Resting-State Functional Connectivity in Children and Adolescents with Major Depressive Disorder: A Deep Learning Approach Using High-density EEG

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***Abstract*— This research focuses on utilizing convolutional neural networks (CNNs) to identify biomarkers for major depressive disorder (MDD) in children and adolescents, compared to age-matched healthy individuals. We analyzed resting-state, eyes-closed electroencephalography (EEG) data, pre-processed and segmented by frequency bands and regions of interest (ROI). Several resting-state functional connectivity (rsFC) measurements were computed using a multi-variate auto-regressive (MVAR) model. The best-performing CNN model was further analyzed to understand its decision-making process and to identify relevant biomarkers. Our approach achieved an F1-Score of 0.790 and a Matthews correlation coefficient (MCC) of 0.745 using the full-frequency partial directed coherence (ffPDC) rsFC measurement. Among the connectivity metrics, partial directed coherence (PDC) outperformed coherence, partial coherence, and the directed transfer function (DTF). Additionally, the full-frequency versions of PDC and DTF demonstrated better performance compared to their standard and variant forms. These results highlight the potential of CNN models and EEG-derived biomarkers in advancing the understanding and diagnosis of MDD in children and adolescents.**

Keywords*— *Electroencephalography, Children, Adolescents, Major Depressive Disorder, Resting-state Functional Connectivity, MVARICA, CNN, Deep Learning.

I. Introduction

Early diagnosis of various forms of depression has garnered significant attention from the scientific community, as more than 350 million people worldwide suffer from this multifactorial psychiatric disorder. Depression is classified in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5, 2013) into several categories, including major depressive disorder (MDD), postpartum depression, disruptive mood dysregulation disorder, persistent depressive disorder (dysthymia), premenstrual dysphoric disorder, and depressive disorder due to another medical condition. This study focuses specifically on MDD, a more severe form of depression that, unlike typical depressive episodes, chronically and significantly impacts patients' daily functioning. As a unipolar and chronic disorder, MDD necessitates prolonged clinical management and tailored therapeutic approaches. Characterized by persistent low mood, feelings of worthlessness, diminished interest, cognitive impairment, vegetative symptoms, excessive guilt, anhedonia, disrupted sleep, fatigue, and suicidal ideation, MDD represents a complex and heterogeneous psychiatric condition [1]. During the last two decades, numerous algorithms have been used by researchers to identify neuro-biomarkers of MDD to improve the diagnostic models and tools as a single stand or in combination with psychiatric evaluation of patients' state which is focused on reported symptoms, events, occurrences, and psychological assessments [2]. The current research concentrates purely on the classification of MDD and the comparison with healthy participants. This aligns with our prior studies attempting to improve classification-based models among children and adolescents suffering from MDD [3–5]. Comprehending the biomarkers associated with MDD holds great significance in diagnosing and treating this condition, and medical specialists can use that as a complementary or confirmatory method for their research and its future applications for diagnostic purposes [3].

EEG is a non-invasive neuroimaging technique known for its high temporal resolution, which has been extensively employed to develop diagnostic tools for a wide array of neurological, developmental, and psychological disorders. Its ability to capture real-time electrical activity in the brain makes EEG particularly valuable in research aimed at understanding and diagnosing these conditions [6–9]. It is possible to distinguish between healthy brain activities and abnormal activities under specific conditions (at rest, eye closed, eye open, etc.) [10].

II. Background

II-A. Resting-state Functional Connectivity in Major Depressive Disorder

In recent years, studies focused on the analysis of resting-state functional connectivity (rsFC) using EEG to uncover how depression affects the brain network in patients diagnosed with depression ([1]; [11]; [12]; [13]). rsFC represents an innovative approach in neuropsychiatric research, offering a dynamic perspective on the brain's functional networks during rest periods. Unlike traditional EEG analysis focusing on isolated brain regions or specific event-related potentials, rsFC investigates the temporal synchronization of neural activity across various brain areas. This approach provides valuable insights into the intrinsic connectivity networks

that may be disrupted in MDD. By revealing patterns of hypo- or hyper-connectivity within these networks, rsFC enhances our understanding of the complex neural underpinnings of MDD, aiding in identifying potential EEG biomarkers that differentiate individuals with MDD from healthy controls. This method deepens our comprehension of MDD pathophysiology and holds promise for improving diagnostic accuracy and guiding personalized treatment interventions.

In this context, an earlier study by [14] found that increased rsFC in the alpha frequency band is associated with depressive symptoms, particularly in the frontal, posterior, and left hemisphere regions. Additionally, heightened rsFC in theta activity was linked to functional connections within the frontal brain regions. Their findings indicated that the right frontal and left posterior areas are the most affected in individuals with depression compared to healthy controls. Similarly, a study by [1] reported increased beta band connectivity in the 12.5-18 Hz and 18.5-21 Hz ranges between the default mode network and the fronto-parietal network. Their results suggested that increased high-frequency connectivity between these networks serves as a neural marker associated with a more recurrent course of illness. Despite numerous studies in this area, including our previous research, there remains a lack of a reliable, multidimensional, and optimized model for accurately detecting abnormal biomarkers that distinguish MDD from healthy individuals, particularly in children and adolescents. Inconsistencies in the literature —such as variations in analytical approaches, participant ages, and sample sizes— have prompted us to explore the use of rsFC combined with deep learning models to classify both normal and abnormal neuro-biomarkers utilizing the same EEG datasets from children and adolescents diagnosed with MDD. Our findings of abnormal rsFC in specific frequency bands contribute to a better understanding of the potential neurophysiological origins of disrupted functional connectivity in MDD. Identifying these abnormalities will enhance our comprehension of the disorder and may inform future diagnostic and clinical applications.

III. Metrial and methods

III-A. Dataset

This study involved 214 datasets of children and adolescents aged 5 to 21, with 44 diagnosed with MDD and 170 classified as healthy (labeled HBN). The data was obtained from the publicly available Healthy Brain Network (HBN) dataset [15]. Resting-state data under closed eyes conditions were chosen for this study, recorded at a sampling rate of 500 Hz and a bandpass of 0.1 to 100 Hz using a 128-channel EEG HydroCel Geodesic system by Electrical Geodesics Inc. However, after excluding outer channels, only 109 channels were retained. The EEG electrode distribution on the scalp is depicted in figure 1.

III-B. Pre-processing

The data pre-processing was divided into two main stages: EEG data pre-processing and the computation of the connectivity model. The EEG pre-processing steps closely followed the methodology described in [3], up to the Independent Component Analysis (ICA) stage. The EEG pre-processing starts with the prep pipeline [16], which involves detecting bad channels and subsequently interpolating them. A bandpass filter (1-70 Hz) was applied, followed by a 60 Hz notch filter to remove power line artifacts. The data was then resampled at 256 Hz and referenced using the average across channels. ICA was applied to identify and remove bad artifacts before further analysis. The EEG data was segmented into non-overlapping chunks of 4000 samples (approximately 15.6 seconds), and for each segment, a Multi-Variate Auto-Regressive ICA (MVARICA) model [17] was fitted.

The decision to use larger segmentation thresholds, as opposed to the more conventional 2-4 second segments, was driven by several key factors. First, longer segments provide more data for fitting the connectivity model, improving its robustness. Second, it allows for a better resolution and focus on lower frequency bands (1-30 Hz) [18]. Another important consideration is the use of non-overlapping segments. While overlapping segments may capture transient patterns in connectivity measurements, this effect is mitigated by extending the segment length. The choice of non-overlapping segments is crucial for training the CNN model because overlapping segments can produce correlated or dependent connectivity measurements [19, 20], which impairs the model's ability to generalize. This is especially problematic when the data is imbalanced, as it can lead to overfitting. Additionally, CNNs are designed to learn hierarchical features from the data [21], and highly correlated inputs may hinder

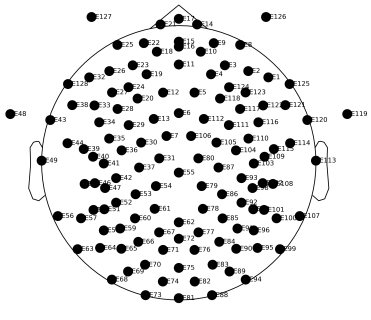

Figure 1. Channel location of 128-channels in the HBN dataset

the model's ability to identify distinct biomarkers, such as those related to MDD.

III-C. Resting-state Functional Connectivity

The connectivity model's hyperparameters were first optimized. To achieve this, the segmented EEG data was further divided into one-second epochs, resulting in 15 epochs per segment. Model order parameter, which is the amount of data in the past (lags) used to predict the current value in the time series data, was optimized by minimizing the mean squared generalization error using leave-one-out cross-validation (LOOCV) on the epoched data. The optimization search for the model order was in the range of 1 to 20. Additionally, the delta ridge penalty parameter was optimized using the bisection search method [22]. It is important to note that this optimization process was conducted independently for each EEG chunk, assuming that the EEG signal is non-stationary. Once optimized, the MVARICA model was fitted to the original EEG segments [17]. From the fitted model, various connectivity measures were computed [23]. These measures included coherence, partial coherence, PDC, ffPDC, PDC factor, generalized PDC (gPDC), DTF, full frequency DTF (ffDTF), direct DTF (dDTF), and generalized DTF (gDTF), all of which were computed between all channels in both directions.

- Coherence measures the statistical dependency between signals, while partial coherence assesses the linear time-invariant relationship between two signals.
- PDC identifies whether two signals are significantly correlated, incorporating Granger causality to reveal directional influences between channels or brain regions.
- ffPDC normalizes across all frequency bands, unlike standard PDC, which is normalized per frequency band. gPDC is a scale-invariant version of PDC, making it resistant to static gain effects [24].
- PDC Factor focuses on direct channel interactions, excluding indirect effects.
- DTF estimates information flow from one channel to another, accounting for both amplitude and phase shifts.
- ffDTF, dDTF and gDTF mirror in their relationship to DTF, the relationship between ffPDC, PDC Factor, and gPDC to PDC, respectively.

All connectivity measures were calculated with a frequency resolution of 2500 samples, spanning the range from 0 Hz to half the sampling rate (0-128 Hz). The results were then divided into the following frequency bands: Delta (1-4 Hz), Theta (4-8 Hz), Alpha (8-12 Hz), Beta (12-30 Hz), and Gamma (30-70 Hz). Each connectivity measure was used to create an image, as shown in Figure 2, where rows and columns correspond to different EEG channels. The intersection of each row and column represents the connectivity measure between those channels. Channels were organized according to specific regions of interest (FL, FR, TL, TR, OL, OR, Center), and their respective rows and columns were duplicated to represent the different frequency bands, as illustrated in Figure 2.

The arrangement of images at the frequency level was designed to group frequency bands identified in our previous work as significant in MDD [3], grouped into the upper-left corner, making it easier for the CNN to spatially detect any MDD-specific biomarkers. At the ROI level, the order of ROIs was based on their spatial proximity in the brain, ensuring that the CNN could leverage this anatomical organization to better identify relevant patterns linked to MDD. This structured approach helps the model focus on both functionally and spatially significant regions.

III-D. Architecture of CNN

The CNN model's architecture is built upon the VGG16 network, with the top layers replaced by a global average pooling layer. This was succeeded by two fully connected layers, each containing 512 neurons activated by ReLU. Subsequently, a dropout layer of 0.2 was inserted, followed by another dense layer comprising 512 neurons activated by ReLU, further followed by a decision-making layer with 1 neuron activated by Sigmoid. The AdaBelief optimizer was employed [25], with binary cross-entropy serving as the loss function. The evaluation metrics employed were F1 score, Specificity, Cohen Kappa, and MCC.

III-E. ROI analysis

Seven regions of interest (ROI) are identified, illustrated in figure 3. To discern discrepancies in MDD and HBN across different frequency bands, Class Activation Map (CAM) [26] was deployed. CAM is a method used to

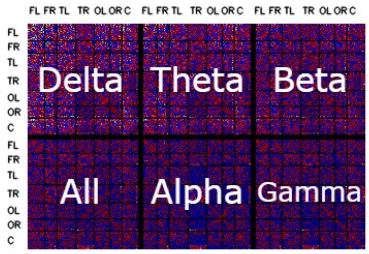

Figure 2. Example of input data of Partial Coherence connectivity measurement for the CNN model, Where ROI C is Center.

interpret CNNs by generating a heatmap, which uses the weight of the last convolutional layer weighted by the importance of the class in the last prediction layer.

IV. Experimental results

IV-A. Setup

The training dataset was segmented, resulting in an expanded dataset of up to 5840 samples (MDD + HBN) for each connectivity measurement, with the RGB channels duplicated, except in the cases of coherence and partial coherence, where one channel was chosen for the imaginary values and two channels for the real values. The training method was 5 K-fold cross-validation training. The fold split was based on subjects. Five different models were trained for each fold. The training was set to 100 epochs with early stopping triggered when the F1-Score hit 0.8, batch size was set to 90, and the learning rate was set to 0.000004. Before initiating training, weights were added to each class to account for the class imbalance. The weights were calculated in each fold according to equation [1].

$$W_j = \frac{n_{samples}}{n_{classes}.n_{jsamples}} \quad (1)$$

W_j is the weight of class j, $n_{samples}$ is the total number of samples used for training, $n_{classes}$ is the total number of classes, and $n_{jsamples}$ is the number of training samples belonging to class j. Additionally, the training of the CNN was done in Python 3.10.12, MNE 1.4.2, scot 0.2.1, Tensorflow 2.12.0, Keras 2.12.0, dask 2022.12.1, scipy 1.10.1, and numpy 1.22.4.

IV-B. Results

Training results are shown in table 1. The best performance was achieved by ffPDC, with an F1-Score of 0.790, MCC of 0.745, and Cohen's Kappa of 0.732. This was followed by ffDTF, which had an F1-Score of 0.746, MCC of 0.687, and Cohen's Kappa of 0.673. Among different PDC and DTF measurements, only the full-frequency versions significantly improved test scores, while other versions showed comparable results. On the other hand, the CNN model failed to learn effectively with Coherence and Partial Coherence. Notably, using only the real values for these metrics was more effective than including the imaginary values.

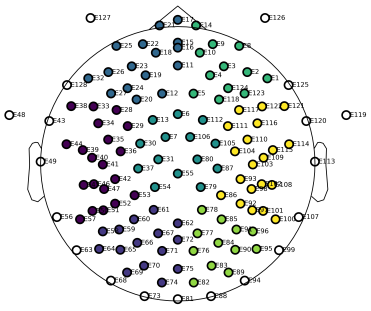

Figure 3. Region Of Interest (ROI)

Table 1. CNN testing score in each connectivity measurement

Connectivity Measurement	F1 Scores	Sensitivity	Specificity	MCC	Cohen Kappa
COH	0.525	0.675	0.790	0.399	0.379
Real COH	0.531	0.645	0.811	0.408	0.396
PC	0.584	0.698	0.767	0.477	0.445
Real PC	0.617	0.798	0.866	0.522	0.510
PDC	0.713	0.772	0.912	0.646	0.639
PDC Factor	0.690	0.701	0.924	0.619	0.614
ffPDC	0.790	0.901	0.914	0.745	0.732
gPDC	0.689	0.842	0.853	0.617	0.596
DTF	0.700	0.772	0.897	0.631	0.620
ffDTF	0.746	0.863	0.890	0.687	0.673
dDTF	0.715	0.751	0.917	0.649	0.641
gDTF	0.715	0.846	0.877	0.650	0.633

Analyzing the CAM heatmap of ffPDC in figure 4, which achieved the highest test score, shows that the model places similar attention on Delta, Theta, and Beta frequency bands. The main focus is on ffPDC interactions from FL to (FL, FR, TL, TR) and from (TR, OL, OR, Center) to FL and from (TR, OL, OR) to Center. In the frequency band containing all frequencies, the emphasis is on interactions from Center to (FL, FR, TL, TR) and from OR to (FL, FR, TL) and from OL to (FL, FR) and from TR to FL. Notably, the alpha band receives little attention, with the strongest interactions from the Center to (FL, FR, TL, TR). In the gamma band, significant focus is on interactions from (TR, OL, OR, Center) to Center.

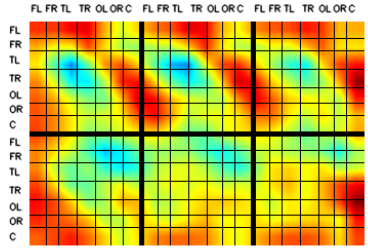

Figure 4. CAM heatmaps for ffPDC on both HBN and MDD datasets

IV-C. Discussion

In our research, we implemented a CNN model to identify MDD biomarkers using several connectivity measurements computed from the MVARICA model. The model achieved its best performance with the ffPDC measurement, yielding an F1-Score of 0.790, Specificity of 0.914, MCC of 0.745, and a Cohen's Kappa of 0.732. When comparing PDC and DTF, PDC outperformed DTF in this study. Neither method is inherently superior, but specific factors in our context contributed to PDC's better performance, particularly the availability of training data for the MVARICA model. Volume conduction, which affects DTF more

prominently than PDC, is likely a contributing issue delimited data does not exacerbate volume conduction, it reduces the MVARICA model's ability to correct for it [27]. Similarly, with less data, the accuracy of the MVARICA model decreases, and PDC is more robust in such cases, making it degrade less than DTF [28].

Based on our findings, we recommend focusing on PDC and PDC-related measurements when working with machine learning models and the MVARICA model, as they handle data scarcity better. Notably, ffPDC and ffDTF performed better than other PDC and DTF variants. This may be due to normalizing over the entire frequency band, which preserves the relative relationships between the electrodes and allows the CNN model to detect meaningful differences more effectively. The results of the classification in our study showcase an improvement in the classification score of MDD using rsFC, compared to previous work [3], which used time-series EEG. Our study demonstrates the results of training the network on a relatively large dataset, focusing on robustness and the model's ability to generalize, emphasized through the training method and the metrics used. Our work deals with an imbalanced dataset and maintains high sensitivity. We also performed a direct comparison on varying connectivity measurements, showcasing the best performing measurement, within the context of MVAR models. Our findings demonstrate that machine learning applied to resting-state EEG FC patterns can objectively identify markers of MDD in children and adolescents with high accuracy, consistent with similar research conducted in adults, as shown in table 2.

Previous studies on MDD classification using EEG with rsFC and machine learning models have shown varying degrees of success, as illustrated in Table 2. For instance, the study [29] utilized a larger and balanced dataset comprising 400 participants (200 healthy and 200 with MDD). They tested several models, including Support Vector Machine (SVM), K-Nearest Neighbor (K-NN), Conformal Kernel (CK), and CK-SVM. This study incorporated coherence along with other features like Power Spectrum Density (PSD). The best test scores achieved were 0.840 for accuracy, 0.880 for sensitivity, and 0.800 for specificity. Comparing the F1-score of our work with the accuracy in study [29] is challenging, particularly due to differences in dataset balance. Nevertheless, our work achieved a higher sensitivity (0.901) and specificity (0.914). The elevated sensitivity is especially advantageous for clinical applications, as it ensures that more true positive cases are correctly identified. This is particularly important when the dataset is unbalanced towards negative (healthy) cases.

Other studies, as in [30–33], have reported a wide range of results. However, our study has utilized a larger dataset, which generally improves the models' robustness and ability to generalize [34]. Study [31] used a Specific-General Functional Graph Convolutional Network (SGFGCN) model, and study [33] employed a CNN-based model. Both studies achieved significant test scores (>0.95) and used 10-fold cross-validation and sample-based data splitting. On the other hand, our study uses subject-based data splitting, which tends to be more robust and has a better generalization ability, which is why sample-based splitting tends to achieve higher test scores [35]. In study [30], multiple models were tested, including Random Forest (RF), SVM, KNN, and Artificial Neural Network (ANN). The best-performing model was RF, with a test score of 0.893 for accuracy and an f1-score of 0.917. These results were achieved after training the models on specific parameters extracted from a connectivity network and only including biomarkers detected in a prior statistical analysis on the network. For a proper comparison between our work and study [30], we would need to retrain the network on the important biomarkers identified in Figure 4, which could be included in future work.

Reflecting adult studies, our analysis of larger MDD and HBN datasets showed encouraging accuracy levels, highlighting the potential of FC patterns as a diagnostic tool for MDD in the age range we focused on. Given that MDD is fundamentally a network connectivity disorder, models leveraging rsFC are expected to outperform others, as suggested by the recent rise in the use of coherence measures for classification model development.

Table 2. Comprehensive comparison of existing state-of-the-art methods using FC for MDD classification. NC: Normal Control

Study	Subject	Channel	Method	Accuracy
[29]	200 MDD and 200 NC	64 electrodes	Multi-model with rsFC	0.840
[30]	24 MDD and 24 NC	128 electrodes	Multi-model with rsFC	0.893
[31]	49 MDD and 49 NC	19-64 electrodes	CNN with rsFC	0.972
[32]	24 MDD and 25 NC	32 electrodes	RF with rsFC	0.600
[33]	24 MDD and 29 NC	128 electrodes	SGFGCN with rsFC	0.972
Our work	44 MDD and 170 NC	128 electrodes	CNN with rsFC	0.790 (f1-score)

For future studies, we suggest testing these models on larger, more balanced datasets to gain a clearer understanding of the optimal connectivity measurements for CNN-based classification. Additionally, exploring different segmentation thresholds for the EEG data could provide insights into their effects on both the CNN and MVARICA models. Lastly, we recommend experimenting with alternative MVAR models that are

better suited to handling limited data, as suggested by [27].

V. Conclusions

We conclude that CNN models, combined with connectivity measurements, are effective in detecting MDD biomarkers in children and adolescents, achieving strong classification results with the ffPDC measurement. This classification approach holds promising potential for clinical applications, but further research is needed with greater sample size and depending on various depressive conditions to interpret the identified biomarkers within a broader, non-technical context.

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