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Single Channel EEG Classification: A Case Study on Prediction of Major Depressive Disorder Treatment Outcome

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ABSTRACT In multichannel EEG, several electrodes are attached to the head that may be annoying for patients and troublesome for operators. Moreover, the number of electrodes is the main reason of the infeasibility of developing EEG based wearable and point of care devices. To address this problem, recently, the concept of single-channel EEG (SCEEG) is presented. The spatial resolution of SCEEG is lower than the multichannel one, but it is easy to use, cost-effective, ubiquitous, and wearable. In this paper, for the first time, we have developed the concept of SCEEG for the classification of responders and nonresponders to repetitive transcranial magnetic stimulation (rTMS) treatment in major depressive disorder (MDD). We also compared the performance of SCEEG and multichannel EEG with the different number of channels in the prediction of responding to rTMS treatment. 19-electrode EEG is recorded from 46 MDD patients before rTMS treatment. Among participants, 23 individuals responded to treatment. The dataset is partitioned into the training (36 subjects) and testing (10 subjects) datasets. Linear and nonlinear features were extracted from every channel of EEG. In training, to select informative features, the minimal-redundancy-maximal-relevance (mRMR) algorithm was applied. The selected features were classified by k-nearest neighbors (KNN) classifier, which is evaluated by leave-one-out cross-validation. Then the obtained classifier is applied to the testing dataset. The results demonstrated that the F8 channel classifies responders and nonresponders with an accuracy of 80%. Moreover, our results revealed that SCEEG could perform as multichannel EEG in the prediction of rTMS treatment outcome in MDD patients. The obtained accuracy indicates that our proposed method based on SCEEG has a high potential for predicting rTMS treatment outcome in MDD patients.

INDEX TERMS Classification, major depressive disorder, prediction treatment response, single channel EEG, transcranial magnetic stimulation.

I. INTRODUCTION

EEG is a non-invasive method for monitoring brain activity and has various applications in the detection and treatment of brain disorders. Compared to other brain monitoring methods like fMRI, MEG, NIRS, etc., the main advantages of EEG are its cost-effectiveness and high time resolution. To use multichannel EEG, several gel-impregnated electrodes should be attached to the head of the patients. These electrodes are also connected to some electrical devices (e.g., amplifiers) with many wires. All of these accessories and even only attaching several electrodes on the head (in case of wireless EEG) can be annoying for patients, troublesome for operators [1]. Besides the mentioned constraints, multichannel EEGs are limited to use in the scientific and clinical labs, and it can make infeasible the variety of continuous and real-time EEG based applications like online detection of epileptic seizures [2]. Infeasibility of at-home application is another constraint for multichannel EEG. Also, in some other applications like neurofeedback training, it is necessary to have frequent recordings that are another critical constraint for multichannel EEGs. Because it is tough to keep lots of electrodes on the head of subjects for several trials [3]. To address these issues, portable EEG devices that have fewer electrodes

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are developed, for example, BR8+ and ENOBIO8 [4] with 8 electrodes, Mindo-4S JellyFish [5] with 4 electrodes, and MindWave [4] with 1 electrode.

The spatial resolution of the EEG system with a low number of electrodes is lower than high-resolution EEG systems, but due to its ease-of-use, cost-effectiveness, ubiquitousness, repeatability, and portability, the lower spatial resolution is negligible. The mentioned merits will be more available in the EEG system with fewer electrodes, especially in single-channel EEG (SCEEG); thus, they can be an appropriate option for EEG studies. There are lots of practical applications that SCEEG signals can be used. One of the most common applications of SCEEG is the recording and analysis of brain activity in sleep-related studies. Many researchers have tried to use SCEEG for sleep stage classifications [6]–[8]. One of the other applications of SCEEG is for epilepsy patients. The epileptic seizure also is one of the prevalent neurological diseases that can be very dangerous, especially when it is not detected before its complete occurrence. Thus, to have a portable, comfortable, and easy-to-use monitoring system, SCEEG is so attractive in detecting and classification of epileptic seizures [9]–[11]. In addition to the mentioned works, there are a variety of other applications that they have used SCEEG, such as affective and emotional recognition [12], fatigue [13], in-flight vigilance states [14], and delirium detections [15].

Depression is a prevalent disease all over the world. Based on world health organization reports, this mental disorder is the leading cause of disability and the main contributor to the world's overall disease burden [16].

Different therapies are used to treat depression [17], and most of the depressed patients underwent more than one of these treatments before remission. The experience of ineffective therapies leads to adverse effects in patients who have not responded to treatment includes exacerbation of disorder. It will also increase the risk of stopping the treatment by patients [18]. Hence to avoid ineffectual therapies and their complications, predicting treatment response can be very helpful. Therefore, applying easy-to-use and affordable SCEEG devices facilitates monitoring patients' brain activities and developing indicators to predict treatment's therapeutic outcome. However, multichannel EEG has been widely used to study brain activity and brain networks [19]–[21] in depressive disorder. SCEEG is only applied to detect depression in only a few studies [22]–[24]. Bachmann *et al.* extracted linear and nonlinear measures from single-channel EEG for classifying depressed and normal subjects. The results revealed that SCEEG could discriminate depression with accuracy in the same range of studies that applied multichannel EEG methods [24]. Continuing our previous work [25], in the current study, we are going to determine whether the signal of a single EEG electrode recorded at baseline (before the treatment) can predict responding to rTMS treatment. In other words, we are aimed to find a marker based on SCEEG for predicting treatment response to rTMS and compare its performance with systems, including a higher number of EEG channels. In this way, we have investigated the predictive ability of systems with the different number of EEG channels recorded before rTMS treatment by extracting some nonlinear features, Hjorth parameter, spectral and bispectral features, and applying a classification technique. After partioning the data to training and testing datasets, we have employed classification techniques to find the most discriminative EEG channels. In classification, to specify the effective features in R and NR discrimination, we have used the minimal-redundancy-maximal-relevance (mRMR) algorithm. Then, the obtained classifier is applied to the testing dataset. This procedure is applied for different number of channels from all to 1.

It is notable that as far as we know, this is the first study on applying SCEEG in the prediction of treatment response in depression. In the rest of the paper, in section 2, subjects of the research and EEG recording and preprocessing are explained. Then extracted features are described. After that, the classification procedure is expressed. The classification results obtained from the different number of EEG channels, including single channel, are reported in section 3. The results are discussed in section 4. Then the paper is ended with the ''conclusion'' section.

II. MATERIAL AND METHODS

A. SUBJECTS

Participants of this study were 46 major depressive disorder (MDD) patients referred to Atieh Clinical Neuroscience Centre, Tehran, Iran. Psychiatrists made MDD diagnoses based on the Diagnostic and Statistical Manual–IV diagnostic (DSM-IV) [26]. Among the MDD patients who were decided to be treated by rTMS, those who had none of the exclusion criteria participated in the study. The exclusion criteria were the presence of Axis I or II disorders, present or history of head injury, seizures, epilepsy, and neurological disorders, substance abuse, suicidal risk, unstable medical conditions, implanting devices, cardiac arrhythmia, and pregnancy. Moreover, the participants were not on antidepressant medication or had unchanged medication taking during the rTMS. All of the patients gave informed consent for the study. The details of used medication along with other clinical information of subjects are represented in TABLE 1. Rank-sum and Friedman tests are applied to compare demographic and clinical data of two groups of R and NR. The results of these tests are represented in the last column of TABLE 1. rTMS treatment was applied to left DLPFC with the frequency of 10 Hz as three sessions per week for five weeks for all of the subjects. This procedure was continued for two weeks for responder patients, whereas, for nonresponders, one of the left 10 Hz, right 1 Hz, or bilateral rTMS was randomly selected.

Assessment of depression level was done by Beck Depression Inventory (BDI-II) and 24-item Hamilton Rating Scale for Depression (HRSD) before the first session and after the end of the treatment. Furthermore, depression severity was also assessed by the HRSD after every 5 rTMS sessions.

TABLE 1. Demographic and clinical information [25].

	Nonresponders	Responders	Statistics
N	23	23	
Age	39(±14.6)	30.9(±12.3)	p=0.052
Gender(M/F)	8/15	8/15	p=0.9
Treatment(L/R/Bilateral)*	17/3/9	19/4/13	X^2=0.323,p=0.57
Pre-treatment BDI-II	28.1(±9.4)	32.5(±9.3)	p=0.08
Post-treatment BDI-II	23.1(8.4)	8.6(±5.9)	p=2.672e-07
Pre-treatment HRSD	28.9(±12.1)	34.2(±12.2)	p=0.103
Post-treatment HRSD	22.4(±10.6)	6.3(±5.2)	p=2.093e-07
Medications(AD/AD + MS / AD + MS + AP)**	5/8/1	6/6/0	X^2=0.2, p=0.65
Illness duration(years)	7.9(±7.8)	6.5(±8.2)	p=0.278
Current episode length(years)	3.2(±2.2)	2.6(±2.5)	p=0.759
Number of previous medications	2.7(±1.5)	2(±2.1)	p=0.108

* Protocol of rTMS includes left (L), right (R), or bilateral.

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

Responding is considered as a more than 50% decrease in BDI_II scores or HRSD or by BDI≤8 (HRSD≤9). As TABLE 1 demonstrates, only post-treatment BDI-II and HRSD scores are significantly different (p <0.05) between responders and nonresponders. This study has the approval of the Iran University of Medical Sciences' ethics committee.

Among 46 subject datasets, 10 subjects are selected randomly as the testing dataset, and the remaining are used as the training dataset.

B. EEG RECORDING AND PREPROCESSING

EEG recording was done in resting state before the first rTMS session and at the end of treatment duration. In each recording, five minutes EEG was acquired by a Mitsar-EEG 201 with 19 Ag\AgCl electrodes and a sampling frequency of 500 Hz. Channel location was based on the international 10–20 system and included Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, and O2. The channel locations are illustrated in Figure 1.

During EEG recording, subjects were eye closed sitting on a comfortable chair in a shielded room. They also were instructed to avoid falling asleep. EEGLAB Toolbox [27] was used for the preprocessing of EEG data. The preprocessing includes applying a 1-42 Hz bandpass FIR filter and Independent component analysis (ICA) [28] algorithm for removing artifacts. A multiple artifact rejection algorithm (MARA) [29] has been utilized to eliminate noisy independent components. Moreover, to remove the remaining artifacts, we have visually inspected the EEG data. In the end, the data have re-referenced against a new reference that was the average reference.

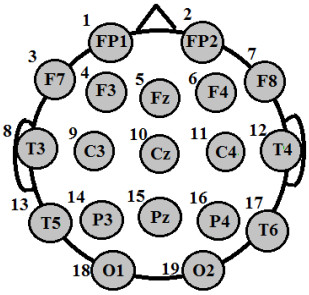


FIGURE 1. Channel locations.

C. FEATURE EXTRACTION

The features that are applied in this study include Katz fractal dimension (KFD), Higuchi fractal dimensions (HFD), Correlation dimension (CD), Rényi Entropy (RE), Hjorth parameters, bispectrum, and power spectrum features. These features are explained briefly in this section.

1) KATZ AND HIGUCHI FRACTAL DIMENSION

Fractal dimension (FD) measures a time series's self-similarity based on counting the appearance of a pattern in that time series. Complexity and self-similarity can be interpreted in different ways, so there are various algorithms for FD computation. Two of the most known algorithms for FD are KFD and HFD. Each algorithm has its pros and cons, so we used both of them in our analysis [30], [31]. Both KFD and HFD are based on changes in the distance of points in time series. For time series $x(n)$ with length N, the average distance of consecutive points is $a = L/N - 1$ where

$$L = \sum_{i=2}^{N} \|(x(i), x(i-1))\| \tag{1}$$

and $\|\,.\,\|$ is distance. If d is the maximum distance between $x(1)$ and other points of times series, KFD will be obtained by:

$$KFD = (\ln(L/a))/(\ln(d/a)) \tag{2}$$

HFD is computed by the construction of k new time series, $x_k^m = \{x(m), x(m+k), x(m+2k), \ldots, x(m+k[N-m/k])\}$ that $m = 1, 2, \ldots, k$ and [.] denotes the floor function. The length of each time series x_k^m is defined by:

$$L_m(k) = ((N-1)/(k[N-m/k])) \left(\sum_{i=1}^{[N-m/k]} |x(m+ik) - x(m+(i-1)k)| \right) \tag{3}$$

where $|\,.\,|$ indicates the absolute value and [.] shows floor function. These computations are done for different values for k. If $L(k)$ is the average of $L_m(k)$ over k, then HFD is the slope of the line best fitted to $\ln(L(k))$ versus of $\ln(1/k)$.

2) CORRELATION DIMENSION

Correlation dimension (CD) is computed by time-delay embedding theory in phase space [32], [33]. By applying time

delay embedding theory to the time series $x(n)$, the state i of the time series in another space with d dimensions is defined as $X_i = (x(i), x(i+\tau), \ldots, x(i+(d-1)\tau))$,where τ is the time delay. The average probability that the states of the system be closer than a threshold is given by:

$$C(r) = \frac{2}{N(N-1)} \sum_{i \neq j} \theta(r - |X_i - X_j|) \tag{4}$$

where r is the threshold or radius of similarity and $\theta(X)$ is Heaviside step function. CD is obtained by estimation of the slope of the line best fitted to $\ln(C(r))$ versus of $\ln(r)$.

3) RÉNYI ENTROPY

Rényi entropy for a random variable x with discrete probability distribution $P = (p_1, p_2, \ldots, p_N)$ is obtained by [34]:

$$RE_\alpha = (1/1-\alpha) \log(\sum_{i=1}^{n} (p_i)^\alpha) \tag{5}$$

where α is the order of the RE. $\alpha = 2$ is assumed in this study.

4) HJORTH PARAMETERS

Hjorth parameters that include Hjorth activity (HA), Hjorth mobility (HM), and Hjorth complexity (HC) show statistical properties of the signal in the time domain. If $x'(n)$ and $x''(n)$ show the first and second derivative of time series $x(n)$ respectively, the Hjorth parameters of $x(n)$ are calculated as following [35]:

$$\begin{aligned} HA &= \sigma_x^2 \\ HM &= \sigma_{x'}/\sigma_x \\ HC &= (\sigma_{x''}/\sigma_{x'})/(\sigma_{x'}/\sigma_x) \end{aligned} \tag{6}$$

5) BISPECTRUM FEATURES

Bispectrum, which is based on third-order statistics, demonstrates phase coupling of different frequency components [36]. For $x(t)$ which is a non-Gaussian signal, bispectrum,$B(f_1, f_2)$ is defined as the two-dimensional Fourier transform of third-order cumulant:

$$B(f_1, f_2) = E\left[X(f_1)X(f_2)X^*(f_1 + f_2)\right] \tag{7}$$

where $X(f)$ is the Fourier transform of $x(t)$ and * denotes the complex conjugate. Bispectrum has symmetry in the frequency range, which is calculated, and it is non-redundant in a triangular region where $f_1 \geq f_2 \geq 0$. This bispectrum region can characterize the whole bispectrum, so the extracted features of bispectrum are computed in this region. For a frequency range of [0, h], the bispectrum plot area and non-redundant region of the bispectrum plot are illustrated in Figure 2.

The extracted features are related to moments and entropy of the bispectrum plot. In all following formula Ω indicates the non-redundant region:

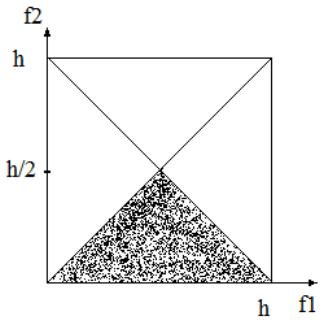


FIGURE 2. The bispectrum plot area. The dotted area is the non-redundant region.

- The sum of logarithmic amplitudes of the bispectrum (BispSL):

$$BispSL = \sum_{f_1, f_2 \in \Omega} \log(|B(f_1, f_2)|) \tag{8}$$

-The sum of logarithmic amplitudes of diagonal elements in the bispectrum (BispSLD) that is obtained by applying summation in eq (8) on only diagonal elements.

-The first-order spectral moment of the amplitudes of diagonal elements in the bispectrum (Bisp1M):

$$Bisp1M = \sum_{k=1}^{N} k \log(|B(f_k, f_k)|) \tag{9}$$

-The second-order spectral moment of the amplitudes of diagonal elements in the bispectrum (Bisp2M):

$$Bisp2M = \sum_{k=1}^{N} (k - (Bisp1M))^2 \log(|B(f_k, f_k)|) \tag{10}$$

- Normalized bispectral entropy (BispEn):

$$BispEn = -\sum_{n} p_n \log(p_n) \tag{11}$$

where

$$p_n = |B(f_1, f_2)| \Big/ \sum_{\Omega} |B(f_1, f_2)| \tag{12}$$

- Normalized bispectral squared entropy (BispSqEn):

$$BispSqEn = -\sum_{n} q_n \log(q_n) \tag{13}$$

where

$$q_n = |B(f_1, f_2)|^2 \Big/ \sum_{\Omega} |B(f_1, f_2)|^2 \tag{14}$$

The mentioned bispectrum features are extracted from all frequency bands.

TABLE 2. Features extracted from every EEG channel. D, T, A, and B denote Delta, Theta, Alpha, and Beta frequency bands, respectively.

No	Feature	No	Feature	No	Feature
1	HFD	14	BispSL_T	27	BispSLD_B
2	KFD	15	BispSLD_T	28	Bisp1M_B
3	CD	16	Bisp1M_T	29	Bisp2M_B
4	Renyi	17	Bisp2M_T	30	BispEn_B
5	HjA	18	BispEn_T	31	BispSqEn_B
6	HjM	19	BispSqEn_T	32	D_pow
7	HjC	20	BispSL_A	33	T_pow
8	BispSL_D	21	BispSLD_A	34	A_pow
9	BispSLD_D	22	Bisp1M_A	35	B_pow
10	Bisp1M_D	23	Bisp2M_A	36	TA_ratio
11	Bisp2M_D	24	BispEn_A	37	DT_ratio
12	BispEn_D	25	BispSqEn_A		
13	BispSqEn_D	26	BispSL_B		

6) POWER SPECTRUM

The power of EEG signals in all frequency bands is applied for classification. Many previous studies reported the involvement of the power of delta [37], [38], theta [39], [40] and alpha [38], [41] bands in depression. Thus for further study, the ratio of the power of delta to theta bands (DT_Ra) and the ratio of the power of theta to the alpha band (TA_Ra) are also investigated as features.

All of the extracted features are listed in TABLE 2.

D. FEATURE SELECTION

Before applying the classifier, the minimal redundancy-maximal-relevance (mRMR) algorithm was employed to choose the most informative features for applying to the classifier. The mRMR is a feature selection algorithm that selects features that maximize the relevancy of features to the target classes while minimizing redundancy between them [42]. The applied mRMR code in this study was based on the mutual information quotient scheme available at the Matlab source codes exchange site [43].

E. CLASSIFICATION

Different classifiers are applied to the dataset, including support vector machine (SVM), decision tree, logistic regression, and discriminant analysis classifiers. Based on the obtained performance, we have selected k-nearest neighbors (KNN) to discriminate between responders and nonresponders. The KNN classifier parameters, including the number of nearest neighbors, are chosen by hyper-parameter optimization. The number of applied features is selected in such a way as to obtain the highest classification performance.

F. PERFORMANCE EVALUATION

The classification performance was evaluated by three criteria, including specificity, sensitivity, and accuracy.

As mentioned in section A, the dataset is divided into training and testing datasets. The testing dataset contains 10 randomly selected subjects. The feature reduction procedures are applied only to the training dataset. After feature selection, the KNN classifier is applied to the training dataset. During training the classifier to reduce the bias, we used the leave-one-out cross-validation method. In this technique, we trained the classifier using 36 subjects' data and validated it on the remaining one. This procedure is repeated such that the dataset of each subject is used as the validation dataset once. After the training procedure, the obtained classification is applied to the testing dataset. The described classification procedure was applied to EEG data of the different number of EEG channels (from 19 to 1) separately.

G. EEG CHANNEL SELECTION

As mentioned before, we are going to study the performance of single channel EEG in the prediction of rTMS treatment response in MDD patients and compare its performance with multichannel EEG systems. Thus we have M systems that everyone is based on EEG data of M channels $M = 1, 2, \ldots, 19$. In this way, to select the best M channels in every system, the ideal method is to consider all M-channel combinations of 19 channels and find the combination, which leads to the highest performance. But as an example, for M=9 it will be 92378 9-channel combinations that should be checked, which in the case of leave-one-out cross-validation (36 Subjects) it will be multiplied by 35 (3233230). Therefore it is not a computationally practical way to check all combinations. To solve this issue, we can have two approaches [44].

The first approach is based on adding channels one by one. So in the first round, we select only one channel with the highest performance among 19 channels. Then in the second round, we want to build a system with two channels, which its first channel is already selected in round 1. So we should check the performance of all remaining 18 channels together with the previously selected channel. The channel which yields the highest performance will be selected as the second channel. This procedure is repeated until we find the best 19 channels. Thus best M channels for all M systems are obtained.

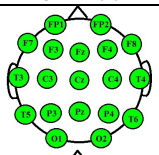
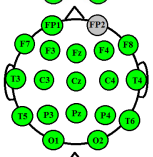
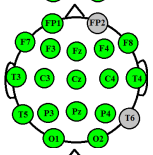
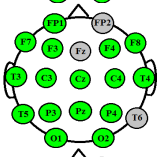
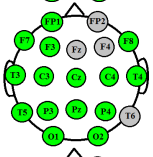
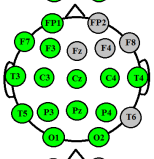
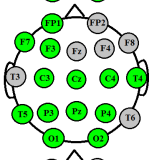
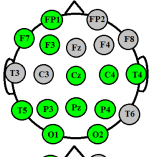
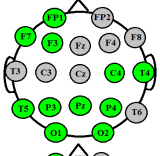
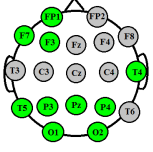
The second approach is similar to the first one, but it is in the reverse direction. In this approach, firstly, we consider all 19 channels. Then in each round, we delete one channel that its removal leads to the best performance by the remaining channels. This procedure is continued till 1 channel remains. Therefore in this approach, we find the best M channels for all M systems too.

After applying both approaches for every one of the M systems, the selected channels that yields higher performance is chosen to use for analysis.

III. RESULTS

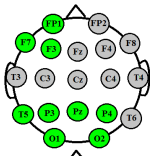
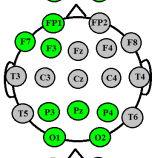
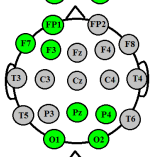
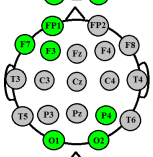
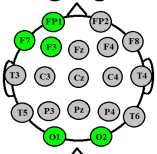
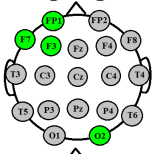
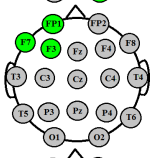
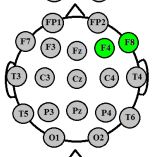
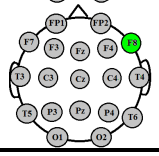
The applied channels, selected features and the KNN classification performance with the highest accuracy for the different number of channels $(1, 2, \ldots, 19)$ for both training and testing datasets are reported in TABLE 3. In Table 3 the location of applied channels are specified by green and removed channel are marked by grey color. The name of channels are depicted in Figure 1 clearly. It can be seen that the highest accuracy of 80% in the testing dataset is obtained by classification based on 17 to 3 channels and also single

TABLE 3. The applied channels, selected features, classification accuracy (AC), specificity (SP), and sensitivity (SE) for different number of EEG channels in training and testing datasets. The applied channels (green) and removed channel (grey) are shown in column 2. D, T, A, and B denote Delta, Theta, Alpha, and Beta frequency bands, respectively.

			Training			Testing		
No of Channels	The Applied Channels	Selected Features	Ac (%)	Se (%)	Sp (%)	Ac (%)	Se (%)	Sp (%)
19		Bi_En_B2*, Bi_2M_D4, Bi_En_T18, Bi_SqEn_D15, B_pow17, Bi_Sdiag_B1, CD4, TA_ratio3, DT_ratio11	86.11	88.89	83.33	60	40	80
18		B_pow17, HjM14, TA_ratio8, BispSLD_B1, CD4, BispSqEn_D15, BispSL_D4	94.44	94.44	94.44	60	20	100
17		CD4, Bisp2M_B1, D_pow3, TA_ratio3, BispSqEn_A10, BispSL_D4, DT_ratio11, BispEn_T18, BispSqEn_D15	91.67	100	83.33	80	60	100
16		CD4, Bisp2M_B1, D_pow3, TA_ratio3	91.67	100	83.33	80	60	100
15		CD4, Bisp2M_B1, D_pow3, TA_ratio3	91.67	100	83.33	80	60	100
14		CD4, Bisp2M_B1, D_pow3, TA_ratio3	91.67	100	83.33	80	60	100
13		CD4, Bisp2M_B1, D_pow3, TA_ratio3	91.67	100	83.33	80	60	100
12		CD4, Bisp2M_B1, D_pow3, TA_ratio3	91.67	100	83.33	80	60	100
11		CD4, Bisp2M_B1, D_pow3, TA_ratio3	91.67	100	83.33	80	60	100
10		CD4, Bisp2M_B1, D_pow3, TA_ratio3	91.67	100	83.33	80	60	100

channel. The obtained results of classification by 17 to 3 channels are similar for both training and testing datasets. The corresponding selected features of these classifications indicates that only four features including CD4 (correlation

TABLE 3. ***(Continued.)*** **The applied channels, selected features, classification accuracy (AC), specificity (SP), and sensitivity (SE) for different number of EEG channels in training and testing datasets. The applied channels (green) and removed channel (grey) are shown in column 2. D, T, A, and B denote Delta, Theta, Alpha, and Beta frequency bands, respectively.**

9		CD4, Bisp2M_B1, D_pow3, TA_ratio3	91.67	100	83.33	80	60	100
8		CD4, Bisp2M_B1, D_pow3, TA_ratio3	91.67	100	83.33	80	60	100
7		CD4, Bisp2M_B1, D_pow3, TA_ratio3	91.67	100	83.33	80	60	100
6		CD4, Bisp2M_B1, D_pow3, TA_ratio3	91.67	100	83.33	80	60	100
5		CD4, Bisp2M_B1, D_pow3, TA_ratio3	91.67	100	83.33	80	60	100
4		CD4, Bisp2M_B1, D_pow3, TA_ratio3	91.67	100	83.33	80	60	100
3		CD4, Bisp2M_B1, D_pow3, TA_ratio3	91.67	100	83.33	80	60	100
2		BispSL_D6, HjC6, HjM7	94.44	88.88	100	70	40	100
1		Renyi7, BispSqEn_D7, TA_ratio7	91.67	100	83.33	80	60	100

*The number after each selected feature indicates the number of the corresponding channel that the feature is extracted.

dimension of channel 4), Bisp2M_B1 (The second-order spectral moment of the amplitudes of diagonal elements in the bispectrum of channel 1 in the beta band), D_pow3 (power of delta band of channel3), TA_ratio3 (power ratio of theta to the alpha band of channel 3) are selected for classification. These four features that are extracted from channels 4 (F3),1 (FP1), and 3 (F7) yields 91.67 % and 80% accuracy in training and testing datasets, respectively. Single channel classification by channel 7 (F8) provides the same results by using only one channel. The selected features during training for the F8 channel include TA_ratio (power ratio of theta to the alpha band), Renyi entropy, and BispSqEn (normalized bispectral squared entropy) in the delta band of the F8 channel. Classification by all channels (.i.e. 19 channels) provides the lowest accuracy 86.11% in the training dataset and 60% in the testing dataset.

Although applying 19 channels for classification provides more features but increasing the number of features will not necessarily improve the performance of the classifier [45], [46].

The increase or decrease of classification error by adding features depends on the nature of the problem and classifier and the discriminatory effect of added features [46].

About the classification by 18 and 2 channels, although the accuracy for the training dataset is reached to 94%, for the testing dataset, they have inferior performance than a classification by other numbers of channels.

The results in Table 3 also demonstrate that the specificity of the testing dataset is 100% in almost all classification while sensitivity is lower. However, the ideal is both specific and sensitivity to be 100%, but as the aim of our classification is to find the effectiveness and response to rTMS treatment, the specificity can be considered as a more important criterion than sensitivity. The observed 100% specificity indicates that the proposed method can predict all of NR correctly as nonresponders; however, the rate of prediction of the original R as responders is lower.

IV. DISCUSSION

In the current study, we proposed a framework based on EEG signals recorded before treatment to predict rTMS treatment response in MDD. We have compared the performance of single channel EEG with multichannel EEG systems in the prediction of treatment outcome.

Our results clarified that SCEEG of the F8 channel can predict treatment responding as multichannel systems with an accuracy of 80%. F8 is also reported to have higher spectral power in depressed patients compared to healthy control subjects [47]. Moreover, F8 provided high accuracy in the classification of healthy and depressive individuals in another study [22]. Based on our results, since a single channel of F8 same as multichannel EEG, can obtain the maximum testing accuracy of 80% and also high training accuracy of 91.67%, it can be deduced that SCEEG can be useful in the prediction of rTMS treatment response in depression. Not to mention that the fewer channel s we reach the goal of the study, the better.

The results of TABLE 3 shows that in classification by 17 to 3 channels, only features extracted from F3, FP1, and F7 channels are involved, and other channels don't have any role in obtained classification results. This observation and also the high classification accuracy of the F8 channel can confirm the involvement of the frontal region in the prediction of treatment outcome of depression. Many other researchers also reported the frontal lobe as a region involved in depression [30], [48], [49].

One of the selected features in classification is theta alpha power ratio of F8 and F3 channels. Alpha theta power ratio is one of the known neurofeedback training that is used for the treatment of deep levels of depression [50]. Alpha power is reported to be involved in responding to depression treatment [38], [41]. The correlation dimension is chosen in most classifications. Our previous study shows that the CD of nonresponders to rTMS treatment is significantly higher than responders. Moreover, CD of all channels yields high classification accuracy in discriminating responders from nonresponders to rTMS treatment [25].

About the bispectrum features, it can be observed from TABLE 3 that most of the selected bispectrum features are from the beta and delta bands. It is reported that the bispectrum of beta and delta bands outperforms theta and alpha bands in discriminating rTMS responders and nonresponders [25].

In single channel EEG classification by the F8 channel, the other selected measures are Rényi entropy and normalized bispectral squared entropy. In other studies, the results indicated that Rényi entropy [51] and normalized bispectral squared entropy [52] are significantly different between depressed patients and healthy groups.

Checking the gender of the testing dataset shows that it includes 4 female and 6 male subjects. Investigating the results indicates that for the F8 channel, 100% of females and 66.67% of males are classified by correct labels (i.e., R or NR). However, since we have a few test subjects and as the same female/male subjects, we cannot have any reliable conclusion on this observation. To analyze the gender effect, a study with many male and female subjects is required, including a separate classification on each gender.

The proposed SCEEG and also some of the multichannel EEG frameworks in training outperformed our previous study [25], which provides R and NR classification accuracy of 91.3%.

Some other studies used machine learning techniques to predict treatment response in MDD patients. The performance of classification by the different number of channels, even SCEEG in our proposed framework for the training dataset, is superior to other previous studies that applied many EEG channels in predicting R and NR. These studies did not check their method on the testing dataset and only reported training results. The obtained maximum classification accuracy of the current research for the testing dataset is 80% that is lower than the accuracy reported by previous studies. But it should be considered that previous studies reported only training accuracy, which is lower than our obtained training accuracy. The best classification results of former studies that applied machine learning techniques for MDD treatment response prediction and our obtained result for training and testing datasets are reported in TABLE 4. Comparing our results with the results illustrated in TABLE 4; it can be deduced that SCEEG has high potential to be applied in predicting rTMS treatment response and maybe in general EEG application.

Although our results represented high classification accuracy, the results should be interpreted with caution as our sample size was not very large. The limitations of the current study include the small number of studied electrodes and the small sample size. The reported F8 channel for applying single-channel EEG in predicting treatment responses is

TABLE 4. Classification results of previous studies that applied machine learning techniques for prediction of MDD treatment response.

Study	Number of Channel	Training			Testing		
		Ac (%)	Sp (%)	Se (%)	Ac (%)	Sp (%)	Se (%)
[53]	30	86.60	89	84	No Testing		
[54]	30	91	92	91	No Testing		
[55]	16	87.9	80.9	94.9	No Testing		
[56]	64	76 (Mood)	-	-	No Testing		
[57]	19	87.5	95	80	No Testing		
[25]	19	91.3	91.3	91.3	No Testing		
Proposed system	1	91.67	100	83.3	80	60	100

also selected among the small number of electrodes, while investigating more EEG electrodes may lead to more single EEG candidate electrodes to predict treatment response. Furthermore, as we mentioned, some of the participants were on antidepressant medications about the applied treatment. Thus if it was possible to study the participants that only underwent rTMS treatment, not medications, interpreting the results would be easier. The other point is that hyperparameter optimization of the KNN classifier slows down the implementation of the method; however, the variety of distance criteria and different number nearest neighbors to be chosen in the KNN classification make it a flexible algorithm. One of the positive points about the applied method is that in addition to leave-one-out cross-validation, we have used an unseen part of data as testing dataset however it is vital to test the proposed method on a broader set of MDD patients to prepare for clinical applications.

V. CONCLUSION

For the first time in this paper, we proposed a framework based on single channel EEG for predicting treatment outcome of rTMS in MDD patients. We also compared the performance of single channel EEG with multichannel EEG with the different number of channels in predicting rTMS treatment responding. In this direction, EEG before treatment of 46 MDD patients who were under rTMS treatment was analyzed. mRMR feature reduction technique and KNN classifier were applied to linear, nonlinear, spectral, and bispectral features extracted from the different number of channels to differentiate responders from nonresponders.

The obtained results indicate that single channel EEG of F8 channel can provide similar high classification accuracy (91.67% for training and 80% for testing datasets) of multichannel EEG systems. Compared to previous studies, our proposed method, even by using single channel EEG, outperforms in the classification of MDD responders and nonresponders to treatment. Considering the results, the proposed method by single channel EEG can be a proper candidate to be applied in the prediction of rTMS treatment response.

For future work, we can apply the proposed method to large sample size to provide more reliable results. Furthermore, the effect of gender can be checked by the proposed method to investigate whether the gender of patients affect responding to treatment or not.

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