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https://doi.org/10.1016/j.bspc.2024.106613

Analysis of EEG-Derived Brain Networks for Predicting rTMS Treatment Outcomes in MDD Patients

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ABSTRACT

Major depressive disorder (MDD) is a common and debilitating mental illness. One of the MDD treatments is Repetitive transcranial magnetic stimulation (rTMS) which has shown promise in treating MDD but predicting individual patient response remains a challenge. In this paper, we analyzed EEG signals recorded at four different time points including baseline, and after 3rd, 6th, and 10th rTMS sessions in 18 MDD patients receiving rTMS treatment. Brain networks were constructed using partial transfer entropy of EEG signals in four frequency bands. Graph theory metrics were extracted from these networks, and their correlations with patients' depression levels during treatment were assessed. Furthermore, the ability of these networks' metrics obtained from EEG data of four separate time points in discerning between treatment responders and non-responders to treatment was assessed by classification analysis. Results showed a high correlation between depression severity and certain network metrics, such as node betweenness centrality, diameter, and local efficiency in the delta band, as well as global and local efficiency in alpha frequency bands. Furthermore, based on the results, brain network metrics derived from EEG signals collected at second week of rTMS treatment can predict treatment response with an accuracy of 94.44%. This study investigates the relation between brain network metrics and treatment outcomes for MDD and suggests that analyzing topological changes in brain networks may be a useful approach for predicting patient response to rTMS treatment.

Keywords: Brain network, EEG, Graph theory, Major depressive disorder, Prediction treatment response, Transcranial magnetic stimulation.

1 INTRODUCTION

Major depressive disorder (MDD) is a highly prevalent and debilitating mental illness that affects millions of individuals worldwide (Organization 2021). Despite the availability of various treatments, response rates vary widely, with up to 30-40% of patients failing to achieve remission after initial treatment (Voineskos, Daskalakis et al. 2020, Gałecki, Samochowiec et al. 2022). Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive technique that has shown

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promise in treating MDD (McClintock, Reti et al. 2017), However, the prediction of rTMS treatment response in individual patients remains a challenge. Given the significant personal and societal burden of depression(Organization 2021), studying the effect of treatment and identifying reliable predictors of treatment response is an important area of research that could improve clinical outcomes, diminish economic burden, and alleviate unnecessary distress for individuals affected by MDD.

Recent advances in neuroimaging and machine learning techniques have led to the development of new methods to investigate treatment responses in MDD. Neuroimaging methods have allowed researchers to study the neural correlates of MDD and identify biomarkers that may be predictive of treatment response(Drysdale, Grosenick et al. 2017). In particular, electroencephalography (EEG) has great potential as a non-invasive tool for studying the neural mechanisms underlying depression treatment and predicting treatment outcomes(Hasanzadeh, Mohebbi et al. 2019, Watts, Pulice et al. 2022). Different studies used features extracted from EEG and machine learning techniques or statistical analysis to explore MDD treatment and predict rTMS treatment response in MDD. Features based on the power of EEG in different frequency bands (Khodayari-Rostamabad, Reilly et al. 2011, Bailey, Hoy et al. 2023), cordance (Arns, Drinkenburg et al. 2012, Bares, Brunovsky et al. 2015, Erguzel, Ozekes et al. 2015), nonlinear features including complexity measures(Arns, Cerquera et al. 2014, Hasanzadeh, Mohebbi et al. 2019), bispectral measures(Hasanzadeh, Mohebbi et al. 2019), permutation entropy(Shalbaf, Brenner et al. 2018), and current source densities obtained by exact low-resolution brain electromagnetic tomography (eLORETA) (Vlcek, Bares et al. 2020) are analyzed in former studies to evaluate the treatment responding and develop methods for prediction of rTMS treatment outcome in MDD. Shahabi et al. employed Raw EEG data in predicting the treatment outcome of rTMS using a hybrid model of pre-trained convolutional neural networks and bidirectional long short-term memory cells(Shahabi, Shalbaf et al. 2022). In addition to the analysis of convectional multichannel EEG Hasanzadeh *et al*. investigated the performance of single-channel EEG in discriminating responders and non-responders to rTMS treatment in MDD. They show that EEG of a single channel (F3) can classify responders and non-responders with an accuracy of 80% and can perform as well as multichannel EEG in predicting rTMS treatment outcomes (Hasanzadeh, Mohebbi et al. 2020).

Although brain complex functions are reported to arise from the connection of various brain regions in networks (Sporns 2016, Hasanzadeh, Mohebbi et al. 2020), most studies on predicting the response to rTMS treatment in MDD focused on analyzing EEG features, particularly those based on power spectral density. Few studies have investigated the relationship between brain connectivity and treatment outcomes. Cook *et al*. examined the functional connectivity of MDD patients before and after rTMS treatment using coherence in a double-blind study. They discovered that improved depression symptoms were associated with elevated coherence in the alpha and beta bands of the anterior and central areas(Cook, Wilson et al. 2019). Conversely, another study by Krepel *et al*. found no difference in pretreatment EEG coherence in responders and non-responders to rTMS (Krepel, Sack et al. 2018). Using coherence, envelope correlation, and alpha spectral

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correlation measures, Corlier *et al*. investigated the functional connectivity of patients with MDD before and after rTMS treatment. They presented a novel connectivity measure of spectral correlation in the alpha frequency band across regions and found that changes in alpha spectral correlation from pre- to post-treatment were significantly associated with clinical outcomes (Corlier, Wilson et al. 2019). Bailey et al. predicted responses to rTMS treatment for depression by classification of EEG features including power density, weighted phase lag index (wPLI) in gamma (Bailey, Hoy et al. 2018), alpha and theta frequency bands, and, alpha peak frequency (iAPF) and frontal theta cordance (Bailey, Hoy et al. 2019). they achieved a mean sensitivity of 90% and specificity of 92% by analyzing EEG data recorded during working memory(Bailey, Hoy et al. 2018). Moreover, they used resting EEG recorded at baseline and the end of the first week of treatment duration to predict response to rTMS. They achieved a mean sensitivity of 84% and specificity of 89% in predicting responders using a combination of mood and EEG features(Bailey, Hoy et al. 2019). Nobakhsh et al. applied a Support Vector Machine (SVM) classifier to direct directed transfer function extracted from baseline EEG to predict the treatment response of rTMS in MDD patients. They reported that combining the selected direct Directed Transfer Function (dDTF)features in the delta and theta frequency bands can accurately detect the treatment response with an accuracy rate of 89.6%(Nobakhsh, Shalbaf et al. 2022).

Among the few studies on rTMS treatment outcomes in MDD patients that analyzed EEG-based brain connectivity, none of them have studied topological changes of brain networks with treatment. Moreover, most of these studies have primarily focused on signals recorded before treatment. Therefore, in the current paper, we present a more comprehensive analysis to understand changes in brain networks with rTMS treatment. We analyzed EEG signals recorded at four different time points: baseline (before treatment) and after the 3rd, 6th, and 10th sessions of rTMS treatment. The brain networks were constructed based on partial transfer entropy (Partial TE) of EEG signals recorded at the aforementioned 4 time points in 4 frequency bands of delta, theta, alpha, and beta. We further investigated the relationship between topological measures of brain network and response to treatment by extracting graph theory metrics from these networks and assessing the correlations between these measures and patients' depression levels during treatment. The extracted network metrics include node degree and betweenness centrality, global and local efficiency, and diameter. Additionally, we applied classification techniques on these metrics recorded at successive sessions to evaluate the performance of these metrics in predicting the responders and non-responders to the rTMS treatment.

As we know this is the first study to explore how the topological features of brain networks, quantified through graph theory metrics like node centrality, efficiency, and network diameter, are changed during treatment in MDD patients and how these measures are affected by depression severity levels. The longitudinal analysis across multiple time points during treatment provides a view into the dynamic reconfiguration of brain network organization as patients respond to rTMS therapy. Moreover, the application of PartialTE is particularly significant, as it addresses the limitations of traditional connectivity measures by accounting for multivariate interactions and nonlinear dynamics while avoiding assumptions about the underlying models. This advanced

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approach enhances the reliability and interpretability of the obtained brain networks. By exploring the relationship between topological brain network features and depression severity, as well as leveraging machine learning techniques for treatment response prediction, this study provides insights into changes in functional networks related to rTMS during the treatment.

The remainder of this paper includes four sections. The first section details the materials and methods, comprising participants, rTMS procedure, EEG data recording and preprocessing, and network analysis including Partial TE and graph theory analysis. Then we explain the details of the correlation analysis and classification procedure that we applied to the graph theory metrics. The results section covers the correlation between graph theory metrics and depression levels in MDD patients, followed by the results of the classification of responder and non-responder based on the graph theory metrics of brain networks at different time points. The discussion section will discuss the observed results, and the conclusion section will summarize the paper.

2 MATERIALS AND METHODS

2.1 Participants

This study involved 18 participants diagnosed with MDD, comprising 14 females and 4 males, undergoing rTMS treatment at Atieh Clinical Neuroscience Center, Tehran, Iran. Diagnosis of MDD was confirmed using the DSM-IV diagnostic criteria DSM-IV)(Association 2000). Participants were screened to exclude individuals with Axis I or II disorders, substance abuse, suicidal risk, unstable medical conditions, and various other conditions including cardiac arrhythmia, pregnancy, head injury history, seizures, epilepsy, and neurological disorders. This careful screening aimed to ensure homogeneity within the sample and minimize confounding variables. Of the 18 participants, 11 responded positively to the rTMS treatment, while 7 did not exhibit significant improvement. Response to treatment was determined based on the reduction of Beck Depression Inventory-II (BDI-II) scores by over 50% from baseline or achieving a BDI-II score of ≤ 8, indicating remission. Comparative analysis between responder and non-responder groups revealed no statistically significant differences in demographics such as age and gender. Similarly, there were no significant variations between the groups concerning pre-treatment BDI-II scores, medication regimens, illness duration, current episode length, number of previous medications, and comorbidity of anxiety. However, notable differences emerged in post-treatment BDI-II scores between responders and non-responders, with responders exhibiting significantly lower scores. Furthermore, the medication status of participants was managed, with medication stabilized several weeks before and during the study. This study was approved by the ethics committee of Tehran University, and all patients provided informed consent for treatment.

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Table 1: Subject Information

	Responder	Non-Responder	p-value
N	11	7	
Age	٣١.٢±١٢.٥	٤١.١±١٣.٥	٠.٠٨
Gender(F/M)	8/3	6/1	٠.٩٧
Pre-treatment BDI-II	٣٢.٦±٨.٧	٣٢.٨٥±١٥.٥	٠.٩٣
Post-treatment BDI-II	٦.٩±٥.٥	٢٥.٤±١٠.٦	٠.٠٠٠٢
Medications (AD/AD + MS / AD + MS +AP)*	٣/١/٢	١/١/٢	٠.٩٧
Illness duration (years)	٤.٣±٤	١٢.٦±١١.٢	٠.٠٧
Current episode length (years)	٣.٢±٢	٩.٧±٩	٠.٠٥
Number of previous medications	١.١٦±١	١.١٤±١.٠٦	٠.٤٧٧
Anxiety (Y/N)	10/1	7/0	١

*AD (Antidepressant), MS (mood stabilizer), AP (antipsychotic).

2.2 rTMS Procedure

The rTMS treatment includes 21 sessions (3 sessions per week) of the left dorsolateral prefrontal cortex (DLPFC) 10 Hz rTMS treatment. During the treatments for the patients who did not show responding, the rTMS continued to left 10 Hz, right 1 Hz, or bilateral rTMS based on the psychiatric and psychologist's decision. The BDI-II score was recorded at baseline and after the 3rd, 6th, and 10th sessions of treatment to evaluate the severity of depression. At the end of treatment, the depression severity was assessed, and non-responders were identified.

2.3 EEG Recording and Preprocessing

The EEG data along with the depression severity (BDI-II score) of the subjects was recorded in four sessions: before the treatment, after the third, sixth, and tenth sessions of the treatment.

The EEG was recorded at resting state for 5 minutes with eyes closed condition while the patients sat on a comfortable chair in a soundproof room. Care was taken during the recording to prevent the subjects from falling asleep. EEG signals were recorded using a 19-channel Mitsar-EEG 201 device with a sampling frequency of 500 Hz. The electrodes were placed according to the 10-20 standard at Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, and O2 locations. After recording the EEG signals, these signals were pre-processed using the EEGLAB toolbox(Delorme and Makeig 2004). At first, the signals were filtered by a 1 to 42 Hz band-pass filter. To remove the remaining artifacts, independent component analysis (ICA) was applied. To identify artifacted components, Multiple Artifact Rejection Algorithm (MARA) (Winkler, Haufe et al. 2011) and ICLabel(Chaumon, Bishop et al. 2015) extensions were used in EEGLAB. MARA classifies the components into artifact and non-artifact categories based on spectral, spatial, and temporal features (Winkler, Haufe et al. 2011). The ICLabel extension, trained on 6000 data, classifies components into seven groups including components related to the brain, muscle, eye, heart activity, line noise, and other sources(Chaumon, Bishop et al. 2015). The artifacted components were selected and removed based on the results of these algorithms as well as visual inspection of the power spectrum of the independent components. In cases where the results of

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these two algorithms did not match, the results of a third algorithm called SemiAutomatic Selection of Independent Components for Artifact correction (SASICA)(Pion-Tonachini, Kreutz-Delgado et al. 2019) were used. Then, the remaining artifacts are removed by visual inspection of the EEG signal. Finally, the reference of the EEG signals was changed to the average reference and the signal length was equalized by taking 10,000 samples. The mentioned pre-processing steps were applied to the EEG signals of all subjects in all 4 sessions.

2.4 Network Analysis

The construction of brain networks from EEG signals is illustrated in Figure 1. Firstly, to examine the effect of different frequency bands on the functioning of brain networks, the pre-processed signals were decomposed into delta (1-3), theta (4-7 Hz), alpha (8-12 Hz), beta (13-30 Hz) using a band-pass filter with mentioned cutoff frequencies. Furthermore, considering the non-stationarity of the EEG signal, they are segmented into epochs of 2000 samples for each frequency band. Then, in each of these epochs, the connectivity matrix was obtained by computing Partial TE between EEG signals.

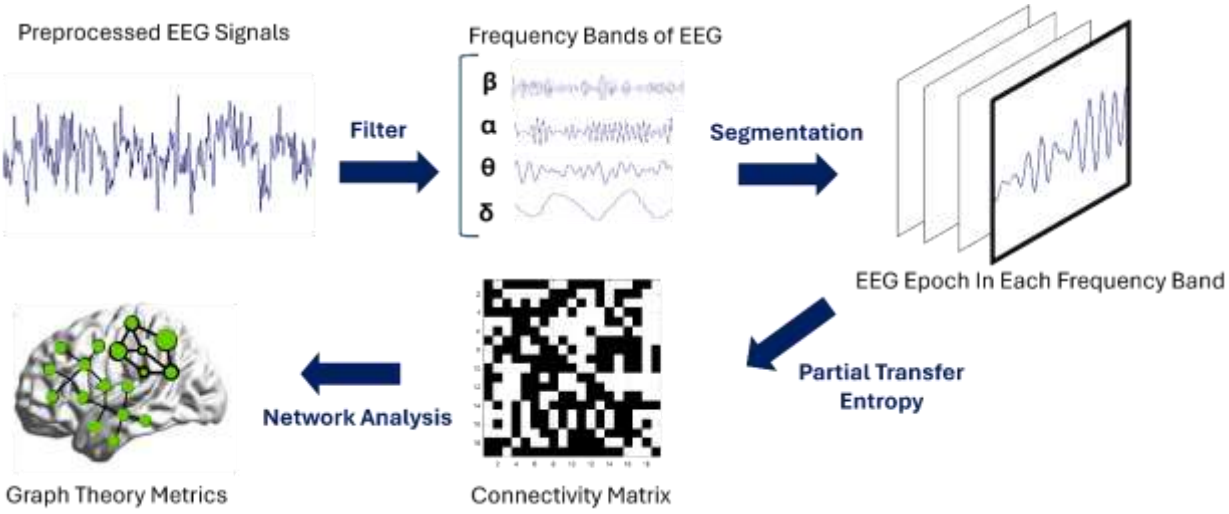

Figure 1: Network construction from EEG signal

2.5 Partial Transfer Entropy

Partial TE is a multivariate extension of transfer entropy (TE). TE is a nonlinear and nonparametric connectivity measure that is based on the Granger causality concept(Barnett, Barrett et al. 2009), however, it suffers from the problem of indirect influences or spurious causalities, which can lead to erroneous results. To overcome this limitation, Partial TE was introduced as an improvement over TE. The Partial TE connectivity measure is a multivariate measure that can calculate the connectivity between any pair of channels considering the other channels.

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Assume M interacting subsystems compose an overall dynamical system and, and that the states of these subsystems are represented as discrete-time stationary stochastic processes. Consider a source system, denoted by process X, to a destination system, represented by process Y, and the remaining systems are described by a set of processes $\boldsymbol{Z} = Z_{k=1,2,\dots,M-2}^{(k)}$.

If X_n , Y_n , $\boldsymbol{Z}_n$ are random variables obtained from sampling the processes at time n, $X_n^- = \{X_{n-1}, X_{n-2}, \dots\}$, $Y_n^- = \{Y_{n-1}, Y_{n-2}, \dots\}$ and $\boldsymbol{Z}_n^- = \{\boldsymbol{Z}_{n-1}, \boldsymbol{Z}_{n-2}, \dots\}$ represent the sets of variables that describe the past behavior of the processes, then the Information flow from X to Y in presence of remaining systems Z is called partial transfer entropy and is defined as follows (Faes, Marinazzo et al. 2014):

$$\begin{aligned} Partial\ TE_{(X\to Y)} &= TE_{(X \to Y|\boldsymbol{Z})} = I(Y_n; X_n^- | Y_n^-, \boldsymbol{Z}_n^-) \\ &= H(Y_n|Y_n^-, \boldsymbol{Z}_n^-) - H(Y_n|X_n^-, Y_n^-, \boldsymbol{Z}_n^-) \end{aligned} \quad (1)$$

where $I(.)$ is the mutual information and $H(.)$ is the Shannon entropy.

Since the Partial TE has reliable results on low dimensional systems (Vakorin, Krakovska et al. 2009, Hasanzadeh, Mohebbi et al. 2021) and to decrease the computational cost, we assume that our dataset contains 3 time series. In other words, in the computation of Partial TE between EEG of every pair of channels from one channel (source) to another channel (sink) we select one of the channels among the 17 remaining channels to be applied as the third signal. To minimize redundancy, we chose the third channel in such a way that it has maximum relevancy with the signal of the sink channel and minimum relevancy with the source channel signal and its delays. To this aim, we used β minimum Redundancy Maximum Relevance (βmRMR), a mutual information-based input selection method(Hejazi and Cai 2009) to select the third signal. This method selects the inputs in such a way that it has the maximum relevancy with the output of the model and the minimum relevancy with other model inputs, so it minimizes redundancy.

We specified the significance of Partial TE values by surrogate data. In this way, at first, we calculated the Partial TE for the original data. After that, we generated the surrogate data by mixing the original data and then we calculated Partial TE for the surrogate data. Data shuffling (generation of surrogate data) and calculation of Partial TE for surrogate data are repeated 100 times and a histogram of Partial TE (permutation distribution) is constructed. Based on the Partial TE of the original data and the constructed histogram, we calculated the p-value. If its value was smaller than the alpha-sensitive level (0.05), it can be concluded that the obtained Partial TE of the original data is statistically significant(Farokhzadi, Soltanian-Zadeh et al. 2016). We applied the mentioned surrogate data procedure separately to the Partial TE of each pair of channels. After the permutation test, we set the significant values to one and non-significant values to zero. As a result, the connectivity matrix generated from the analysis consists of binary values representing significant and non-significant connectivity. Each row and column of the connectivity matrix corresponds to a node, which in our study corresponds to an electrode. For example, the first row

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of the connectivity matrix shows the edges going from all other electrodes (i.e., the columns) to the first electrode.

We performed this process for all individuals in both the MDD and healthy groups across all frequency bands. After computation of the Partial TE between all pairs of channels, we obtained connectivity or adjacency matrices (19*19) for all epochs of the signals in each frequency band of each EEG session for all subjects. Since Partial TE is an effective connectivity measure and considers the direction of connectivity, the obtained adjacency matrices are not symmetrical. Thus, the brain networks corresponding to the obtained connectivity matrix will be binary directed networks.

2.6 Graph Theory Analysis

After constructing binary directed brain networks, we used graph theory metrics to analyze the topological characteristics of the obtained networks. These metrics include node degree (Deg), node betweenness centrality (BC), global efficiency (GE), local efficiency (LE), and diameter (Diam). We used the Brain connectivity toolbox(Rubinov and Sporns 2010) to compute network metrics. The mentioned network metrics are explained in the following part.

Let N denote the set of all nodes in the network, and let n be the total number of nodes in the network. Similarly, let L represent the set of all edges in the network, and let l be the total number of edges. For any link connecting nodes i and j $(i,j \in N)$ in the network, a_{ij} is 1 if i and j are connected, and 0 otherwise. The degree of node i is the number of edges connected to it and is given by(Rubinov and Sporns 2010):

$$k_i = \sum_{j \in N} a_{ij} \tag{2}$$

Betweenness centrality of node i is the proportion of all shortest paths in a network that include that node and is obtained by(Rubinov and Sporns 2010):

$$BC_i = \frac{1}{(n-1)(n-2)} \sum_{\substack{h,j \in N \\ h \neq j, h \neq i, j \neq i}} \frac{\rho_{hj}(i)}{\rho_{hj}} \tag{3}$$

where ρ_{hj} is the number of shortest paths between nodes h and j and $\rho_{hj}(i)$ is the number of shortest paths between h and j that includes node i.

GE is the average of the reciprocal of the shortest path length of the network and is obtained as follows (Rubinov and Sporns 2010):

$$E_{glo} = \frac{1}{n} \sum_{i \in N} \frac{\sum_{j \in N, j \neq i} d_{ij}^{-1}}{n-1} \tag{4}$$

where d_{ij} is the distance between two nodes of i and j and is defined as:

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$$d_{ij} = \sum_{a_{uv} \in g_{i \leftrightarrow j}} a_{uv} \tag{5}$$

where $g_{i \leftrightarrow j}$ is the shortest path between *i* and *j*.

The local efficiency of node *i* is the global efficiency computed on the neighborhood of that node(Rubinov and Sporns 2010):

$$E_{loc} = \frac{1}{n} \sum_{i \in N} E_{loc,i} = \frac{1}{n} \sum_{i \in N} \frac{\sum_{j,h \in N, j \neq i} a_{ij} a_{ih} \left[d_{jh}(N_i) \right]^{-1}}{k_i (k_i - 1)} \tag{6}$$

where $E_{loc,i}$ is the local efficiency of node *i*, and $d_{jh}(N_i)$ is the length of the shortest path between nodes *j* and *h* that the path only includes neighbors of node *i*.

GE and LE metrics are measures of a network's ability to transmit information globally and locally, which show functional integration in the whole network and functional separation in different areas of the network, respectively(Latora and Marchiori 2001).

Network diam is defined as the maximum of the shortest paths of the network and is given by(Rubinov and Sporns 2010):

$$D = \max_{j \in N} \max_{i \in N} d_{ji} \tag{7}$$

2.7 Correlation and Statistical Analysis

To assess the variations in the brain network in relation to the severity of MDD and identify the network characteristics that are most associated with depression severity, we conducted a correlation analysis. We calculated Spearman's rank correlation coefficient between the average BDI-II of individuals and the average characteristics of the network during the baseline and three treatment sessions (3rd, 6th, and 10th) in each of the four studied frequency bands(Myers, Well et al. 2010).

Furthermore, to assess the variability of network metrics between the two groups of responders and non-responders during treatment, we performed a statistical test. Specifically, we employed the Two-sample t-test on the network metrics of the responders and non-responders groups in four treatment sessions across four frequency bands. This analysis aimed to test the null hypothesis that there are no differences in the mean values of corresponding network metrics between the responders and non-responders groups in the studied frequency band. We performed multiple comparisons using Bonferroni correction(Rupert Jr 2012).

2.8 Classification

As previously mentioned, the recording of EEG signals and the construction of brain networks were done before the treatment and sessions 3, 6, and 10. Since a prompt diagnosis of non-response

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is crucial for minimizing complications resulting from ineffective treatment, we seek to determine the optimal timing for analyzing brain networks to predict treatment response. Specifically, we aim to identify whether analyzing brain networks at baseline, session 3, 6, or 10 is most effective in accurately classifying patients as responders or non-responders to treatment.

To accomplish this objective, we examine four possible scenarios for predicting and classifying treatment responses. The first scenario involves utilizing only the features of brain networks constructed from EEG data collected before treatment. The second scenario involves using the features of brain networks constructed from EEG data collected before treatment, as well as those collected after the third treatment session. The third scenario involves utilizing the features of brain networks constructed from EEG data collected before treatment, as well as those collected after the third and sixth treatment sessions. The fourth and final scenario involves utilizing the features of brain networks constructed from EEG data collected before treatment, as well as those collected after the third, sixth, and tenth treatment sessions.

For the classification process, to increase the number of samples in both the responders and non-responders classes, we considered each epoch as a distinct individual. Then we employed 80% of the data as training data for constructing the classification model, using the Leave-One-Out Cross-Validation (LOOCV) method. Then we utilized the remaining 20% of the data for classification testing. We performed the feature selection using the minimum Redundancy Maximum Relevance (mRMR) algorithm(Peng, Long et al. 2005). After feature selection, we applied the K-Nearest Neighbors (KNN), SVM, and decision tree classifier to the selected features in each frequency band, as well as across all frequency bands, to classify individuals as R or NR.

3 RESULTS

3.1 Correlation between EEG-based Brain Network Metrics and Depression Severity Scores

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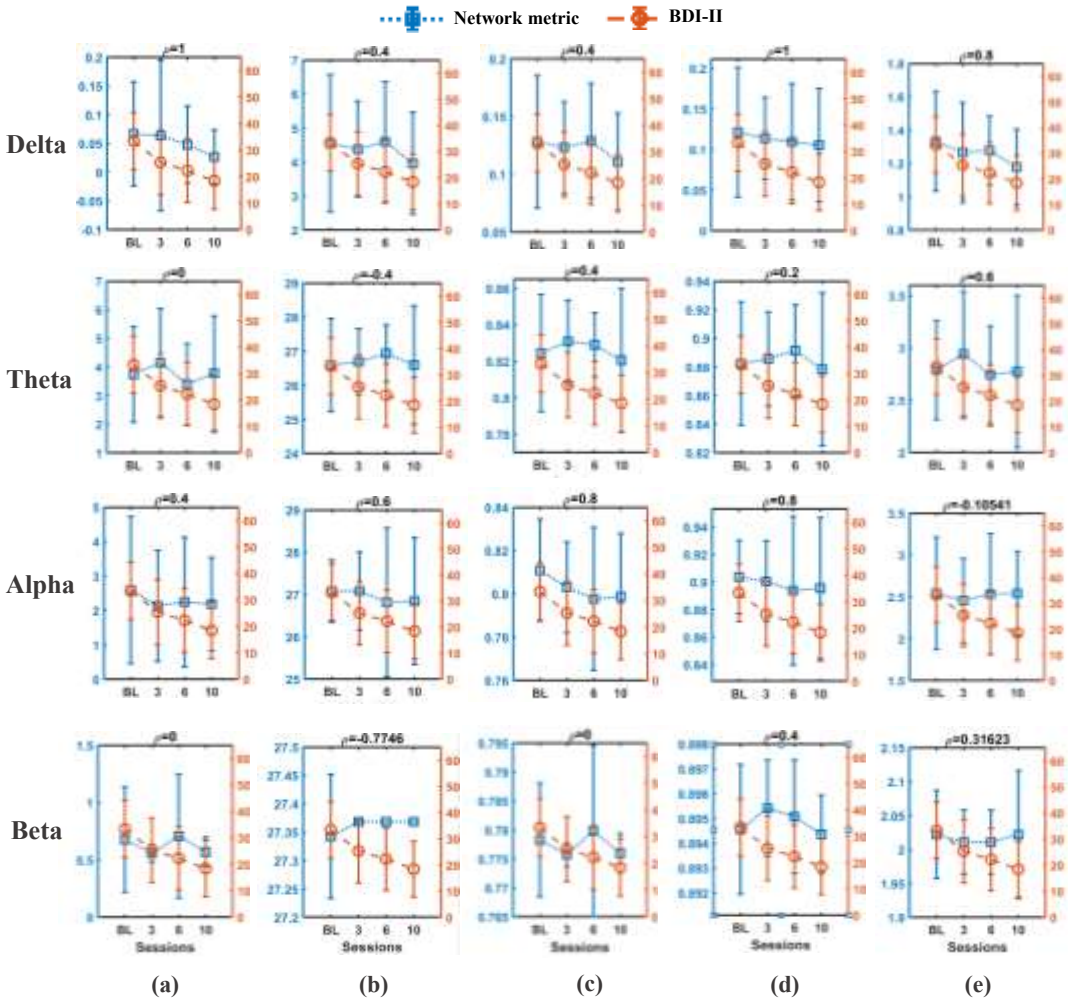

Figure 2. Average BDI-II (in red) and average (a) node betweenness centrality, (b) node degree, (c) global efficiency, (d) local efficiency, and (e) diameter (in blue) of EEG-based brain networks of the pre-treatment session (BL) and sessions 3, 6, and 10 of treatment for all subjects in delta, theta, alpha, beta frequency bands. Error bars indicate the standard deviation, ρ denotes the Spearman's rank correlation coefficient between BDI-II and network metric.

Figure 2 displays the mean and standard deviation of the BDI-II score and EEG-based brain network metrics for all participants in the pre-treatment session, as well as sessions 3, 6, and 10 of treatment, across the delta, theta, alpha, and beta frequency bands. Additionally, the correlation coefficient (ρ) of BDI-II and network metrics, calculated using Spearman's rank correlation coefficient, is indicated at the top of each figure. From Figure 2, it can be seen that the average measures of BC, Diameter, and LE in delta band, and GE and LE in the alpha band have a correlation of 0.8 or higher with the average BDI-II. Results from the applied statistical test indicated that there are no significant differences between the obtained network metrics in responders and non-responders during the treatment.

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https://doi.org/10.1016/j.bspc.2024.106613

3.2 Classification of Metrics of EEG-Based Brain Networks for Treatment Response Prediction

The classification results for predicting treatment response using the brain network metrics extracted from EEG data at different time points are presented in figure 3 and Table A1 (Appendix A). Four scenarios were evaluated, utilizing the network features obtained from EEG of individual frequency bands and all frequency bands recorded at 1) baseline (before treatment), 2) baseline and after the 3rd treatment session, 3) baseline, after 3rd and 6th sessions, and 4) baseline, after 3rd, 6th and 10th sessions.

In the first scenario using only baseline EEG data, the highest test accuracy was achieved by KNN for delta band (accuracy train: 88.89%, accuracy test: 83.33%). The KNN results for theta band also were close to delta band (accuracy train: 86.11%, accuracy test: 83.33%) with slightly lower training accuracy and test sensitivity but higher test specificity. The second scenario, incorporating data from baseline and the 3rd treatment session, demonstrated improved classification performance. The KNN classifier achieved a maximum training accuracy of 93.06% and test accuracy of 88.89% using features from the theta band. The results for classification by delta band also yield 88.89% test accuracy and 100% test specificity but lower train performance and test sensitivity compared to theta band (sensitivity train: 95.65% and sensitivity test: 77.78%).

Further incorporating data from the 6th treatment session in the third scenario and 6th and 10^{th} in the final scenario improve substantially the testing accuracy to the highest value of 94.44% but with the same highest training accuracy obtained in scenario 2 (accuracy train: 93.06%). The KNN classifier demonstrated 93.06% training accuracy and 94.44% testing accuracy using theta band features in both scenarios. In addition to KNN, the SVM classifier also performed strongly with 94.44% training accuracy and 88.89% testing accuracy in scenario 3, and 88.89% training and testing accuracy in scenario 4.

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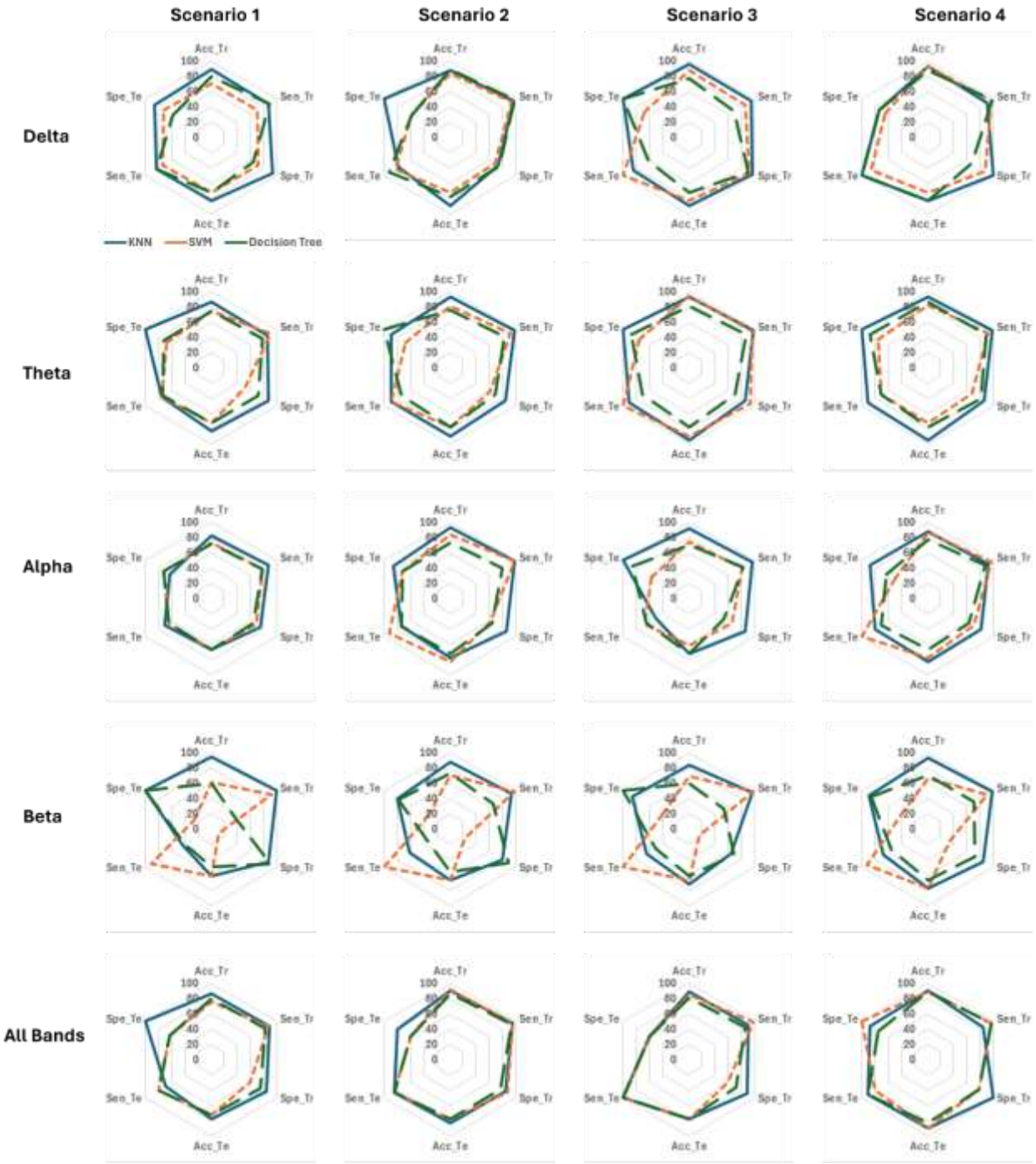

Figure 3: Accuracy (ACC), sensitivity (SEN), and specificity (SPE), of classification of responders and non-responders groups by KNN, SVM, and decision tree based on the metrics of the network in each frequency band and all bands in the train and test data set in scenario 1 (EEG before treatment), scenario 2 (EEG before and the third session of treatment), Scenario 3 (EEG before, and after third and sixth session of treatment) and scenario 4 (EEG before and after third, sixth and tenth session of treatment).

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4 DISCUSSION

In the current study, we analyzed the EEG-based brain networks of MDD patients undergoing rTMS treatment, before and after the 3rd, 6th, and 10th sessions of rTMS treatment, using Partial TE. The decision to record EEG signals during the first half of the treatment period was motivated by the main goal of the study, which was to provide a method for predicting rTMS treatment response in MDD patients and preventing ineffective treatment. Thus, it would be more desirable to find the responding results earlier, based on the data obtained from early sessions of treatment.

A comparison of the present study with previous works investigating the use of EEG for predicting rTMS treatment response in MDD is presented in Table 2. Most prior studies have focused on analyzing conventional EEG features, such as power spectral density, cordance, complexity measures, and connectivity metrics like coherence. In contrast, our study is one of the first to explore the brain networks by multivariate, nonlinear, non-model-based connectivity measure namely PartialTE. Furthermore, our study is the first to investigate the relationship between graph theory metrics of brain networks and depression severity levels during the course of treatment. The observed correlations between measures like betweenness centrality, global/local efficiency, and network diameter with depression scores offer insights into the network-level alterations associated with symptom improvement or persistence. These findings may contribute to a better understanding of the neural mechanisms underlying rTMS treatment response in MDD. While several studies have reported promising classification accuracies using EEG features, ranging from 75% to 98.51%, our approach achieved comparable accuracies of up to 94.44% using topological metrics of EEG-derived brain networks.

The obtained networks are explored by evaluating various characteristics of the networks using graph theory metrics and conducting correlation and classification analyses. The results of correlation analysis have revealed that there is a significant correlation between the level of depression in individuals and BC of the brain network, particularly in the delta band. This correlation was found to be 1, indicating a strong relationship between the two factors. Interestingly, this finding is consistent with previous studies that have also reported a strong association between BC of brain networks and depression levels in MDD patients. It has been reported that MDD patients exhibit increased nodal centralities in the left hippocampus and left caudate nucleus, and these changes are linked to the duration and severity of the depression(Zhang, Wang et al. 2011). Our study indicated a significant correlation between the level of depression and GE in the alpha band brain networks. This finding is aligned with previous research that has reported higher GE in individuals with MDD compared to healthy individuals (Zhang, Wang et al. 2011, Hasanzadeh, Mohebbi et al. 2020) .Additionally, we found that the average LE in both the delta and alpha bands was also positively correlated with depression level. However, some previous studies have reported that MDD patients have more randomized brain network structures (lower clustering coefficient and characteristic path length (Sporns 2016) or higher GE and lower LE (Latora and Marchiori 2001)) compared to healthy individuals (Sun, Li et al. 2019). Therefore, we initially expected LE to increase with depression level. The discrepancy between current

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findings and previous studies may be due to the averaging of LE, which is a local measure. Furthermore, there is a noticeable trend where a decrease in the BDI-II level corresponds to a decrease in the diameter of the network in the delta band. A smaller network diameter implies that information is processed more efficiently between remote regions of the brain (Cao, Hao et al. 2020). Therefore, the observed reduction in network diameter with decreasing depression levels suggests an enhancement in the efficiency of information processing in the brain. The observed high correlations between network metrics and depression severity were primarily in the delta and alpha frequency bands. This is in line with findings of previous studies that reported the association of variation of EEG power within the delta(Knott, Telner et al. 1996, Knott, Mahoney et al. 2000) and alpha frequency band(Ulrich, Renfordt et al. 1984, Suffin and Emory 1995, Knott, Mahoney et al. 2000, Bruder, Stewart et al. 2001, Bruder, Sedoruk et al. 2008, Hasanzadeh, Mohebbi et al. 2019) with treatment response in MDD. These results further underscore the importance of investigating delta and alpha power and related network metrics in the context of MDD and its treatment.

We also applied a statistical test to compare the extracted brain network metrics in responders and non-responders before and during treatment. This test was conducted separately for all frequency bands, and we further performed multiple comparisons to ensure the accuracy of the results. The results indicated that there was no significant difference between the two groups for the studied metrics. However, it is important to note that this lack of significant differences could potentially be attributed to the relatively small sample size used in our study.

The classification analysis investigated the ability to predict rTMS treatment response in MDD patients based on topological properties of EEG-derived brain networks at different stages of the treatment process. By evaluating four scenarios spanning from baseline to the 10th treatment session, we could assess the optimal timing for leveraging network metrics to accurately identify responders and non-responders. The results revealed a progressive improvement in the highest classification accuracy as data from later treatment sessions were incorporated, up until the 6th session. However, utilizing even the baseline data could achieve a test accuracy as high as 83.33%. The scenario incorporating data from the 3rd treatment session demonstrated higher accuracies compared to baseline data, with the KNN classifier attaining 88.89% for testing and 93.06% for training using theta band features. Remarkably, the highest classification testing accuracies of 94.44% were achieved when data from the 6th or 10th treatment sessions were incorporated, particularly using the KNN classifier with theta band network features. Similar highest performance by third and fourth scenarios indicates that inclusion of network measures extracted from EEG signals recorded in a larger number of treatment sessions may not significantly improve the prediction of treatment response. Thus, inclusion of brain network metrics extracted from EEG signals acquired during the early stages of treatment can be sufficient for predicting treatment response with a high accuracy. The superior performance of the theta band network metrics can be considered aligned with previous studies that have reported associations between theta power, theta connectivity, and rTMS treatment response in MDD (Arns, Drinkenburg et al. 2012, Bares,

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Brunovsky et al. 2015, Bailey, Hoy et al. 2019) However, more specific analysis regarding the extracted brain network measures is required to conclusively affirm this finding.

Despite the insights gained from this study, it's essential to acknowledge its limitations. The relatively small sample size may have influenced the generalizability of the results. Additionally, the analysis focused on a specific set of graph theory metrics; incorporating a broader range of network measures could potentially yield further insights into the network-level changes associated with treatment response.

Table 2: Summary of studies on prediction of TMS treatment response using EEG in major depressive disorder

Study	Participants	Features	EEG Recording	Main Findings
(Khodayari-Rostamabad, Reilly et al. 2011)	27 MDD (18 NR, 9 R)	EEG power ratios at various frequencies	Before treatment	predicting rTMS treatment outcome with pre-treatment EEG. (Specificity: 83%, Sensitivity: 78%, Combined accuracy: 80%)
(Arns, Drinkenburg et al. 2012)	90 MDD (20 NR, 70 R)	theta power, individual alpha peak frequency, P300 amplitude, pre-frontal delta and beta cordance	Before treatment	Increased fronto-central theta power, slower anterior alpha peak frequency, larger P300 amplitude, decreased pre-frontal delta and beta cordance in NR. (AUC: 0.814)
(Arns, Cerquera et al. 2014)	90 MDD (20 NR, 70 R), 17 HC	Lempel-ziv complexity, false nearest neighbors, largest Lyapunov exponent	Before treatment	NR showed decreased Lempel-Ziv Complexity over time compared to R and HC.
(Bares, Brunovsky et al. 2015)	50 MDD (31 NR, 19 R)	Prefrontal theta band cordance	Baseline, Week 1	R showed reduced theta cordance at Week 1 for both rTMS and venlafaxine. (AUC: 0.75 for rTMS , 0.89 for venlafaxine)
(Erguzel, Ozekes et al. 2015)	55 MDD (25 NR, 30 R)	Frontal QEEG cordance	Before treatment	Identified R with 93.33% sensitivity, 89.09% accuracy
(Bailey, Hoy et al. 2018)	50 MDD (29 NR, 10 R), 20 HC	Theta, alpha, gamma power, connectivity, theta-gamma coupling EEG during working memory task	Before treatment, Week 1	higher fronto-midline theta power, theta connectivity, and gamma connectivity increase from baseline to W1 in R. similar fronto-midline theta power and connectivity in R and controls. (sensitivity: 0.90, specificity: 0.92)
(Krepel, Sack et al. 2018)	196 MDD (66 NR, 130 R)	Frontal theta, P300 amplitude, individual alpha peak frequency	Before treatment	No significant differences in frontal theta, P300 amplitude, or individual alpha peak frequency between R and NR
(Shalbaf, Brenner et al. 2018)	51 MDD, 25 HC (20 NR, 31 R)	Permutation entropy of obtained intrinsic mode	Before treatment	R had increased permutation entropy index of IMF 2 compared

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		functions by Empirical Mode Decomposition		to non-responder at F3, FCz and FC3. (AUC: 0.8)
(Bailey, Hoy et al. 2019)	50 MDD (30 NR, 12 R), 21 HC	Theta and alpha power and connectivity, frontal theta cordance, alpha peak frequency	Before treatment and week 1	Elevated theta connectivity in R at baseline and week 1; predictive potential for rTMS response. (Sensitivity: 0.84, Specificity: 0.89)
(Hasanzadeh, Mohebbi et al. 2019)	46 MDD (23 NR, 23 R)	Lempel-Ziv complexity, Katz fractal dimension, correlation dimension, power spectral density features	Before treatment	Beta power, bispectrum diagonal elements (delta and beta), and Correlation Dimension were discriminative features
(Cook, Wilson et al. 2019)	16 MDD	EEG power, coherence	Before treatment, Week 1, Week 6	No significant differences in power measures between active and sham groups. Changes in alpha current source density correlated with symptom changes in active sTMS, not in sham.
(Corlier, Wilson et al. 2019)	109 MDD (45% R)	Coherence, envelope correlation, alpha spectral correlation	Before and after treatment	Changes in functional connectivity by alpha spectral correlation predicted clinical outcome with highest accuracy. (AUC: 0.83 for alpha spectral correlation)
(Hasanzadeh, Mohebbi et al. 2020)	46 MDD (23 NR, 23 R)	Power spectral density, nonlinear and bispectral features	Before treatment	F8 channel classified R and NR with 80% accuracy
(Vlcek, Bares et al. 2020)	25 MDD (9 R)	eLORETA current density, spectral absolute power, inter-hemispheric and intra-hemispheric EEG asymmetry	Before treatment	R had lower alpha-2 and beta-1 current source densities in frontal regions
(Nobakhsh, Shalbaf et al. 2022)	34 MDD (17 R, 17 NR)	Direct Directed Transfer Function	Before treatment	Fp2 region in delta and theta bands differed between R and NR. (Accuracy: 89.6%)
(Shahabi, Shalbaf et al. 2022)	46MDD (23 R, 23 NR)	Raw EEG signal	Before treatment	Ensemble of hybrid CNN-BLSTM models showed high classification performance. (Accuracy: 98.51%, Sensitivity: 98.64%, Specificity: 98.36%)
(Bailey, Hoy et al. 2023)	39 MDD, 21 HC (30 NR, 12 R)	N100 amplitude, N100 slope, theta power of EEG during working memory task	Before treatment	Neither N100 amplitude nor theta power differed between R and NR, higher negative N100 slope for single pulses and higher positive slope for pp100 pulses at F3 in R compared to NR.
Current Study	18 MDD (7 NR, 11 R)	Graph theory metrics from EEG-derived brain	Before treatment, after 3rd, 6th, and 10th	betweenness centrality and Diameter in Delta band, alpha band global efficiency and local efficiency in delta/alpha bands

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	networks based on Partial Transfer Entropy	treatment sessions	correlated with depression severity. Classification of R and NR utilizing network metrics based on EEG data up to 6th session achieved high training accuracy of 93.06% and test accuracy of 94.44%

5 CONCLUSION

In the current study for the first time, we examined EEG-based brain networks and their topological measures in MDD patients during the rTMS treatment. The results suggest that network metrics including node betweenness centrality, diameter, and local efficiency in the delta band and global and local efficiency in alpha frequency bands have a high correlation with depression severity. The classification results indicate that using metrics of brain networks constructed from EEG signals recorded at second week of treatment can predict treatment response with an accuracy higher than 94%. Overall, this study provides insights into the potential effects of treatment on brain networks, and the utility of EEG-based brain network measures for predicting treatment response and highlights the importance of selecting an optimal time frame for EEG signal recording to facilitate effective treatment approaches.

DECLARATION OF INTEREST

None.

ROLE OF THE FUNDING SOURCE

None.

ACKNOWLEDGMENT

We would like to acknowledge the Atieh Psychiatry Center for collecting data and express our gratitude to all the participants who participated in this study.

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Appendix A:

Table A1: Accuracy, sensitivity, and specificity, of classification of responders and non-responders groups by KNN, SVM, and decision tree based on the metrics of the network in delta, theta, alpha and beta frequency band and all bands in the train and test data set in scenario 1 (EEG before treatment), scenario 2 (EEG before and the third session of treatment), Scenario 3 (EEG before, and after third and sixth session of treatment) and scenario 4 (EEG before and after third, sixth and tenth session of treatment).

#Scenario	Frequency bands	Train				Test		
		Classifier	Accuracy	Sensitivity	Specificity	Accuracy	Sensitivity	Specificity
Scenario 1	Delta	KNN	88.89	86.36	92.86	83.33	81.82	85.71
		SVM	70.83	70.45	71.43	72.22	72.73	71.43
		D Tree	79.17	88.64	64.29	72.22	81.82	57.14
	Theta	KNN	86.11	86.05	86.21	83.33	75	100
		SVM	75	90.7	51.72	72.22	75	66.67
		D Tree	75	77.27	71.43	72.22	72.73	71.43
	Alpha	KNN	81.94	86.67	74.07	66.67	70	62.5
		SVM	73.61	77.27	67.86	66.67	63.64	71.43
		D Tree	72.22	77.27	64.29	66.67	63.64	71.43
	Beta	KNN	94.44	100	86.21	61.11	41.67	100
		SVM	61.11	91.11	11.11	61.11	90	25
		D Tree	59.72	35	90.63	50	40	100
	All bands	KNN	86.11	88.1	83.33	77.78	69.23	100
		SVM	76.39	86.67	59.26	72.22	80	62.5
		D Tree	79.17	82.22	74.07	72.22	80	62.5
Scenario 2	Delta	KNN	87.5	95.65	73.08	88.89	77.78	100
		SVM	83.33	93.18	67.86	72.22	81.82	57.14
		D Tree	88.89	97.73	75	77.78	90.91	57.14
	Theta	KNN	93.06	97.83	84.62	88.89	88.89	88.89
		SVM	80.56	91.3	61.54	77.78	88.89	66.67
		D Tree	76.39	82.5	68.75	77.78	73.33	100
	Alpha	KNN	93.06	97.73	85.71	77.78	72.73	85.71
		SVM	83.33	97.73	60.71	83.33	90.91	71.43
		D Tree	73.61	79.55	64.29	72.22	72.73	71.43
	Beta	KNN	87.5	92.86	80	66.67	61.54	80

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		SVM	70.83	97.83	23.08	66.67	100	33.33
		D Tree	73.61	65.22	88.46	55.56	33.33	77.78
	All bands	KNN	90.28	95.24	83.33	83.33	84.62	80
		SVM	91.67	95.24	86.67	77.78	84.62	60
		D Tree	86.11	92.86	76.67	77.78	84.62	60
Scenario 3	Delta	KNN	95.83	95.24	96.67	88.89	84.62	100
		SVM	87.5	84.78	92.31	83.33	100	66.67
		D Tree	77.78	69.05	90	72.22	61.54	100
	Theta	KNN	93.06	97.78	85.19	94.44	90	100
		SVM	94.44	95.56	92.59	88.89	100	75
		D Tree	80.56	86.67	70.37	77.78	70	87.5
	Alpha	KNN	91.67	95.56	85.19	72.22	50	100
		SVM	75	80.43	65.38	61.11	66.67	55.56
		D Tree	70.83	81.82	53.57	72.22	63.64	85.71
	Beta	KNN	83.33	95.45	64.29	72.22	63.64	85.71
		SVM	69.44	97.87	16	66.67	100	40
		D Tree	59.72	53.66	67.74	61.11	50	100
	All bands	KNN	88.89	89.36	88	77.78	100	60
		SVM	84.72	97.87	60	77.78	100	60
		D Tree	80.56	85.11	72	77.78	100	60
Scenario 4	Delta	KNN	93.06	89.58	100	83.33	100	72.73
		SVM	93.06	95.83	87.5	72.22	85.71	63.64
		D Tree	87.32	97.87	66.67	83.33	100	72.73
	Theta	KNN	93.06	97.78	85.19	94.44	90	100
		SVM	81.94	91.11	66.67	72.22	70	75
		D Tree	86.11	88.89	81.48	77.78	70	87.5
	Alpha	KNN	87.5	91.11	81.48	83.33	80	87.5
		SVM	86.11	95.56	70.37	77.78	100	50
		D Tree	77.78	86.67	62.96	66.67	70	62.5
	Beta	KNN	93.06	97.83	84.62	77.78	66.67	88.89
		SVM	66.67	90.48	33.33	77.78	92.31	40
		D Tree	70.83	70.45	71.43	66.67	54.55	85.71
	All bands	KNN	90.28	84.44	100	88.89	90	87.5
		SVM	88.89	95.56	77.78	88.89	80	100
		D Tree	88.89	95.56	77.78	83.33	90	75