Graph-Based Analysis of Brain Connectivity in Children and Adolescents Diagnosed with Major Depressive Disorder Compared to Aged-matched Healthy Control: An EEG Study

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Major Depressive Disorder (MDD) is a complex and heterogeneous psychiatric condition that affects individuals across the lifespan, from childhood to old age [1]. Its widespread prevalence worldwide highlights the urgent need for advancements in early diagnosis and improved treatment strategies, particularly in pediatric populations. Achieving accurate early diagnosis, especially through electroencephalography (EEG), demands a multidisciplinary approach that brings together expertise in neuroscience, psychology, and computational methods. This collaborative effort is essential to meet the needs of both researchers and clinicians in addressing the challenges of MDD. In this research, in line with our previous studies focused on MDD [2, 3, 4], we employ a graph-based network applied to resting-state EEG Functional Connectivity (FC) to investigate and gain deeper insights into the brain networks involved in MDD in children and adolescents. Graph-based networks are among the most widely used deep learning models for representing graph data structures, such as networks, due to their exceptional ability to handle complex pairwise relationships [5, 6]. These relationships span both imaging and non-imaging features across different subjects, enabling more detailed and comprehensive data analysis [7]. The motivation behind this research is to enhance classification diagnostic models for MDD in children and adolescents by comparing them with healthy, age-matched controls. While most studies have focused on fMRI data, we emphasize the use of high-density EEG, a non-invasive and widely recommended method with high temporal resolution for measuring brain functional activity [8].

METHOD

In this research, we developed a comprehensive pipeline for EEG data pre-processing and connectivity model computation. The pre-processing was divided into two main steps: EEG data preparation and connectivity model calculation. The EEG pre-processing steps closely followed the methodology described in [2], including detecting bad-channels, interpolation, resampling, filtering, re-referencing, and up to the removal of bad artifacts using Independent Component Analysis (ICA). EEG data was segmented into chunks of 4,000 samples (equivalent to 15.6 seconds per segment). For each segment, a Multi-Variate Auto-Regressive Independent Component Analysis (MVARICA) model [9] was fitted to the data. The model's hyperparameters were optimized before fitting on each EEG chunk independently, under the assumption that the EEG signals were non-stationary. Once the MVARICA model was fitted to the segmented EEG data, it was possible to compute several connectivity measures. The noise covariance matrix and model coefficients extracted from the MVARICA model were used to calculate various connectivity measures, including Coherence, Partial Coherence, Partial Directed Coherence (PDC), full-frequency PDC (ffPDC), PDC factor, generalized PDC (gPDC), Directed Transfer Function (DTF), full-frequency DTF (ffDTF), dDTF, and generalized DTF (gDTF) across all channels in both directions. These connectivity measurements were then divided into specific frequency bands: Delta (1–4 Hz), Theta (4–8 Hz), Alpha (8–12 Hz), Beta (12–30 Hz), and Gamma (30–70 Hz). The model was trained using data from the Healthy Brain Network (HBN) [10], which comprised 214 datasets of children and adolescents aged 5 to 21. Among these, 44 participants were diagnosed with MDD, and 170 were classified as healthy. During the model training process, the input data was structured in a tabular format, with rows representing segmented data samples from each participant across the different frequency bands and connectivity channel interactions. The final dataset consisted of 31,290 rows: 4,995 from individuals with MDD and 26,295 from typically developing participants. The

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columns represented attributes, which included the connectivity measurement for each channel interaction (11,881 attributes per measurement). A Random Forest model was employed using 5-fold cross-validation, with data split subject-wise, and class weights were applied to address the issue of class imbalance. The performance metrics used to evaluate the model included F1-Score, Cohen's Kappa, and Matthews Correlation Coefficient (MCC). The best model was selected based on the highest F1-Score achieved across all folds. Furthermore, the Random Forest model provided a ranking of attribute importance through the Gini importance method, allowing for insight into the most relevant connectivity features for classification.

Results and Discussion

Table 1. Random Forest testing score in each connectivity measurement, channelwise

Connectivity Measurement	F1 Scores	MCC	Cohen Kappa
COH	0.451	0.491	0.395
Real COH	0.481	0.512	0.423
PC	0.892	0.876	0.869
Real PC	0.921	0.907	0.903
PDC	0.954	0.945	0.943
PDC Factor	0.975	0.970	0.969
ffPDC	0.964	0.956	0.955
gPDC	0.942	0.930	0.928
DTF	0.836	0.816	0.802
ffDTF	0.819	0.796	0.782
dDTF	0.848	0.827	0.816
gDTF	0.813	0.793	0.776

Our model demonstrated strong performance, as shown in Table 1, achieving an F1-Score of 0.975, a MCC of 0.970, and a Cohen's Kappa score of 0.969 for the PDC Factor. In comparison, the DTF and its related measurements performed worse than PDC and its variants. This is likely due to data limitations during the construction of the MVARICA model. We suggest adjusting the segmentation threshold to improve the performance of DTF and related metrics while maintaining sufficient training data for effective model optimization. Interestingly, connectivity measurements that exclude indirect influences outperformed those that included them. This can be attributed to the nature of direct measurements, which more explicitly capture causal interactions. Graph-based models, such as those used in this study, tend to excel in environments where causal interactions are central, as emphasized by [11]. Furthermore, the best-performing model highlighted notable channel interactions, specifically between E115-E111 and E67-E67, as shown in Figure 1. These findings underscore the potential of using direct connectivity measures, like the PDC Factor, to capture key interactions relevant to distinguishing MDD from healthy controls.

Conclusions

In conclusion, our study demonstrates the feasibility and effectiveness of using graph-based networks, particularly Random Forest models, to classify MDD in children and adolescents. The strong classification metrics achieved in this study underscore the potential of these networks to enhance our understanding of the neurophysiological disruptions associated with MDD by identifying clinically relevant alterations in functional brain connectivity. However, to further validate and refine these findings, replication with larger datasets is recommended. Additionally, future research should explore the impact of using a larger segmentation threshold, which may improve the performance of metrics such as the DTF and its related measures, including dDTF. Overall, this study highlights the promise of graph-based approaches in advancing the diagnosis and understanding of MDD and sets the foundation for future investigations into brain network dynamics in psychiatric disorders.

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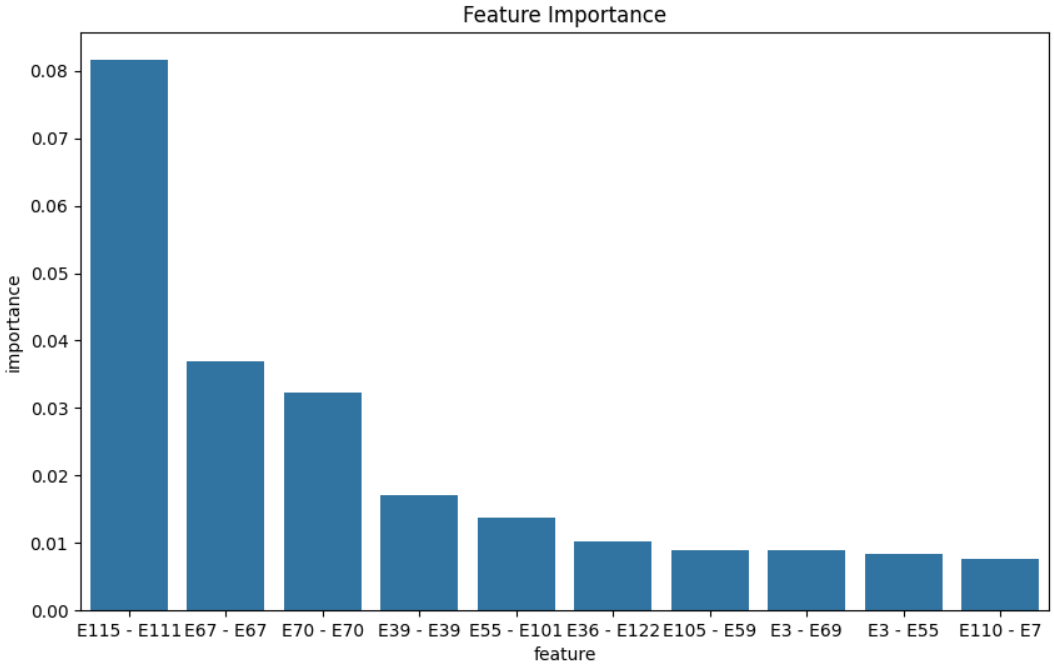

Figure 1. Learned feature importance for PDC Factor

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Graph-Based Analysis of Brain Connectivity in Children and Adolescents Diagnosed with Major Depressive Disorder Compared to Aged-matched Healthy Control: An EEG Study

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Project Idea and Background

- Major Depressive Disorder (MDD) as a heterogeneous psychiatric disorder distinguished by continuous low mood, feelings of worthlessness, diminished interest, cognitive impairment, vegetative symptoms, feelings of excessive guilt, anhedonia, disturbed sleep, lethargy, and suicidal tendencies / ideation.
- Current assessments are mainly based on standardized diagnostic interviews (SDIs), systematic and semi-systematic psychiatric evaluation, and interviews of the state of patients using reported symptoms, events, occurrences, and psychological evaluations (Self report)
- Results of resting-state functional connectivity demonstrated increased alpha, decreased beta; alpha activities were observed in the subgenual prefrontal cortex and left dorsolateral and mediolateral prefrontal cortex.
- Prior research using graph theory analysis revealed accuracy of 80.74% for recognizing the abnormal organization of functional connectivity networks in mild depression (aged 18-24 y.o) and Lower clustering coefficient and a greater characteristic path length (MDD vs healthy; Qin et al., 2022; Olbrich et al., 2014; Li et al. 2011).
- Current research utilize graph theory analysis to identify biomarkers for MDD in children and adolescents, compared to age-matched healthy individuals.

Methods

Pre-processing

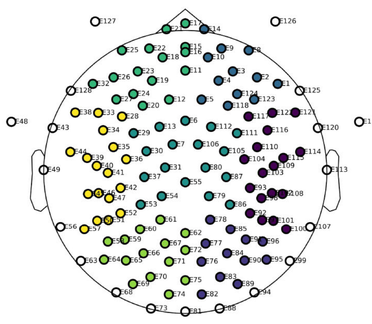
- EEG pre-processing starts with bad channel identification (through PREP pipeline) and interpolation, followed by Band pass filter (1-70 Hz) and a notch filter at 60 Hz.
- Resampling 500 to 256 Hz and channels referenced based on average of channels.
- ICA is used to remove bad artifacts.
- The data was then segmented into chunks of 4000 samples. Each chunk was used to fit and train a MultiVariate AutoRegressive ICA (MVARICA) model.
- The model hyperparameters were optimized and used to compute Coherence and Direct Transfer Function (DTF) and their other variations.

Dataset

The dataset used was from the Healthy Brain Network, measured in the US, on participants age from 5-21, with eye closed in resting state. The dataset used utilized 214 recording, of which 170 are classified as healthy and 44 classified as MDD. The data was recorded using 128 channels, of which 109 was kept.

ML setup

- Random Forest (RF) model was trained on data in tabular format, with rows representing the segmented data, with the column representing the channel connectivity interaction.
- The model was trained using 5-fold cross validation, with class weights added to account for data imbalance.
- F1-score, Matthew Correlation Coefficient (MCC), Cohen Kappa were recorded



Results

Performance

- Results are shown in table 1
- Highest F1-score of 0.975, MCC 0.970, Cohen Kappa of 0.969
- Highest score achieved in PDC Factor.
- DTF performed worse than PDC
- Coherence performs the worst at 0.451 F1-score
- Direct measurements (PDC Factor and dDTF) perform the best in their respective type of measurements

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Features Analysis

- Figure 1 shows the features importance analysis, extracted from the random forest model.
- The model was trained on the PDC Factor connectivity measurement
- The importance score was extracted from the Gini importance method.
- It is noteworthy that the interaction between E115 and E111 emerges as the most important feature
- The next three most important interactions are channel relationship with themselves (R67, E70, E39)
- The importance scores showcase that the model did not overfit, as there are no overly dominant score
- Interaction E115-E111 is a ROI interaction between Temporal right to Center, E67 and E70 are in the Occipital Left. While E39 is in the Temporal Left.

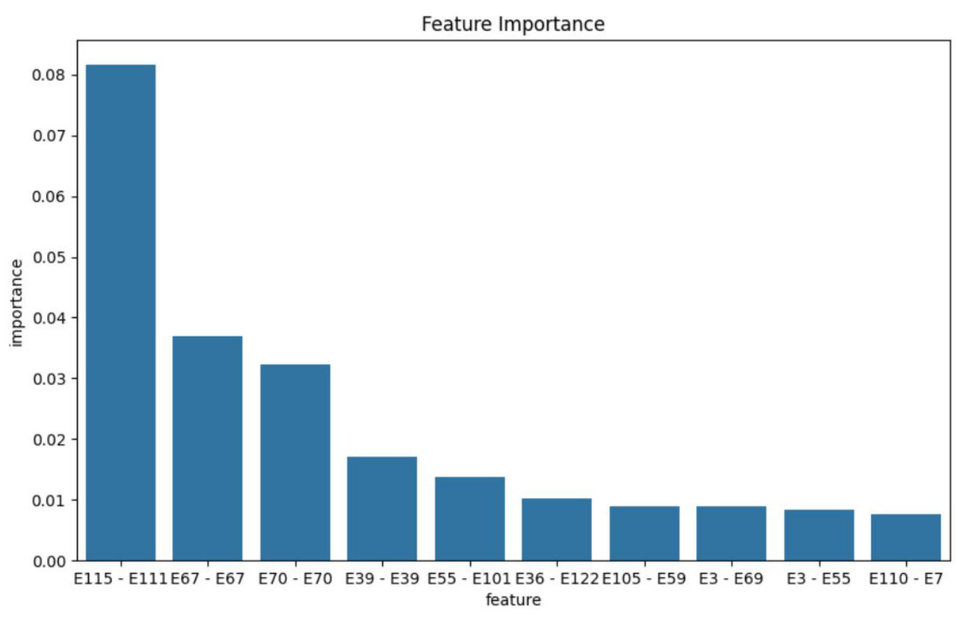

Figure 1. Learned feature importance for PDC Factor

Performance Analysis

- PDC appears to be more robust than DTF, specially when training MVARICA on sparse data.
- RF is best suited to train on direct measurement, which ignores an indirect interactions. an environment where these causal interactions are captured is where graph based model excel
- The performance is robust across all metrics, specially in an imbalance environment (similar to clinical setting)

Connectivity Threshold

- The method had a segmentation threshold, which require optimization. Increasing it, improves the MVARICA model, but decreases the training data for the RF model and vice versa.
- Threshold used is longer than one used in other works in MDD, with the high performance of the RF model, we can assume that the RF model is better suited for classifying MDD by capturing stable and consistent brain patterns, ignoring transient noise and fluctuations. Longer segments also better capture the dynamic nature of brain connectivity.
- The longer segments used also help improve the resolution of the connectivity measurements, which is beneficial when trying to analyse connectivity in lower frequency band, which tend to be shorter in length (2-4 Hz).

Conclusion

- Feasibility and effectiveness of graph-based networks, particularly Random Forest models, in classifying MDD in children and adolescents.
- Strong classification metrics highlight the potential to enhance understanding of neurophysiological disruptions in MDD.
- Identification of clinically relevant alterations in functional brain connectivity.
- Recommendation for replication with larger datasets to validate and refine findings.
- Suggestion to explore the impact of using a different segmentation threshold or models to improve performance metrics like DTF and dDTF.
- Emphasis on the promise of graph-based approaches in advancing MDD diagnosis and understanding.
- Foundation set for future investigations into brain network dynamics in psychiatric disorders

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