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Predicting treatment response in adolescents and young adults with major depressive episodes from fMRI using graph isomorphism network

Jia Duan [a,1], Yueying Li [b,1], Xiaotong Zhang [b], Shuai Dong [c], Pengfei Zhao [d], Jie Liu [d], Junjie Zheng [d], Rongxin Zhu [d], Youyong Kong [b,e,*], Fei Wang [d,a,*]

[a] Department of Mental Health, School of Public Health, Nanjing Medical University, Nanjing, China
[b] Jiangsu Provincial Joint International Research Laboratory of Medical Information Processing, School of Computer Science and Engineering, Southeast University, Nanjing, China
[c] School of Biomedical Engineering and Informatics, Nanjing Medical University, Nanjing, China
[d] Early Intervention Unit, Department of Psychiatry, The Affiliated Brain Hospital of Nanjing Medical University, Nanjing, China
[e] Key Laboratory of Computer Network and Information Integration, Southeast University, Ministry of Education, Nanjing, China

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ABSTRACT

Background: Major depressive episode (MDE) is the main clinical feature of mood disorders (major depressive disorder and bipolar disorder) in adolescents and young adults and accounts for most of the disease course. However, 30%-40% of MDE patients not responding to clinical first-line interventions. It is crucial to predict treatment response in the early stages and identify biomarkers associated with treatment response. Graph Isomorphism Network (GIN), a deep learning method, is promising for predicting treatment response for individual MDE patients with more powerful representation ability to capture the features of brain functional connectivity.

Methods: In this study, GIN was used to predict individual treatment response in 198 adolescents and young adults with MDE. The most discriminating regions were also identified for the treatment response prediction.

Results: Using GIN approach, the baseline functional connectivity could predict 79.8% responders and 67.4% non-responders to treatment (accuracy 74.24%). Furthermore, the most discriminating brain regions were mainly involved in paralimbic and subcortical areas.

Conclusions: GIN has shown potential in predicting treatment response for individual patients, which may enable personalized treatment decisions. Furthermore, targeted interventions focused on modulating the activity and connectivity within paralimbic and subcortical regions could potentially improve treatment outcomes and enable personalized interventions for adolescents and young adults with MDE.

1. Introduction

Mood disorders, as major depressive disorder (MDD) or bipolar disorder (BD), are a common mental disorder that often occur in adolescents and young adults (Nesvåg et al., 2018). In recent years, there has been a rapid increase in the incidence of mood disorders in this population (Costello et al., 2006; Beesdo et al., 2009). Major depressive episode (MDE) is the main clinical feature of mood disorders in adolescents and young adults. Most BD patients present with a MDE as their first mood episode (Tondo et al., 2010; Etain et al., 2012), and MDE accounts for most of the disease course (Judd et al., 2002; Judd et al., 2003). A considerable proportion of adolescents and young adults diagnosed with MDD will ultimately develop BD (Uchida et al., 2015; Uchida et al., 2015; Yatham et al., 2018), posing a clinical challenge in distinguishing BD from MDD. Therefore, a specific focus on MDE in mood disorders is of clinical relevance. MDE is also the most correlated psychiatric illness with increased suicide risk, with about 65 % of MDE patients having suicidal ideation (Lutz et al., 2017; Cavanagh et al., 2003). This poses a serious threat to the life and health safety of adolescents and young adults. Furthermore, clinical treatment for MDE in

* Corresponding authors at: Early Intervention Unit, Department of Psychiatry, The Affiliated Brain Hospital of Nanjing Medical University, Nanjing 210000, Jiangsu, PR China (Fei Wang). Jiangsu Provincial Joint International Research Laboratory of Medical Information Processing, School of Computer Science and Engineering, Southeast University, Nanjing 210000, Jiangsu, PR China (Youyong Kong).
E-mail addresses: kongyouyong@seu.edu.cn (Y. Kong), fei.wang@yale.edu (F. Wang).
[1] These authors contributed equally to this article.

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this population is more complex, with 30 %-40 % of MDE patients not responding to clinical first-line interventions (March et al., 2004; Brent et al., 2008; Dwyer et al., 2020). Therefore, it is crucial to predict treatment response in the early stages and identify biomarkers associated with treatment response, which is essential for adjusting future treatment targets and improving treatment efficacy.

A large body of literature indicates that brain functional connectivity has shown potential in predicting treatment response in MDE (Taylor et al., 2021; Cohen et al., 2021; Fischer et al., 2016; Martens et al., 2021). Some studies found that increased rostral anterior cingulate cortex activity was a predictor of treatment response in depression (Pizzagalli, 2011). Another studies found that functional connectivity between the dorsolateral prefrontal cortex and the subgenual cingulate predicts antidepressant response (Weigand et al., 2018; Cash et al., 2019). With the development of deep learning and graph neural networks (GNN) in recent years, an increasing number of studies have begun to apply these methods to psychiatric disorders (Kong et al., 2021; Chang et al., 2021; Choi et al., 2021). Graph Isomorphism Network (GIN), as one of GNN (Scarselli et al., 2009) variants, is proposed for implementing the Weisfeiler-Lehman (WL) (Weisfeiler and Leman, 1968) graph isomorphism test in GNNs. The network structure design of GNN models is usually derived from experience, and the amount of experience directly affects the quality of the final network structure, which makes the learning of graph representation and network design difficult. In this case, GIN proves that GNN can work in the best case with the WL test (Xu et al., 2018). In GIN, node embeddings are obtained by aggregating the node's own features and embeddings of its neighboring nodes, which are then nonlinearly transformed by multi-layer perceptron to capture the local information of the node better than graph convolutional network (GCN). GIN is particularly promising for predicting treatment response in MDE with more powerful representation ability to capture the features of functional connectivity (Kim and Ye, 2020), and identify brain regions that are most pertinent to treatment response.

Deep learning methods have recently been used to predict individual responses in depression using imaging data. Nguyen et al. used brain functionality to evaluated 800 distinct neural networks models on 37 MDD patients, and identified the 10 most important regions (Nguyen et al., 2019). They also used deep learning to predict antidepressant outcomes using fMRI and to form multimodal treatment biomarkers (Nguyen et al., 2022). A spatiotemporal GCN framework was developed to learn discriminative features from functional connectivity for antidepressant response prediction (Kong et al., 2021). There was also study that combined fMRI connectivity with deep learning techniques to predict treatment response of repetitive transcranial magnetic stimulation in MDD patients (Squires et al., 2023). However, these studies have been conducted on adults patients, with little focus on adolescents and young adults.

In this study, we used GIN, a deep learning method, to learn discriminative features from functional connectivity in order to automatically predict treatment response for adolescents and young adults with MDE. We also aimed to identify the brain regions that are most discriminative for treatment response prediction, which may be the predictive imaging biomarker for the early identification of treatment efficacy in adolescents and young adults with MDE.

2. Materials and methods

2.1. Participants

The study was conducted at a single site and included 198 adolescents and young adults mood disorder patients (MDD and BD, currently in major depressive episode) aged 13 to 25 years. All participants were recruited from the inpatient services at Nanjing Medical University Affiliated Brain Hospital. The study was approved by the Medical Science Research Ethics Committee of the Nanjing Medical University Affiliated Brain Hospital (approval reference number 2020-KY027-01). All participants provided written informed consent by themselves or by their parents/guardians if they were under 18 years old after a complete description of the study.

All participants were evaluated by 2 trained psychiatrists to determine the presence or absence of Axis I psychiatric diagnoses using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders-IV-Text Revision (DSM-IV) Axis I Disorders (SCID) in those 18 years old and older and the Schedule for Affective Disorders and Schizophrenia for School-Age Children-present and Lifetime Version (K-SADS-PL) in those younger than 18 years. Symptom severity was measured using the 17-item Hamilton Depression Rating Scale (HAMD-17) both at baseline and after 2 weeks of treatment.

All patients met the following inclusion criteria: (1) met DSM-IV diagnostic criteria for MDD or BD and not any other Axis I disorder, (2) currently in major depressive episode, (3) baseline HAMD-17 total score $\geq$ 17. Participants were excluded if any of the following were present: (1) the existence of substance/alcohol abuse or dependence or concomitant major medical disorder, (2) any magnetic resonance imaging (MRI) contraindications, and (3) history of head trauma with loss of consciousness for $\geq$ 5 min or any neurological disorder.

2.2. Treatment and measurement

Following baseline scans and clinical assessment, participants received 2 weeks of real-world, standardized acute treatment. Depending on the patient's condition, appropriate medication was prescribed by each patient's clinician. Medication includes mood stabilizer, antipsychotics and sedative-hypnotic, based on clinical guidelines and standard practice in the treatment of adolescent mood disorders (Dwyer et al., 2022; Tournier et al., 2019). It should be noted that, as a real-world study, we did not interfere with the patients' medication strategies. The medication details can be found in Table 1.

The primary outcome was measured through HAMD total score. HAMD is the most widely used clinician-administered depression

Table 1
Demographics and medication information of patients.

	ALL (n = 198)	Responders (n = 109)	Non-responders (n = 89)	t/χ^2 Values	*P* Values
Age at scans (year)[a]	15.58 ± 2.03	15.46 ± 2.07	15.72 ± 1.99	0.896	0.37
Gender (male, %)[b]	49 (24.7 %)	26 (23.9 %)	23 (25.8 %)	0.104	0.75
Years of education[a]	9.44 ± 2.37	9.23 ± 2.38	9.69 ± 2.34	1.27	0.20
HAMD total score at baseline	24.53 ± 4.78	25.78 ± 4.99	23 ± 4.04	4.24	0.001*
Post-treatment HAMD total score	11.77 ± 5.06	8.71 ± 3.64	15.53 ± 3.88	12.74	0.001*
Medication					
Mood stabilizer (%)[b]	180 (90.9 %)	98 (89.9 %)	82 (92.1 %)	0.18	0.67
Antipsychotics (%)[b]	178 (89.9 %)	98 (89.9 %)	80 (89.9 %)	0.45	0.51
Sedative-hypnotic (%)[b]	92 (46.5 %)	52 (45.9 %)	40 (44.9 %)	0.26	0.61

Data are presented as either n (%) or means ± standard deviations.
[a]Two sample *t*-test between responders and nor-responders.
[b]Chi-square between responders and nor-responders.
*$P < 0.05$.
MDD, major depressive disorder.

assessment and treatment response definition scale (Rost et al., 2023), with high inter-observer agreements (Hamilton, 1976; Hamilton, 1960).

Percent of symptom reduction was calculated as percent change from HAMD baseline ([baseline HAMD score – Post-treatment HAMD score]/ baseline HAMD score *100 %). The responders were defined as ≥ 50 % reduction from the baseline score, and the remaining patients were classified as non-responders.

2.3. MRI data acquisition and processing

The baseline fMRI data were acquired in a SIEMENS Magnetom Prisma 3.0 T scanner. Functional images were collected with a gradient-echo planar imaging (EPI) sequence. The parameters were as follows: TR = 500 ms, TE = 30 ms, flip angle = 60, field of view = 224 × 224 mm^2, matrix = 64 × 64, time points = 960. Thirty-five axial slices were collected with 3.5 mm thickness with 0.5 mm gap. The scan lasted for 8 min and 7 s. Participants were instructed to rest and relax with their eyes closed but remain awake during scanning.

Preprocessing of all R-fMRI images was performed using SPM12 (https://www.fil.ion.ucl.ac.uk/spm/) and DPARSF (Yan and Zang, 2010). The first 10 time points were discarded for magnetic field stabilization and allowing participants to adapt to the scanning environment. The subsequent preprocessing steps included slice time correction and head motion correction. Next, the corrected functional images were normalized to Montreal Neurological Institute (MNI) space using the EPI template in SPM12, resampled to 3 mm isotropic voxels, and further smoothed via a Gaussian kernel with a 6 mm full-width at half-maximum. Linear detrending was performed and several confounding covariates, including the Friston-24 head motion parameters, white matter, cerebrospinal fluid, and global signals, were regressed from the BOLD time series for all voxels. Finally, temporal band-pass filtering (0.01–0.8 Hz) was applied to the regressed fMRI data.

Construction of functional connectivity matrices was also performed by DPARSF using the anatomical automatic labelling atlas (AAL-90). Each region represented a node of the function network. Fisher's z-transform was performed to convert the data into z-values for normal distribution, which represented the edges of network. A graph (90 × 90 connectivity matrix) was calculated for each participant. Considering the sparsity of the connections between brain regions, we used sparse maps for composition. Following the approach of previous literature (Kim et al., 2021; Li et al., 2021; Sebenius et al., 2021); the adjacency matrix A of a connected graph was obtained by thresholding the top specific percentile values of functional connectivity matrix as connected, and otherwise unconnected. We take the top 20 % FC matrix as the sparse matrix and input the binarized sparse matrix into the network as the final adjacency matrix. The result of the quantified proportion, the adjacency matrix, was then input into the network.

2.4. Graph isomorphism network

Recently, graph convolutional network has become a powerful and promising framework for processing the non-Euclidean graph data. The human brain can be naturally modelled as graph with each brain region as node and the connectivity between brain regions as edges. The connections of the current brain region with other brain regions was the node feature of the current node, and the 0–1 binarized functional connectivities (FCs) were the edges between nodes. Therefore, the human brain can be thus represented as a graph $G = (V,E)$ with node feature vector Xv for node $v \in V$. In this paper, G represents the constructed subject brain network, V represents brain regions, and E represents the correlation between brain regions. Given a set of graphs $\{ G_1, \ldots, G_N \} \in G$ and their labels $\{ y_1, \ldots, y_N \} \in Y$, our goal is to learn a representation vector h_G to predict the label of the graph G.

The powerful GNN models use the topological structure and node feature to learn the representation of the graph G or the node feature Xv. Most GNNs use the neighborhood aggregation strategy, which iteratively updates the representation of nodes by aggregating the representation of neighbors. After k iterations, the node can obtain structural information about its k-hop neighbors. The k-th layer of a GNN can be expressed as the following equation,

$$a_v^{(k)} = AGGREGATE^{(k)}\left(\left\{ h_u^{(k-1)} : u \in N(v) \right\}\right) \tag{1}$$

$$h_v^{(k)} = COMBINE^{(k)}\left(h_v^{(k-1)}, a_v^{(k)}\right) \tag{2}$$

where $h_v^{(k)}$ is the feature vector of node v on k-th layer. We initialized $h_v^{(0)} = Xv$, and $N(v)$ was the neighbor node set with v. Finally, the features of all nodes in the graph are transformed into graph features by readout function for classification tasks:

$$h_G = READOUT(\{h_v^{(K)}\}_{v \in V}) \tag{3}$$

In brain networks, brain regions with similar structures (isomorphism tests or similarity calculations) may have similar functional properties. Therefore, the effective identification of brain regions with similar structures is of great significance for the analysis of brain diseases. However, the upper limit of GNNs in distinguishing graph structure is the WL test algorithm, which detects whether two graphs are isomorphic by the number of nodes with edges and the connection of edges in the two graphs. To make a GNN as powerful as the WL test algorithm, the powerful GNN does not map two different neighborhoods to the same representation, which means that its aggregation pattern must be injective. GIN aggregates neighbor nodes by acting on multiset injector functions, which improves the learning ability of graph convolutional neural networks on homomorphic graphs. It iteratively aggregates and updates node characteristics using the following formula,

$$h_v^{(k)} = MLP^{(k)}\left((1 + \varepsilon^{(k)}) \times h_v^{(k-1)} + \sum_{u \in N(v)} h_u^{(k-1)}\right) \tag{4}$$

where ε is a learnable or fixed parameter. Brain regions are considered as nodes, and each subject is considered as a graph. For the graph treatment response prediction, given the features of all nodes on the graph, we used the following readout function to obtain the graph-level representation,

$$h_G = \left(SUM(\{h_v^{(k)} | v \in V\}) | k = 0, 1, \cdots, K\right) \tag{5}$$

where h_G was the graph feature learned for each subject. Finally, we used linear layers and log-softmax function to classify features.

2.5. Graph prediction with graph isomorphism network

We used a GIN model for the treatment response prediction. The main framework is illustrated in Fig. 1. GIN model generates graph embeddings to characterize a single graph based on the graph topology structure and node features. The input to the GIN model is G=(N,E), where G represents an undirected graph of an FC matrix, with $n = 90$ nodes obtained from the AAL atlas, E represents the Pearson coefficient between different nodes. The node features aggregated from GIN layers are entered to the multi-layer perceptron (MLP, a class of feedforward artificial neural network) and summation operations. Subsequently, the graph is embedded in the last layer with the log-softmax activation function to generate predictions.

We evaluated the generalizability of the model using ten-fold cross-validation method. K-fold cross-validation is a data splitting technique defined as a method used to estimate model performance on unseen data.Using k > 1 fold can achieve sample division for different purposes so that models with optimal hyperparameter values can be trained. For small sample cases data, overfitting can occur when training a model with all data. By using k-fold cross-validation, the ability to "test" the model on k different datasets helps avoid overfitting. We employed ten-fold cross-validation to evaluate the generalization performance of the

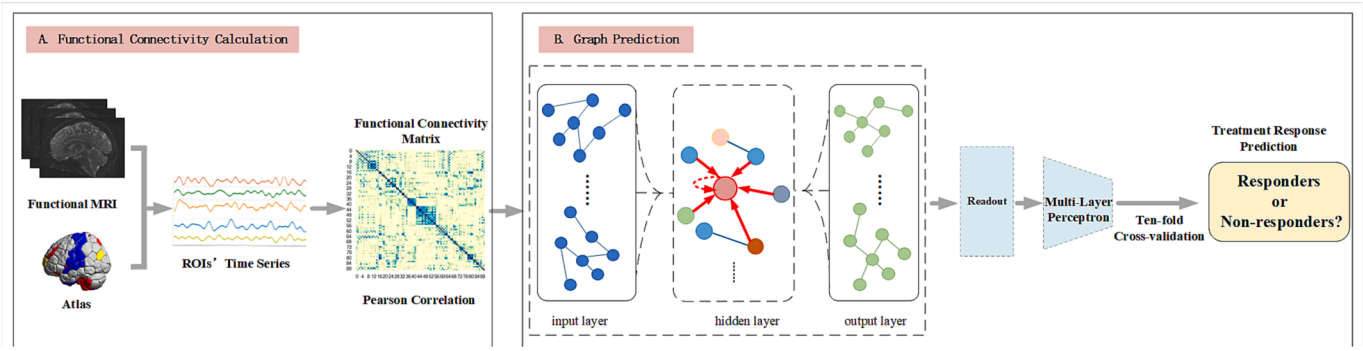

Fig. 1. The framework of the Graph Isomorphism Network (GIN) for predicting treatment response in adolescents and young adults with MDE.

model. All participants were randomly divided into ten parts and the holdout test method was repeated 10 times. Finally, a confusion matrix provided the basis to calculate the prediction performance metrics including accuracy, sensitivity, and specificity. Areas under the receiver operating characteristic (ROC) curve (AUC) was also calculated.

2.6. Most discriminative regions

The most discriminating regions were calculated for the treatment response prediction. We used the attention mechanism to assign weights for brain regions in all samples as shown in Eq. (6). d_k is the dimension of the key vector, and $\sqrt{d_k}$ is a scaling factor in the attention mechanism. For each brain region, the weights were averaged on the 10-fold cross-validation. According to the weights, the top 10 brain regions were retained as the most discriminating regions for the treatment response prediction.

$$att(X) = softmax(\frac{XX^T}{\sqrt{d_k}}) \tag{6}$$

3. Results

3.1. Demographics

There was no significant differences in age, sex, education and medication between the responders and non-responders groups. Significant difference was observed in HAMD total score ($t = 4.24$, $P < 0.05$, Table 1).

Demographic and medication detailes are provided in Table 1.

3.2. Predictive model performance

Based on the percent of HAMD total score reduction, the baseline functional connectivity could predict 79.8 % responders and 67.4 % non-responders to treatment. The GIN achieved the performance with accuracy of 74.24 %, sensitivity of 79.82 %, and specificity of 67.42 % for the treatment response prediction in adolescents and young adults with MDE (Fig. 2). The AUC of predictive model was 0.74.

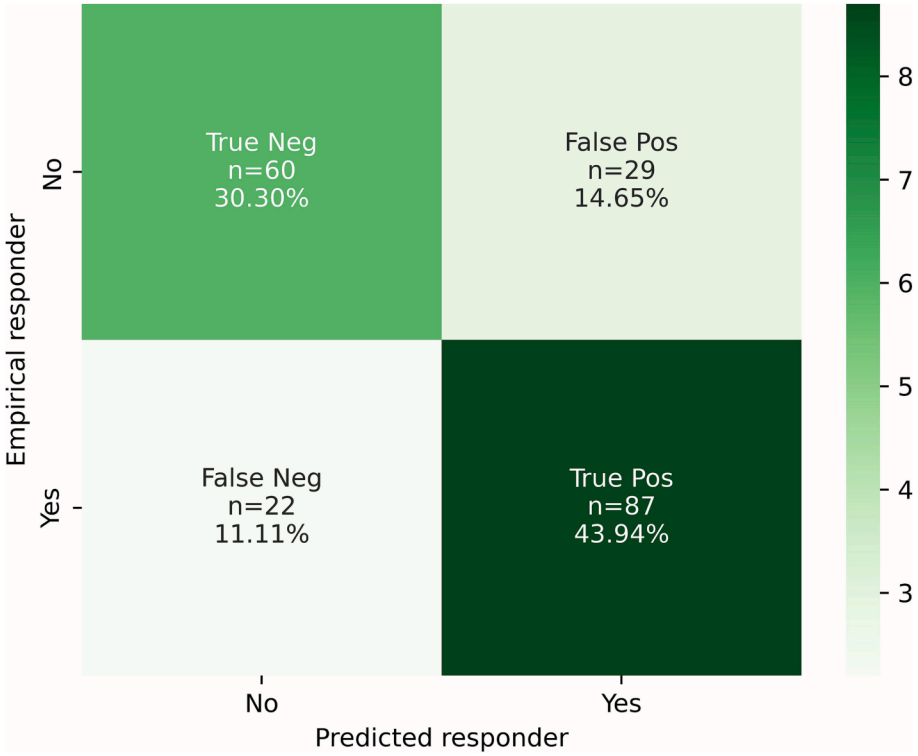

Fig. 2. Prediction of treatment response using GIN model. A confusion matrix for treatment response prediction. Pos, positives; Neg, negatives.

3.3. Most discriminative regions

We further analyzed the most discriminating regions for the treatment response prediction in adolescents and young adults with MDE. The most discriminating regions for treatment response prediction include the bilateral insula (INS), bilateral putamen (PUT), left anterior cingulate and paracingulate gyri (ACG), right orbital part of right inferior frontal gyrus (ORBinf), left rolandic operculum (ROL), right amygdala (AMG), right postcentral gyrus (PCG), right median cingulate and paracingulate gyri (MCG) (Fig. 3).

3.4. Comparasion with other deep learning methods

We have also compared our method with other basic deep learning methods: BrainGNN (Li et al., 2021), Functional Graph Discriminative Network (FDGN) (Li et al., 2021) and Multi-layer Perceptron (MLP). The results showed that GIN has achieved the best prediction performance in evaluation indicators such as accuracy compared with other methods (Table 2).

Table 2
Comparison with different deep learning methods.

Methods	Accuracy (%)	Sensitivity (%)	Specificity (%)	F1-score (%)	Auc (%)
MLP	55.47	62.65	47.11	59.54	54.88
BrainGNN	54.88	74.22	56.20	69.34	65.21
FGDN	65.68	76.18	52.36	70.17	64.27
GIN	74.24	79.82	67.42	77.06	73.50

MLP, Multi-layer Perceptron; GNN, Graph Neural Networks; FDGN, Functional Graph Discriminative Network;GIN, Graph Isomorphism Network.

4. Discussion

To the best of our knowledge, this is the first study to apply the GIN approach to predicts treatment response in MDE using functional connecitvity. The use of GIN allowed us to analyze and interpret the complex patterns of connectivity in the brain, and the predictive model allowed classification of patients into responders and non-responders with an accuracy of 74.24 %. This finding provides valuable insights into the predictive potential of baseline functional connectivity for treatment response in adolescents and young adults with MDE. Furthermore, the most discriminating brain regions were mainly involved in paralimbic and subcortical areas, suggesting their potential importance in the underlying neural mechanisms associated with treatment response.

In order to optimize patient care, reduce treatment resistance, and shorten duration of illness, developing models that predict treatment response on individual patient level is an urgent task (Rost et al., 2023). Our GIN predictive model's performance, with a relatively high accuracy of 74.24 %, sensitivity of 79.82 %, and specificity of 67.42 %, highlights the potential clinical utility of utilizing baseline functional connectivity as a biomarker for treatment response prediction in adolescents and young adults with MDE. In a recent study, Squarcina et al (Squarcina et al., 2021) provided a comprehensive review of research on use deep learning methods to predict response to treatment in depression. Compared to most of the studies in this review, our prediction model shows relatively better performance. This highlights the potential of our approach, utilizing the GIN method, in improving the accuracy and effectiveness of treatment response prediction in depression. Moreover, the prediction model can assist clinicians in making informed decisions and promptly adjusting treatment strategies (such as employing invasive electroconvulsive therapy) for patients who do not respond to standard treatments.

Interestingly, the most discriminating brain regions identified in this study predominantly located in paralimbic and subcortical areas. These regions, including the bilateral insula (Gasquoine, 2014), bilateral putamen (Sacchet et al., 2017), bilateral cingulate and paracingulate gyri (Fornito et al., 2004), right orbital part of the inferior frontal gyrus (Hampshire et al., 2010), left rolandic operculum (Koelsch and Fritz, 2006), right amygdala (Phelps and LeDoux, 2005); and right postcentral gyrus (Hattingh et al., 2013), have been consistently implicated in emotional regulation, reward processing, cognitive control, and

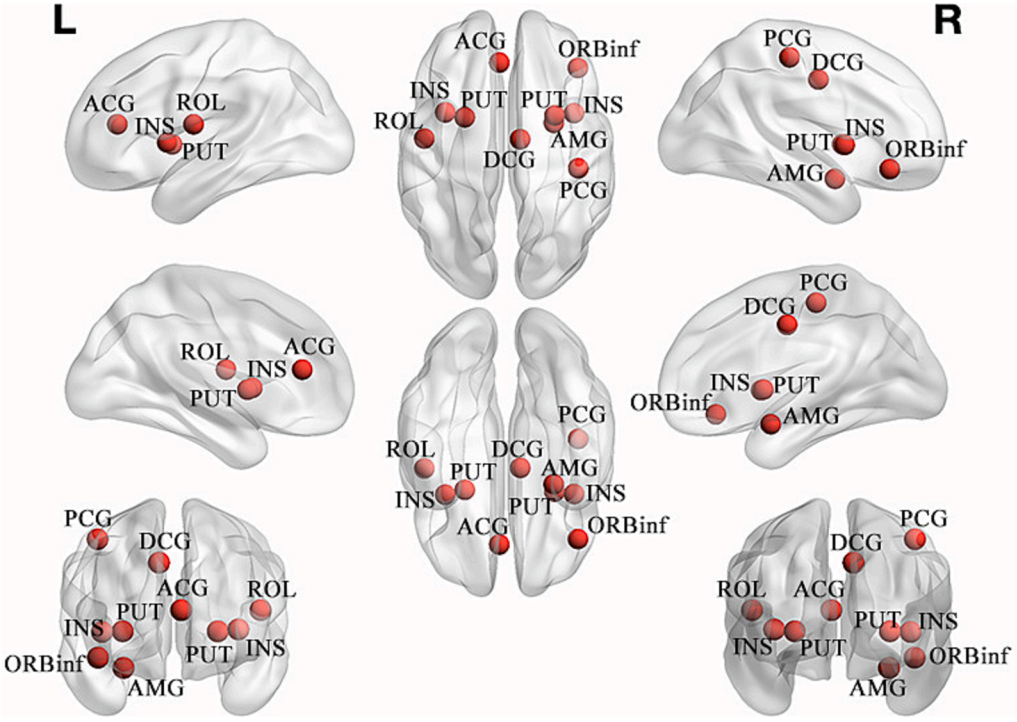

Fig. 3. The most discriminating regions for treatment response prediction. INS, insula; PUT, putamen; ACG, anterior cingulate and paracingulate gyri; ORBinf, orbital part of right inferior frontal gyrus; ROL, rolandic operculum; AMG, amygdala; PCG, postcentral gyrus; MCG, median cingulate and paracingulate gyri.

decision-making.These most discriminating regions provides valuable insights into potential targets for interventions aimed at enhancing treatment response in individuals who are less likely to respond initially. Targeted interventions focused on modulating the activity and connectivity within these regions could potentially improve treatment outcomes and personalize interventions for adolescents and young adults with MDE.

However, several limitations should be acknowledged in this study. First, the sample size was moderate, which may limit the generalizability of our findings. Future multicenter studies with large patient samples that represent clinical heterogeneity are needed to validate the robustness and reliability of our predictive model. Additionally, our study focused specifically on adolescents and young adults with MDE, and caution should be exercised when generalizing these findings to other age groups. The using of AAL atlas might also introduce limitations due to the predefined anatomical regions, and different atlas could be used in the future to furter valide the prediction results. Finally, the assessment of efficacy in this study was conducted two weeks after treatment. Therefore, it is not feasible to anticipate the mid- and long-term effects or the final outcome for patients.

In conclusion, our study contributes to the growing body of research on predicting treatment response in adolescents and young adults with MDE using neuroimaging. This GIN predictive model, which based on baseline functional connectivity patterns, exhibits potential to become a clinical decision support tool aimed at reducing unsuccessful treatments and improving treatment efficacy and efficiency. Furthermore, targeted interventions focused on modulating the activity and connectivity within these paralimbic and subcortical regions could potentially improve treatment outcomes and enable personalized interventions for adolescents and young adults with MDE.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Ethical Considerations

All participants provided written informed consent by themselves or by their parents/guardians if they were under 18 years old after a complete description of the study.

Author contributions

FW and YK conceptualized and supervised the study. PZ, JL, JZ and RZ participated in the acquisition and interpretation of the data. JD, YL, XZ and SD contributed to the data analyses. Data interpretation and manuscript preparation were undertaken by JD and YL. All authors contributed to the article and approved the manuscript submission.

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