity network for differentiating individuals with autism from healthy controls. The comparison of feature importance illustrated that the centrality measures contributed most to classification. Kazeminejad et al. (2017) used similar measures for classifying brain networks from Parkinson's disease patients and healthy controls, from which the authors found that Parkinson's patients showed an increased change in characteristic path length and decreased efficiency. Also, Chaitra et al. (2020) showed that complex network measures of a functional connectivity network can be used in ML approaches to differentiate individuals with autism spectrum disorder (ASD) from healthy controls. In this work, the authors used a recursive cluster elimination (RCE)-based SVM. RCE clusters the features, scores each cluster based on their importance for classification, and then removes clusters with the lowest scores.

2.3 | Normative modeling approach in graphs

An interesting approach that may have utility for integrating group-level measures of graph properties into individual-level prediction is that of normative modeling (Rutherford et al., 2022). Normative models describe, analogous to child growth charts, an approach where the development of a given feature is modeled across the lifespan. This model is built on a large reference population of usually healthy individuals and allows the determination of individual-level deviations from this reference. Normative modeling has been widely applied in the neuroscience field, with a predominant focus on the analysis of neuroimaging data. However, normative models can also be determined on networks, such as genetic co-expression networks. In this case, such models describe the physiological range within which network effects occur and enable the determination of individual-level deviations from such a reference range. If such deviations capture group-level network properties, such as co-expression, they may also be useful to capture deviations from structural network features, such as node centrality or edge betweenness. Such topological measures

also help gain insights into biological hallmarks in psychiatry. (Alamro et al., 2023). utilized topological measures of a PPI graph constructed using differentially expressed genes such as the betweenness centrality, closeness centrality, and degree of the node to rank the genes to estimate the subset of biological markers in Alzheimer's. The authors determined 28 hub genes, of which several were consistent with previous findings such as brain-derived neurotrophic factor (BDNF) or amyloid precursor protein (APP).

2.4 | Network-based deep learning methods in psychiatry

Deep learning methods have been successfully used in many challenging ML tasks, from image classification (Krizhevsky et al., 2012; Wang et al., 2020) and speech recognition (Nassif et al., 2019) to computational biology (Angermueller et al., 2016) and disease diagnosis (Muzio et al., 2021). As deep learning methods are able to encode complex relationships between predictors in a coherent prediction framework, an interesting question is whether network information can be suitably integrated to support predictive performance and mechanistic understanding. One of such approaches are the so-called graph neural networks (GNNs), which are deep learning methods that use graphs as input. In node classification, GNNs predict labels for individual nodes, while in graph classification, GNNs assign labels to entire graphs. These networks employ iterative message passing between nodes, allowing them to capture relational information and update node representations based on the graph's structure. Architectures such as graph convolutional networks (GCN) excel at learning complex relationships within graphs, making them valuable for diverse applications such as predicting user interests in social networks or properties of molecular structures (Wu et al., 2020; Zhang et al., 2020; Zhou et al., 2020).

Typically, GNNs consist of three layer types: input layer, hidden layer, and output layer. In conventional GNNs, the number of hidden layers depends on aspects including the size of the graph, the complexity of the data, and others. Hernández-Lorenzo et al. (2022) implemented a GNN tool called GraphGym (You et al., 2020) on a PPI network that integrates the number of missense variants to predict an early diagnosis of Alzheimer's disease. There are several variants of GNNs, including the graph convolutional neural network (GCN), the graph attention neural network (GAT), and the graph recurrent neural network (GRN), which are further discussed below.

2.5 | Graph convolutional neural network

GCN was first introduced by Bruna et al. (2013) and these neural networks operate by aggregating the information from neighboring nodes with filters. GCN has been successfully applied to various biological networks for several applications. For example, Zhang et al. (2020) applied GCN to the graph representation of multi-modal brain imaging data to differentiate patients with Parkinson's disease from healthy controls. In another study, Rhee et al. (2018) used GCN for breast cancer subtype classification. The authors proposed a novel method that integrates GCNs and relational networks (RNs), which are the components of neural networks that capture the relationships among the data. Specifically, gene-expression data from patients were integrated with PPI networks, and this network structure was analyzed using GCN and RN. In this approach, GCN learns the local graph information, including the complex pattern among the nodes, whereas RN learns the relationship among those patterns. This method was shown to outperform SVM, RF, k-nearest neighbor, multinomial naive Bayesian, and Gaussian Naive Bayesian models. Similarly, Matsubara et al. (2019) proposed a method that combines spectral clustering with GCNs to predict lung cancer from a PPI network integrated with gene-expression data. Finally, Han et al. (2019) proposed a novel method combining GCN and matrix factorization with the aim of predicting gene–disease associations.

Several interesting variants of GCNs have previously been applied in psychiatric research. Song et al. (2022) implemented a multicenter and multichannel pooling GCN that integrated diffusion tensor imaging with resting-state functional magnetic resonance imaging (rs-fMRI) to diagnose early Alzheimer's disease. The authors constructed a brain functional connectivity network that was fused with diffusion tensor imaging (DTI). For the analysis of multi-site data, a multicenter attention graph was constructed using non-imaging information including age, data source, data acquisition mode, and disease status, as edge weights and a feature vector from the fused brain connectivity network as nodes. Furthermore, the authors divided the multi-attention graph into multiple subgraphs based on the importance of features using a multichannel algorithm. These subnetworks were then pooled into a single-layer GCN to perform the classification task. Zhu et al. (2023) used a similar approach that comprised a novel pooling approach to improve classification performance even on distorted images. The authors classified the functional connectivity networks of patients with major depressive disorder and controls and found that the method outperformed SVM, RF, and conventional GCN. The F1 score of the proposed method is 69.9%, whereas the F1 score of SVM and RF were 61.2% and 63.3%, respectively.

2.6 | Graph attention neural network

Another interesting variant of the GNN is the so-called GAT where each node in the neural network weights their connection based on the importance of the neighboring node (Velickovic et al., 2017). Xing et al. (2022) proposed a novel method based on multi-level graph attention graph neural networks. In this method, the authors utilized a weighted co-expression network of patients to explore the topological information and predict disease progression and diagnosis. The method outperformed conventional ML approaches such as SVM and random-forest. The F1 score of the proposed method was 72.99%, whereas the F1 score of SVM and RF were 58.08% and 69.93%, respectively.

2.7 | Graph recurrent neural network

GRN is another variant of GNNs, whereas it incorporates recurrent connections to capture temporal dependencies within the graph (Li et al., 2017). This principle makes GRNs quite effective for handling time-series data and predicting trends in a network. Dvornek et al. (2018) utilized time-series rs-fMRI data as an input and incorporated phenotype information in GRNs to classify ASD patients and neurotypical subjects.

In addition to GNNs, there are other deep learning methods that have been used for integrating biological network information. For example, Wang et al. (2018) proposed a deep Boltzmann machine (DBM) where the conditional and lateral connections were adapted based on a genetic co-expression network. A DBM consists of deep layer networks where each layer captures a complex, higher-order correlation of activation between the hidden layers below. Unlike other GNNs, the input nodes are connected with each other in DBM to efficiently share information among nodes. This model was subsequently applied to predict schizophrenia diagnosis based on genotype data and was shown to outperform other ML approaches including logistic regression, a conditional Boltzmann Machine, and a conditional deep Boltzmann machine (cDBM).

3 | FUTURE PERSPECTIVES

These studies demonstrate that network information has been used successfully as part of ML approaches in multiple model architectures and disease contexts. As discussed, graph-related information can be used for the engineering of features that can subsequently be used in conventional ML approaches. Similarly, graphs can be used directly as input for more advanced methods, such as GNNs.

While the integration of biological network information in these models can lead to increased predictive performance, they also give deeper insights into key regulatory processes underlying the studied phenotypes and thus support the biological validity of the identified models. This contributes to the "explainability" of the models and is particularly important for their potential downstream translation into clinical use. Selecting important features that contribute to successful network-based ML approaches is a critical step in this context. For example, Chaitra et al. (2020) identified the fMRI features contributing most to a graph-based classification of ASD and identified a pronounced role of the prefrontal, lateral temporal, and parietal cortices on the classification. Similarly, in a study using topological information from the rs-fMRI functional network to classify Parkinson's disease, the most predictive features were identified and found to include the precuneus and cuneus and were found to be associated with a high metabolic reduction in patients (Kazeminejad et al., 2017). While these approaches to support the interpretability of network-based ML models via feature selection fall within the context of classical ML, and are comparatively straightforward from a computational perspective, this often does not apply to more complex approaches, such as GNNs. Here, universal approaches to explain predictions are lacking, and the "black-box" nature of the algorithm as well as the often complex graph structure may necessitate a model interpretation on a case-by-case basis. In a study using gene co-expression networks on multi-level attention graphs for diagnostic classification, the authors introduced a novel full gradient saliency (FGS) method to interpret the model (Zhang et al., 2020). One of the datasets used by this model was the co-expression network constructed from COVID/non-COVID patients' sera for diagnostic prediction. The FGS method was used for the extraction of the top 40 genes contributing to successful classification and enrichment analysis of the 40 genes revealed that they are involved in lipid transport, platelet activation, and other pathways of potential relevance for COVID. In another study, a deep learning model, the deep structured phenotype network (DSPN), was used to predict a phenotype from genotype and gene-expression data (Wang et al., 2018). Model interpretation was performed by identifying the connections that were modified during the learning process by DSPN. Enrichment analysis of the genes contributing to the successful classification of schizophrenia identified several pathways to be of importance, including glutamatergic-synapse and cascade pathways. While improved model explainability can support the biological validity and trustworthiness of the models, it may also help to identify and mitigate potential biases arising during data collection.

The ML and deep learning models reviewed in this paper bear substantial promise for application in psychiatry, as they capture the dependency between related features and may thus be suitable to account for the complexity of mental illness both through the integration of features within, but also across, data modalities. This may, on one hand, make algorithms more predictive, because they can be geared toward feature combinations that are more illness-relevant. On the other hand, it may also aid in the discovery and validation of illness mechanisms. If mechanistically relevant information such as biological processes relevant for, for example, synaptic functioning (Faskowitz et al., 2022), can be encoded in graph form, the application of graph-based ML may allow testing its relevance in a prediction setting and, for example, allow the identification of patient subgroups that are particularly affected by such mechanisms. Previous studies have focused, for example, on the derivation of illness-relevant knowledge graphs that encode mechanistic information based on text mining of the scientific literature. Encoding such networks in artificial intelligence approaches could guide such models toward biological dimensions that are likely relevant to illness.

Another interesting perspective of integrating graph information into ML approaches is that it may reveal changing network configurations during critical age periods and make these networks amenable for individual-level prediction. As normative models have been used to capture the trajectory of physiological variables across the lifespan and measure individual-level deviations thereof, it is conceivable that, for example, graph neural networks can capture systems-level network information and its evolution across the lifespan. This may aid in more precisely characterizing mechanistic effects and their development across time, and allow the definition of individual-level, developmental trajectories with respect to the underlying network configurations. This could, in turn, be useful not only from

personalized psychiatry and early risk stratification perspective but also for the identification of relevant mechanistic effects that may be relevant only during specific developmental periods.

4 | CONCLUSION

Integrating graph information into ML applications is a promising approach toward improving our understanding of illness biology in psychiatry and advancing personalized medicine. Here, we described approaches that focus on integrating graph topological properties as features into supervised ML, as well as on methods that integrate graphs directly into the learning process. ML techniques, in particular in the area of deep learning, may, in principle, learn complex dependencies from the data without the need for graph information. However, assisting the learning process with such information may be an effective means to guide AI models toward signatures that are more illness-relevant, predictive, and reproducible. Future developments that capture how complex biological and phenotypic networks evolve along critical age periods may help us shed light on the biological hallmarks that contribute to illness susceptibility and uncover novel targets for therapeutic development.

AUTHOR CONTRIBUTIONS

Sivanesan Rajan: conceptualization; investigating; writing and editing - original draft preparation. **Emanuel Schwarz:** conceptualization; writing; review and editing - original draft preparation; supervision.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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