Title: Graph-Based Analysis to Predict Repetitive Transcranial Magnetic Stimulation Treatment Response in Major Depressive Disorder Patients Using EEG Signals

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Abstract

Repetitive transcranial magnetic stimulation (rTMS) is considered a non-pharmacological treatment for drug-resistance Major Depressive Disorder (MDD) patients. Since the outcome rate of rTMS treatment is about 50-55 %, it is essential to predict the treatment outcome before starting the treatment based on electroencephalogram (EEG) signals, which can lead to the identification of effective biomarkers and could reduce the burden of health care centers. Pretreatment EEG data with 19-channel in the resting state from 34 drug-resistant MDD patients were recorded. All patients received 20 sessions of rTMS treatment, and a reduction of at least 50% in the total Beck Depression Inventory (BDI-II) score before and after the rTMS treatment is defined as a reference. In current study, effective brain connectivity features are determined by the direct directed transfer function (dDTF) method from pre-treatment EEG data of patients in all frequency bands separately. Then, the brain functional connectivity patterns are modeled as graphs by the dDTF method and examined with the local graph theory indices including degree, out-degree, in-degree, strength, out-strength, in-strength, and betweenness centrality. The results indicated that the Betweenness centrality index in node Fp2 and delta frequency band is the best biomarker and has the highest area under the receiver operating characteristic curve (AUC-ROC) value of 0.85 for prediction of the rTMS treatment outcome in drug-resistance MDD patients. The proposed method investigates the significant biomarkers that can be used to obtain the rTMS treatment outcome in drug-resistance MDD patients to help clinical decisions.

Keywords: Effective connectivity, Electroencephalogram (EEG), Graph theory, Major depressive disorder (MDD), Repetitive transcranial magnetic stimulation (rTMS).

Introduction

Major Depressive Disorder (MDD) is a common mental disorder that affects over 264 million people of different ages. Depression is an important cause of disability and contributes significantly to the overall burden of illness associated with personal, social, and economic problems [1, 2]. People with MDD experience symptoms such as low and chronic mood, decreased pleasure from previous activities, sleep disorders, mental retardation, fatigue and energy loss, weight change, and negative thoughts. They also include pessimism to sin and the idea of suicide [3].

Medicines and psychotherapy are the first lines of treatment for MDD. However, around one-third of patients failed to respond to these treatments and were identified as treatment-resistant MDD patients [4]. Electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS) are considered non-pharmacological treatments for drug-resistant MDD patients. ECT has anesthesia risk, memory changes, and social stigmatization, whereas the rTMS is less invasive and painful than the ECT [5-7]. The rTMS is based on the patient's and treatment procedure stimulation parameters such as coil's shape, intensity, frequency, train duration, and inter-train interval, applied a series of magnetic pulses to the cerebral cortex. These magnetic pulses can modulate the neuronal activity of target points [8]. rTMS can change brain activity according to its frequency: high frequency (HF) (usually $\geq$ 10 Hz) is used to stimulate the target point, whereas low frequency (LF) (usually $\leq$ 1 Hz) inhibits the target point. [9]. Due to the left hypoactivity and right hyperactivity dorsolateral prefrontal cortex (DLPFC) in MDD patients, HF rTMS and LF rTMS are applied to the left and right DLPFC, respectively [10, 11]. Recent studies indicated that the outcome rate of rTMS treatment in people with MDD is about 50-55% [12, 13]. According to the fact that the rTMS treatment period is long (about 20 sessions) and the costs on healthcare systems are high, predicting the response to treatment through a personalized medicine approach is necessary and helps clinical decisions [14].

Currently, the prescription of rTMS treatment is based on clinical evaluation and lacks sufficient accuracy to predict the rTMS treatment outcome, especially before starting the treatment [15]. In one study, demographic indicators, depressive characteristics, and medicinal history were used as clinical predictors, and results demonstrated that MDD patients who are younger and show less refractory to medication have a better response to the rTMS treatment [16]. Another study, in addition to age, examined the effects of gender, menopausal status, and ovarian hormone levels in women. It was shown that there was no difference in rTMS response between men and premenopausal women (68.8% and 70.6%, respectively). Besides, the rTMS treatment outcome in postmenopausal women is low. The regression analysis has indicated that menopause and ovarian steroid levels play a key role in the rTMS treatment outcome in women [17]. In one study, Rostami et al. evaluated clinical and demographic data. It

has resulted that patients who showed better cognitive-emotional symptoms responded better to rTMS treatment than the somatic symptoms [18]. As observed in these studies, the use of clinical data, due to the MDD patients' differences in individual characteristics and brain structures, does not have sufficient accuracy in predicting the rTMS treatment outcome.

The search for biomarkers to predict the rTMS treatment outcome in MDD patients has expanded on neuroimaging methods based on electroencephalogram (EEG). EEG is widely used in clinical decisions and can lead to the identification of effective biomarkers due to many advantages, including ease of use, sufficient temporal resolution, non-invasiveness, and accessibility in the clinic [19, 20]. Several linear and nonlinear measures from EEG signals have been proposed as predictors of the rTMS treatment outcome in patients with drug-resistant MDD. In one study, nonlinear EEG features including Lempel – Ziv Complexity (LZC) and Largest Lyapunov Exponent in alpha frequency band were used. Non-responders indicated a significant decrease in LZC, while responders showed an increase in LZC [21]. In another study, MDD patients were classified into responder and non-responder for rTMS treatment using feature selection of EEG signals based on a genetic algorithm and an artificial neural network [22]. In other studies, additional features such as Permutation Entropy [15], Katz fractal dimension, and correlation dimension [23] were extracted from EEG signals and investigated to predict the rTMS treatment outcome in drug-resistant MDD patients. These methods contribute to analyzing the complexity of EEG signals, but the EEG signal is non-stationary, and these methods have limitations in estimating accurate temporal patterns.

Using neuroimaging techniques, it has become clear that a single EEG channel cannot represent complicated neurophysiological changes in psychiatric disorders. Recent research has indicated that the human brain is a complex integrated network consisting of the brain’s areas interconnected to form subnets of the brain. Examining these networks can provide a new perspective on how the brain works. Consequently, understanding the brain’s neural dynamic patterns and behavior provides the best features to predict rTMS treatment response. Complex interactions across brain regions can be described through two categories of brain connectivity measures: functional, and effective [24]. Functional connectivity indicates only coordinated activity and statistical dependency between brain areas, while effective connectivity provides information about the causal relationship between brain areas [25]. Granger Causality (GC) is widely used to estimate the effective brain connectivities which characterize the directed information flow and causal interaction between time-series of EEG signals. Graph theory methods are often used for quantitative analysis of brain connection. Graph theory is a theoretical platform to examine complex networks like the brain, which can provide valuable information about the local organization of the functional brain networks [26].

The novelties of the current study are the use of effective brain connectivity measures by pre-treatment EEG signals to estimate the graph theory indices, which helps to identify the brain's complex networks and its best patterns to find significant biomarkers between two groups of responder and non-responder MDD patients. These will lead to a decrease in the time and cost of the patients before starting the rTMS treatment.

Materials and methods

Participants and Clinical assessment

The EEG Data were recorded at the Atieh Clinical Neuroscience Center from 34 MDD patients with refractory to medication (mean age 37.1, standard deviation = 13.4, 25 women) who were referred to rTMS treatment. An experienced psychiatrist with a structured clinical interview for Axis I DSM-IV [27] made the diagnosis of MDD, and the patient was subjected to a baseline clinical assessment that confirmed the Beck Depression Inventory (BDI-II) score [28]. The BDI-II is an inventory of twenty-one self-report questions dealing with the status of the subjects in their past week. Each question consists of four answers ranging in intensity. All MDD patients received 20 sessions of rTMS treatment, three sessions per week, in the right DLPFC area of the brain. BDI score for all MDD patients was assessed one week before rTMS treatment and after 20 sessions of rTMS. A reduction of at least 50% of the total BDI score is defined as the rTMS treatment outcome. In the current study, all participants' written consent has been obtained and authorized by the Shahid Beheshti University of Medical Sciences ethics committee. The demographic data and clinical characteristics of participants have been summarized in Table 1.

rTMS treatment parameters

Atieh Clinical Neuroscience Center is utilized a Neuro MS rTMS device (Neurosoft, Russia) for patients referred to the rTMS treatment. Magnetic pulses are delivered through a 70 mm stimulation coil (air film coil). Each patient's motor threshold is defined as the lowest intensity needed to stimulate the motor cortex that is caused a contraction of the Abductor Pollicis Brevis (APB) muscle in at least 5 out of 10 attempts. The coil position is defined as 5 cm anterior along a parasagittal line from the site of optimum APB stimulation. All patients received the LF-rTMS protocol. In this protocol, stimulation was delivered over the right DLPFC, at 120% of the resting motor threshold, for 10 s 1-Hz with 2 s intervals. This procedure is repeated 200 times (2000 pulses) per session (40,000 pulses over 20 sessions).

Pre-treatment EEG acquisition

All EEG signals were recorded in the resting state with closed eyes condition for 300 seconds with 19-channel of Ag/AgCl electrodes (Mitsar-EEG 201 machine). The position of the electrodes was according to the 10-20 standard (Fp1, Fp2, F7, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, O1, and O2) and the sampling rate of recorded EEG signals was 250 Hz.

EEG pre-processing

The EEGLAB open-source toolbox [29] has been used to preprocess and remove the environmental and movement noise from EEG data. At first, a high-pass filter (1 Hz) filtered EEG signals to remove the baseline drift. EEG signals were re-referenced by the average reference. The CleanLine open-source plugin [30] in the EEGLAB toolbox has been used to remove the line noise from EEG signal channels. The CleanLine plugin uses a sliding window to estimate sine wave amplitude to decrease, and in comparison with a notch filter, it does not make a hole in the EEG spectrum. EEG data were cleaned visually by the "reject continuous data by eye" section to remove the motion artifacts (that existed in all channels). After relative cleanliness, Independent Component Analysis (ICA) was utilized to clean the data from blinking and head movements. In the end, to unify the data, we hold 150 seconds of all subjects.

Effective Connectivity

Effective connectivity provides information on the causal interaction relationship between time-series of EEG signals and characterizes the directed information flow [25]. Effective connectivity is extracted by the SIFT open-source plugin [31] in the EEGLAB toolbox. The Granger Causality (GC) is widely used to calculate effective brain connectivities. The directed transfer function (DTF) is a GC-based scale defined in the frequency domain and could compute based on a multivariate autoregressive model (MVAR) [32]. For an $X(t)$ as k-channel multivariate time series, it obtains:

$$X(t) = (X_1(t), X_2(t), \dots, X_k(t) \tag{1}$$

$$X(t) = \sum_{j=1}^{p} A(j)X(t-j) + E(t) \tag{2}$$

Coefficients of A and $E(t)$ are $k \times k$ -sized matrices and k -size vectors, respectively. Then the model is transformed into a multivariate autoregressive in the frequency domain to obtain the system transfer matrix:

$$E(f) = A(f)X(f)$$
$$X(f) = A^{-1}(f)E(f) = H(f)E(f) \quad (3)$$
$$H(f) = \left(\sum_{m=0}^{p} A(m)e^{-2\pi imf\Delta t}\right)^{-1}$$

The filter coefficients matrix $H(f)$ is known as the system transfer matrix. The transfer matrix makes it possible to find cross-spectra and partial coherences:

$$C_{ij}(f) = \frac{M_{ij}(f)}{\sqrt{M_{ii}(f)M_{jj}(f)}}$$
$$F_{ij}^2(f) = \frac{\left|H_{ij}(f)\right|^2}{\sum_f \sum_{m=1}^{k} |H_{im}(f)|^2} \quad (4)$$

Where $C_{ij}(f)$ is partial coherence and M_{ij} is a minor of the spectral matrix, and the DTF modification ($F_{ij}^2(f)$) concerned the function normalization to make the denominator independent of frequency. The dDTF ($\chi_{ij}(f)$) indicates direct propagation from channel j to i:

$$\chi_{ij}^2(f) = F_{ij}^2(f)C_{ij}^2(f) \quad (5)$$

There exists a direct causal relation between channels $j \rightarrow i$ when both functions $F_{ij}^2(f)$ and $C_{ij}^2(f)$ are non-zero. So, the dDTF method has compensated for the lack of other effective connectivity by combining the advantages of DTF and partial coherence methods and has indicated more reliable effective connectivity.

Graph analysis

Graph theory analysis has been used to obtain a new perspective on complex networks such as the brain. The brain nervous system is a complex network, and it can be modeled in the form of a graph. The EEG channels (brain regions) are defined as nodes, and the edges represent the brain connections calculated by the dDTF method. Then, brain function based on graph indices can be assessed [33]. For each obtained graph, the local indices have been calculated [33, 34]. The first index is degree; the node's degree represents the number of neighbors connected to the given node. This index can be computed inward and outward links as in-degree and out-degree, respectively. Each edge (link) has a weight that indicates whether the connection is strong or weak. Strength is the sum of all neighboring link weights. Furthermore, the strength of nodes can be computed inward and outward links as in-strength and out-strength. Another important graph-based index is the centrality, which makes it possible to assess the

node's importance interactions with other nodes [35]. Betweenness centrality calculates these types of nodes and demonstrates the fraction of all shortest paths in the network that pass across a given node. Graph-based indices are calculated using functions implemented in the BCT open-source toolbox [33].

Statistical analysis

The statistical analysis assesses the significance of the extracted features. The current study has used the Wilcoxon rank-sum test to examine the sample independence of the two groups [36]. The area under the receiver operating characteristic curve (AUC-ROC) has been used to evaluate the performance of two group classification algorithms to select the best features. [37].

Overview of the proposed method

The proposed method's block diagram has summarized in Figure 1. First, the raw EEG data will be processed using the EEGLAB open-source toolbox. The pre-processing block utilizing to remove the environmental and subject artifacts to extract the pure brain activity, including frequency filtering and line noise cancellation, artifacts removal, ICA (to remove blinking and head movements), and time correction. Then, the effective brain connectivity between 19 EEG signal channels is calculated using the dDTF method in all frequency bands of the delta, theta, alpha, beta, and gamma and used as the extracted feature using the SIFT plug-in [38] in the EEGLAB toolbox. The connectivity matrix (dDTF) is 19 × 19 per patient. In the following, brain function is modeled as a graph by the dDTF method and examined with the local graph theory indices such as degree, out-degree, in-degree, strength, out-strength, in-strength, and betweenness centrality. Finally, the Wilcoxon rank-sum test (p-value) and AUC-ROC utilizing to identify the best indices and significant biomarkers to predict the rTMS treatment outcome in MDD patients with drug-refractory.

Results

Each EEG data after pre-processing were segmented to a window length of 10 seconds. The dDTF values indicate a causal relationship between different brain areas based on parameters of MVAR model. The dDTF brain connectivity features have been extracted in the delta (1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), beta (12-30 Hz), and gamma (30-40 Hz) frequency bands, separately. The MVAR model parameters have been selected according to autocorrelation function and portmanteau tests (model order = 12). Autocorrelation function and portmanteau tests have been used to pass the order selection criteria (whiteness, consistency, and stability). The dDTF method calculated the connectivity matrix by 10-second windows, and the mean values of the 15 windows (150-second) from the whole signal were assigned as a connectivity matrix for each patient. Then, the brain is modeled as a graph so that nodes

represent EEG channels (brain regions) and edges represent the brain connections determined by the dDTF method. Figure 2 illustrates the normalized mean values of brain connectivity matrices and the causal relationship between different brain areas calculated by dDTF method for responding and non-responding MDD patients in delta, theta, alpha, beta, and gamma frequency bands separately.

Then, the brain function is examined with the graph theory indices using the embedded functions in the BCT open-source toolbox. Local indices including degree, out-degree, in-degree, strength, out-strength, in-strength, and betweenness centrality have been calculated for each obtained graph. Graph theory indices for each node (EEG channels) have been calculated for all frequency bands at different thresholds (for example, at the 70% threshold, 30% of the weakest connections in the brain connectivity matrix has been removed). The Wilcoxon rank-sum test (p-value) and the AUC-ROC have been used to identify the best indices that predict the rTMS treatment outcome. The results of this process, including the mean and standard deviation value of the graph theory indices for responder versus non-responder MDD patients for each frequency band with the highest AUC-ROC have been reported in Table 2 separately. In other words, each graph theory index has been calculated at different nodes and thresholds, and the best one based on the highest AUC-ROC has been reported in Table 2. For example, in Betweenness centrality at the delta band, node Fp2 at the threshold of 0.7 has the highest AUC-ROC (0.85) and P-value (<0.001). Also, the best graph theory indices for all frequency bands based on AUC-ROC have been reported in table 3. According to Table 2, graph theory indices have the highest AUC-ROC values in delta and theta bands. By examining the AUC-ROC values of graph theory indices, it is distinguished that the degree, strength, and betweenness centrality, in the delta frequency band and in-degree, out-strength, and in-strength, in the theta frequency band, have the highest AUC-ROC values. Also, by assessing the most notable brain areas, the Fp2 node has the highest AUC-ROC values (Table 2, 3). According to Table 2, degree, strength, out-degree, out-strength, and betweenness centrality in the Fp2 area has the highest AUC-ROC values. The Fp2 area is a source of information for this target, and therefore out-degree and out-strength indices have higher AUC-ROC values than in-degree and in-strength indices. In Table 3, out of the eighteen highest rated indices, fourteen indices were in the Fp2 area as the best brain areas to predict the rTMS treatment outcome. Finally, from the graph theory indices perspective, the betweenness centrality has the highest AUC-ROC values (Table 2, 3). In summary, with the assessment of all graph theory indices, the betweenness centrality in the Fp2 area and the delta frequency band has the highest AUC-ROC value of 0.854 and P-value < 0.001 in the threshold of 0.7.

Discussion

An effective brain connectivity and graph theory criteria have been used in current study to predict the rTMS treatment outcome in MDD patients with drug-refractory. We calculated most local graph theory indices and indicated the prefrontal region, especially the Fp2 area in the delta frequency band, was a critical brain region for this aim.

The dDTF method provides the best effective brain connectivity. This method calculates direct-directed connections and excludes indirect and false connections from the connectivity matrix, unlike the Granger-Geweke causality. This method is one of the multivariate methods based on multi-channel AR models that can identify the causal relationships between signals and determine the direct flow of activity between time series. The definition of dDTF measure in the frequency domain allows us to study the role of different EEG rhythms in information processing. Also, the DTF method has based on the phase difference between the time series, so it is insensitive to the effect of volume conductance and robust to noise. Due to the mentioned advantages of the dDTF method, it can conclude that the dDTF method used in this study provides the best effective brain connectivity. Also, physiological evidence shows their efficiency in other brain studies [39].

Among all calculated graph theory indices, the betweenness centrality index in the Fp2 area and the delta frequency band have the highest AUC-ROC value (Table 2, 3). The betweenness centrality indicates the node that connects different parts of the network that is characterized usually by a high centrality. Thus, an area with the highest betweenness centrality mediates the connection of nodes in other brain areas. Therefore, each node with the highest betweenness centrality is more active than the others. The more activity in prefrontal regions in the delta and theta band, especially the Fp2 area in the delta frequency band, indicated the most significant biomarker.

Out-degree and out-strength indices have the highest AUC-ROC value after the betweenness centrality index. These indices represent the source of information and identify the area that is the cause of information flow in the brain network. In Figures 2 and 3, the individual node that sends the highest values of brain connectivity has the highest out-degree and out-strength values. A high AUC-ROC value in out-degree and out-strength indicates significant differences between two groups of responders and non-responders to the rTMS treatment. Prefrontal region in the delta and theta band and in particular the Fp2 region in the delta band is the source of information, which is expressed by higher differences between out-degree and out-strength indices, corresponding to higher AUC-ROC values, in two groups for this target. Other indices such as in-degree and in-strength indices specify the network nodes where information flow is imported from other areas. Table 2 indicates that only the T8 node has this property,

but since it has a low AUC-ROC value; thus, it is not considered to be an effective biomarker. Consequently, considerable information for distinguishing between responder and non-responder MDD groups is available in the prefrontal region, especially in the Fp2 area. Other brain regions are less involved in this type of disorder. Graph theory indices of this region have significant differences in the delta and theta frequency bands that have been used as one of the rTMS treatment outcome predictors in patients with drug-resistant MDD.

The obtained results from graph theory indices indicated that the greatest differences between indices were observed in delta frequency band, and that the significant differences between indices were found in theta and beta frequency bands and suitable biomarkers for distinguishing between responder and non-responder groups to rTMS treatment in MDD patients (Tables 2 and 3). As in previous studies [40-42], the indices calculated in delta and theta frequency bands have shown higher efficiency than other frequency bands to classify the two groups. The considerable changes in connectivity in delta and theta frequency bands in the frontal cortex of MDD patients can be explained from a neurobiological point of view using theta current density in the rostral anterior cingulate cortex (rACC) [43-45]. This region is the cause of the response to different types of medication for depression. The rACC is the hub in the brain default network and is associated with self-focused processing. Besides, the rACC resting-state activity affects rumination, memory, and planning [46]. Reflective pondering and brooding are rumination's essential elements and are a mechanism for distress responding. Increasing the rACC activity may lead to less self-focused and better response to the treatment due to adaptive self-referential functions. Also, the MRI data in depressed patients indicated better functional connectivity discrimination in the rACC than in the other brain regions[47].

For future work, it is suggested to use more EEG channels and calculate more graph theory indices, then use feature selection methods and machine learning and deep learning methods to classify the MDD patients who respond to the rTMS.

Conclusion

The aim of this study is to investigate the significant biomarkers that can be used to obtain the rTMS treatment response in drug-resistance MDD patients. Personal medicine approaches will reduce the cost of treatment and increase the treatment method's effectiveness in psychiatric disorders. With the assessment of several graph theory indices, it is shown that the Fp2 region plays the most significant role in the prediction of the rTMS treatment response in drug-resistance MDD, especially the betweenness centrality in Fp2 and the delta frequency band is the best and has the highest AUC value of 0.854.

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Ethics declarations

Conflict of interest: The authors declare that they have no conflict of interest.

Ethical approval: The study was approved by the ethics committee of Shahid Beheshti University of Medical Sciences.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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Table 1. Demographic and clinical characteristics of participants

	Responder (n = 17)	Non-responder (n = 17)	Total (n = 34)
Gender(Female/Male)	14/3	11/6	25/9
Age	34.8(±12)	39.3(±14.7)	37.1(±13.4)
Pre-treatment BDI	31(±10.3)	31.2(±10.4)	31.1(±10.2)
Post-treatment BDI	9.4(±5.5)	23.2(±11.8)	16.3(±11.4)

Table 2. Mean and standard division value of the graph-based indices (in-degree, out-degree, degree, in-strength, out-strength, strength, and betweenness centrality) for responder versus non-responder MDD patients for each frequency band with the highest AUC-values in the different nodes and threshold.

Graph indices	Delta	Theta	Alpha	Beta	Gamma
In-degree	Node = C3 9.18±3.88 vs. 7.06±4.71 AUC = 0.6505 P* = 0.1082 Th* = 0.6	Node = T8 8.41±3.08 vs. 5.76±3.23 AUC = 0.7163 P = 0.0146 Th = 0.3	Node = T8 8.53±2.12 vs. 6.53±2.48 AUC = 0.6332 P = 0.0461 Th = 0.5	Node = P4 5.59±3.12 vs. 3.89±2.50 AUC = 0.6401 P = 0.0826 Th = 0.3	Node = T8 10.41±5.78 vs. 7.71±6.59 AUC = 0.6228 P = 0.1236 Th = 0.3
Out-degree	Node = Fp2 13.06±4.88 vs. 6.35±5.43 AUC = 0.7889 P = 0.0017 Th = 0.3	Node = Fp2 16.00±2.74 vs. 11.12±5.29 AUC = 0.7785 P = 0.0019 Th = 0.5	Node = Fp2 9.71±5.98 vs. 3.59±5.41 AUC = 0.7751 P = 0.0026 Th = 0.3	Node = Fp2 5.24±4.72 vs. 1.88±3.72 AUC = 0.7958 P = 0.0011 Th = 0.1	Node = P3 12.24±3.13 vs. 8.29±3.93 AUC = 0.7543 P = 0.0035 Th = 0.6
Degree	Node = Fp2 24.65±4.95 vs. 17.71±7.08 AUC = 0.7751 P = 0.0052 Th = 0.3	Node = Fp2 20.41±3.89 vs. 16.76±5.09 AUC = 0.7197 P = 0.0155 Th = 0.4	Node = Fp2 11.65±4.81 vs. 7.12±4.64 AUC = 0.7197 P = 0.0153 Th = 0.3	Node = P3 28.47±3.64 vs. 24.29±3.80 AUC = 0.7578 P = 0.0039 Th = 0.7	Node = P8 23.18±5.31 vs. 19.65±6.23 AUC = 0.6713 P = 0.0646 Th = 0.6
In-strength	Node = C3 3.20±1.68 vs. 2.73±2.27 AUC = 0.6332 P = 0.1906 Th = 0.5	Node = F7 3.01±1.26 vs. 2.05±0.87 AUC = 0.7405 P = 0.0175 Th = 0.2	Node = Fz 2.00±0.69 vs. 1.41±0.78 AUC = 0.7266 P = 0.0252 Th = 0.1	Node = P4 3.19±2.03 vs. 2.18±1.47 AUC = 0.6540 P = 0.1253 Th = 0.3	Node = T8 5.17±3.42 vs. 4.23±4.36 AUC = 0.6332 P = 0.1906 Th = 0.3
Out-strength	Node = Fp2 6.43±3.67 vs. 2.79±3.42 AUC = 0.7958 P = 0.0034 Th = 0.2	Node = Fp2 9.54±2.64 vs. 5.91±3.69 AUC = 0.8097 P = 0.0022 Th = 0.5	Node = Fp2 6.80±4.05 vs. 3.01±3.86 AUC = 0.7889 P = 0.0042 Th = 0.4	Node = Fp2 3.70±3.75 vs. 1.38±2.88 AUC = 0.7993 P = 0.0014 Th = 0.1	Node = Fp2 4.12±3.00 vs. 1.88±1.81 AUC = 0.7751 P = 0.0065 Th = 0.1

Strength	Node = Fp2 11.33±2.90 vs. 8.04±4.07 AUC = 0.7578 P = 0.0108 Th = 0.2	Node = Fp2 12.17±3.07 vs. 9.42±3.63 AUC = 0.7197 P = 0.03 Th = 0.4	Node = Fp2 8.10±3.54 vs. 5.27±3.26 AUC = 0.7578 P = 0.0108 Th = 0.4	Node = Fp2 5.98±3.82 vs. 3.90±3.67 AUC = 0.7232 P = 0.0275 Th = 0.2	Node = P3 5.50±4.42 vs. 3.77±2.91 AUC = 0.6367 P = 0.1792 Th = 0.3
Betweenness centrality	**Node = Fp2** **27.2±8.74 vs. 14.93±11.97** **AUC = 0.8547** **P = 0.0004** **Th = 0.7**	Node = Fz 2.19±1.65 vs. 1.23±1.06 AUC = 0.6782 P = 0.0790 Th = 0.9	Node = P8 3.50±2.09 vs. 1.94±1.37 AUC = 0.7301 P = 0.0220 Th = 0.9	Node = P3 19.17±31.15 vs. 2.54±3.77 AUC = 0.8166 P = 0.0013 Th = 0.5	Node = Cz 2.53±1.64 vs. 1.07±1.73 AUC = 0.8097 P = 0.0022 Th = 0.9
P*: p-value, Th*: Threshold					

Table 3. The ranked highest graph theory indices for all frequency bands based on AUC-values.

Graph indices	Frequency Band	Node	AUC-ROC value	P-value	Threshold
Betweenness centrality	Delta	Fp2	0.8547	0.0004	0.7
Betweenness centrality	Delta	Fp2	0.8512	0.0005	0.8
Betweenness centrality	Beta	P3	0.8166	0.0013	0.5
Betweenness centrality	Gamma	Cz	0.8097	0.0022	0.9
Out-strength	Theta	Fp2	0.8097	0.0022	0.5
Betweenness centrality	Delta	Fp2	0.8062	0.0024	0.6
Betweenness centrality	Beta	P3	0.7993	0.0031	0.9
Out-strength	Theta	Fp2	0.7993	0.0031	0.6
Out-strength	Beta	Fp2	0.7993	0.0014	0.1
Betweenness centrality	Beta	P3	0.7993	0.0031	0.9
Out-strength	Theta	Fp2	0.7958	0.0034	0.7
Out-degree	Beta	Fp2	0.7958	0.0011	0.1
Out-strength	Delta	Fp2	0.7958	0.0034	0.2
Out-strength	Delta	Fp2	0.7958	0.0034	0.3
Out-strength	Delta	Fp2	0.7958	0.0034	0.4
Out-strength	Theta	Fp2	0.7924	0.0038	0.8
Betweenness centrality	Delta	Fp2	0.7924	0.0038	0.5
Betweenness centrality	Delta	Fp2	0.7924	0.0038	0.3

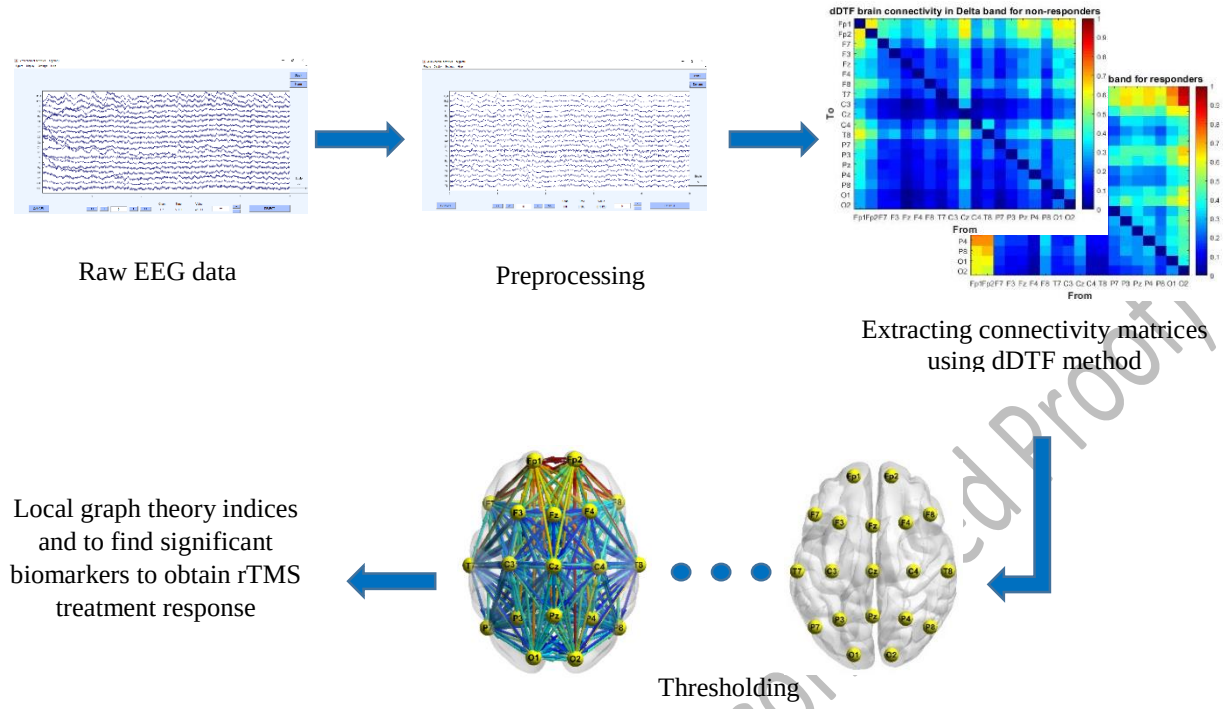

Figure 1. The proposed method's block diagram. First, the recorded raw EEG data from drug-resistant MDD patients are pre-processed, then by using the dDTF method, the brain connectivity matrix is calculated for each patient. In the following, the brain function is modeled as a graph by the dDTF method and analyzed with the local graph theory indices. Finally, the statistical test (Wilcoxon rank-sum) and the area under the ROC curve has used to determine the significant biomarkers for predicting the rTMS treatment outcome.

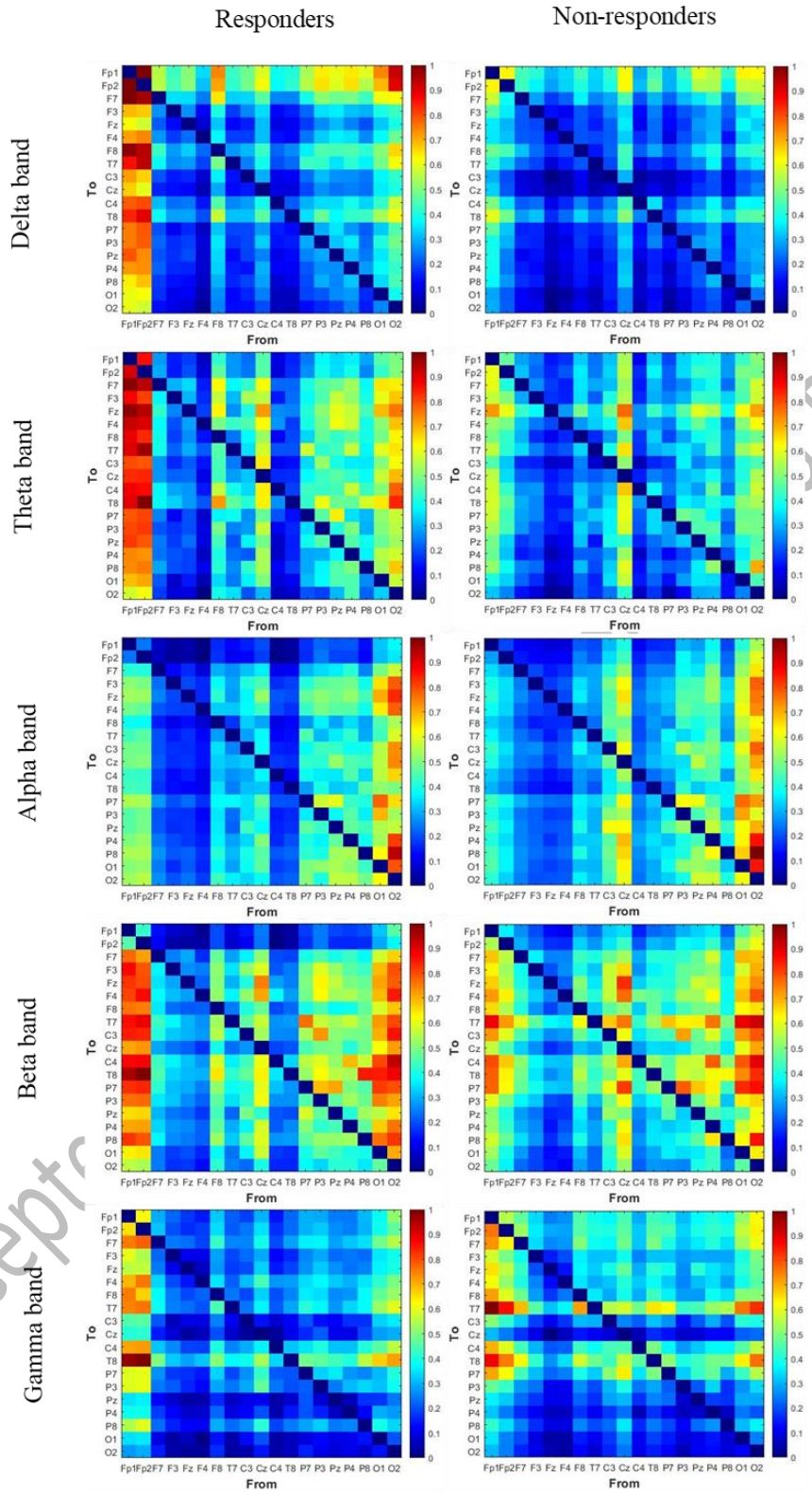

Figure 2. The normalized brain connectivity matrix has been calculated by the dDTF method from EEG signals in two groups of responder and non-responder MDD patients to rTMS treatment in the delta, theta, alpha, beta, and gamma frequency bands. The colors of the matrix indicate the strongness or weakness of the connection.