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Use of EEG for Predicting Treatment Response to Transcranial Magnetic Stimulation in Obsessive Compulsive Disorder

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Abstract

Aim. In this study we assessed the predictive power of quantitative EEG (qEEG) for the treatment response to right frontal transcranial magnetic stimulation (TMS) in obsessive compulsive disorder (OCD) using a machine learning approach. *Method*. The study included 50 OCD patients (35 responsive to TMS, 15 nonresponsive) who were treated with right frontal low frequency stimulation and identified retrospectively from Uskudar Unversity, NPIstanbul Brain Hospital outpatient clinic. All patients were diagnosed with OCD according to the *DSM-IV-TR* and *DSM-5* criteria. We first extracted pretreatment band powers for patients. To explore the prediction accuracy of pretreatment EEG, we employed machine learning methods using an artificial neural network model. *Results*. Among 4 EEG bands, theta power successfully discriminated responsive from nonresponsive patients. Responsive patients had more theta powers for all electrodes as compared to nonresponsive patients. *Discussion*. qEEG could be helpful before deciding about treatment strategy in OCD. The limitations of our study are moderate sample size and limited number of nonresponsive patients and that treatment response was defined by clinicians and not by using a formal symptom measurement scale. Future studies with larger samples and prospective design would show the role of qEEG in predicting TMS response better.

Keywords

qEEG, obsessive compulsive disorder (OCD), treatment response, transcranial magnetic stimulation (TMS)

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Introduction

Obsessive compulsive disorder (OCD) is characterized by repetitive and persistent thoughts that cause distress and anxiety, and repetitive actions performed in an effort to ease the distress and anxiety caused by the repetitive thoughts.[1] The lifetime prevalence of OCD is reported to be 2.3% in the general population, and it is more common in females than males.[2] The obsessions and compulsions associated with OCD often cause severe professional and social impairment.[3] First-line treatment for OCD includes selective serotonin reuptake inhibitors (SSRIs) and behavioral therapy; however, close to 50% of OCD patients do not respond to SSRIs.[4] When first-line SSRI treatment and behavioral therapy fail, a trial of a second-line SSRI or clomipramine is recommended. Patients who do not respond to first- and second-line treatments can be treated with augmentation using antipsychotics, 5-HT3 antagonists, riluzole, memantine, and ketamine, and in patients who do not respond to these pharmacological agents noninvasive brain stimulation techniques, such as electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS) can be used.[5] Finally, ablative surgery and deep brain stimulation can be used as invasive treatment options.[5]

TMS is a noninvasive brain stimulation technique used to externally stimulate the brain cortex via magnetic pulses delivered by coils. For psychiatric purposes TMS is commonly administered by delivering repetitive stimuli (hence rTMS) to modulate brain activity. High-frequency repetitive stimulation

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increases cortical excitability, whereas low-frequency stimulation suppresses excitability.[6] For instance, 20-Hz stimulation of the left dorsolateral prefrontal cortex is effective for the treatment of a major depressive episode and is frequently used for treatment-resistant depression.[7] Various rTMS protocols and stimulation sites are currently used in patients with treatment-resistant OCD. These protocols include stimulation of the left dorsolateral prefrontal cortex, right dorsolateral prefrontal cortex, orbitofrontal cortex, and supplementary motor area.[8] These targets are used as they play a major role in the fronto-striato-thalamo-cortical circuitry implicated in OCD.[9] Greenberg et al[10] first used rTMS to treat OCD in 1997 and observed that compulsions decreased to a greater degree following a single session of 20-Hz rTMS administered to the right-side, as compared with left-side administration. The benefits of right-sided stimulation are particularly interesting, as the researchers explained this finding according to a lateralization hypothesis. Indeed, metabolic studies reported that right-side cerebral activity correlates with the symptoms of OCD and that this correlation no longer exists following successful behavior modification treatment.[11] The literature includes 3 randomized control studies that attempted to replicate Greenber et al's[10] findings, but the findings were inconsistent. Sachdev et al[12] reported improvement in the Yale-Brown Obsessive Compulsive Scale (YBOCS) score after both left- and right-side prefrontal rTMS, Alonso et al[13] did not note any improvement in the YBOCS score in the rTMS treatment and sham groups, and Sarkhel et al[14] reported that both the sham and rTMS treatment groups improved equally. The inconsistency of these findings might have been due to heterogeneity of the stimulation protocol, the number of stimulation sessions, comorbidities, and concomitant medication. Another possibility is that not everyone responds to rTMS. This possibility is important because it requires that researchers determine how to identify which patients will and will not respond to treatment.

Quantitative electroencephalography (qEEG) is a method of measuring brain functions based on calculating the power of oscillations. Power values for each electrode and band (eg, alpha, beta, theta, and delta) are calculated after employing signal processing techniques and can be used to examine brain activity characteristic of particular diseases, as well as to predict response to different types of treatment. For example, Hansen et al[15] reported that OCD patients with excessive frontal theta activity do not respond well to paroxetine. A qEEG study based on source localization techniques reported that lower anterior cingulate and medial frontal gyrus beta activity was associated with poorer treatment response to antidepressants.[16] It was also reported that alpha activity in the corpus striatum—in the orbito-frontal and temporo-frontal regions—was inversely correlated with the response to paroxetine.[17] Krause et al[18] performed qEEG in OCD patients treated with sertraline and reported that the responders had lower frontal and parietal fast activity, and lower alpha activity in the orbitofrontal cortex than did the nonresponders. More recently, Dohrmann et al[19] reported that responders to SSRI and/or psychotherapy had lower levels of resting-state vigilance, as measured by qEEG.

Increasingly, psychiatric research is employing particle swarm optimization (PSO), which is a global optimization algorithm inspired by the collective intelligent behavior of animal groups, such as flocks of birds, schools of fish, and swarms of termites. The PSO algorithm simulates the social behavior of individuals learning from personal experience and interactions with others. Some particles in the algorithm represent individuals in an animal group and other particles represent the swarm (the animal group) working together to achieve a common goal.[20,21]

Another contemporary trend in psychiatric research is the use of artificial neural networks (ANNs), which are inspired by biological neural networks composed of a very complex web of interconnected neurons. The basic processing elements of any ANN are artificial neurons, also known as nodes. Each node consists of 3 basic elements: inputs to the node, which are characterized by a weight or strength of their own; the summing function, which creates a weighted sum of inputs; the activation function, which limits the amplitude range of the output. Additionally, each node has an externally applied bias that is set to a negative or positive value, which then increases or decreases the net input of the activation function.[22,23]

ANN's are organized as layers of nodes, namely the input layer, hidden layers, and the output layer. The number of nodes in each layer, the number of hidden layers, and the number of connections between neurons (ie, the feedforward network and recurrent network) constitute the architecture of an ANN. In a feedforward network the input values flow from the input layer to the output layer, whereas a recurrent network has ≥ 1 feedback loop that acts as the memory of the neural network.[22,23]

The learning (training) process for an ANN involves feeding the input vectors to the network, so that the network improves its performance (ie, the correct recognition rate) by adjusting synaptic weights according to a learning algorithm. One of the most common learning algorithms is the backpropagation (BP) algorithm.[24-28] The BP algorithm utilizes the gradient descent rule to minimize the prediction error of an ANN and is known for its ability to minimize the prediction error in highly nonlinear search spaces.[23]

The present study aimed to be the first to use qEEG to predict treatment response to right frontal rTMS in OCD patients. Before rTMS treatment all OCD patients underwent qEEG recording. Then, following rTMS treatment (right-side frontal low-frequency stimulation) the ability of pretreatment qEEG to predict response to rTMS treatment was determined using PSO and an ANN, specifically a feed-forward neural network and the BP learning algorithm.

Materials and Methods

Patient Characteristics

This study included 50 OCD patients retrospectively selected from the patient database of Uskudar University, NPIstanbul Outpatient Clinic, Istanbul, Turkey. OCD was diagnosed according to *DSM-IV-TR* and *DSM-5* criteria. rTMS at the frequency of 1 Hz was administered to the right dorsolateral prefrontal cortex. In total, 1000 pulses were administered with 110% of the motor threshold. The motor threshold was determined as the lowest setting at which ≥50% of the stimuli produced an observable movement. Patients underwent a mean 22 sessions (range: 12-40). All the patients, except for 1 (due to pregnancy), were receiving an antidepressant (selective serotonin reuptake inhibitor [SSRI]); additionally, 28 were receiving an antipsychotic, 6 were receiving a mood stabilizer, and 2 were receiving a benzodiazepine. The decision to administer rTMS was made on the basis of inadequate response to medical treatment. Post-rTMS remission of OCD was determined based on a clinical evaluation interview conducted by 2 psychiatrists.

qEEG Analysis

The study retrospectively examined qEEG data for 35 OCD patients that responded to rTMS and 15 OCD patients that did not respond to rTMS. All qEEG data were recorded during 3 minutes of rest while the patients sat with eyes closed. During recording 19 electrodes were placed according to the 10-20 system. Linked ear electrodes (A1-A2) were used as a reference. All impedances were maintained at <10 kohm. The acquisition sampling rate was 125 Hz, acquired signals were band-pass filtered at 0.15 to 70 Hz (using a 50-Hz notch filter), and data artifacts were eliminated manually off-line for each patient. To remove artifacts all data were inspected and any segment containing muscle movement, eye movement, electrode popping, or similar types of artifacts were excluded from analysis. Fast Fourier transform (FFT) analysis was performed by averaging across 2-second epochs. Absolute power was computed for the delta (1-4 Hz), theta (4-8 Hz), alpha (8-12), and beta (12-25 Hz) bands. NeuroGuide Deluxe v.2.5.1 (Applied Neuroscience, Largo, FL) software was used for qEEG analysis.

Feature Selection and Classification

The band power feature vectors created for characterization of qEEG signals can contain redundant features that can result in increased computational complexity and degraded classification performance. To avoid these problems the feature subsets that contain complementary information leading to the highest-level classification performance must be determined. The feature subsets that provide the best class separability are highly dependent on the nature of the data set and the classification method employed. One method of determining the optimal feature subset is to perform an exhaustive search in the feature space by checking the performance of the classifier for all possible combinations of features; however, this approach is computationally expensive and impractical, and, therefore, feature selection methods are used for identifying the optimal feature subsets.[29,30]

Feature selection methods fall in to 3 broad categories: filter, wrapper, and embedded. Filter methods perform feature selection based on statistical characteristics of the feature vector without involving any learning algorithms. Wrapper methods require a predetermined learning algorithm that is used to evaluate the performance of the feature combinations, so as to select an optimal feature subset. Embedded methods involve learning algorithms with built-in mechanisms for performing feature selection as a part of their training (learning) process. In general, all these feature-selection methods work by means of choosing the complementary features from the candidate feature set or by assigning a weight (measure of relevance) to all the features in the candidate feature set.[29-31]

In the present study a wrapper method was used for feature selection via PSO, along with an ANN. The PSO algorithm was used for estimating feature weights and the ANN was used for evaluating the classification performance of weighted features.

Particle Swarm Optimization

Optimization is basically maximization or minimization of an objective function based on choosing the optimal parameter set.[32] Within the scope of the present study, the objective was to maximize the classification performance of the ANN classifier via optimization of feature weights using PSO. The weight of a feature describes the relevance of the feature for a given classification task. Using PSO, each particle represented a weight vector for 19 features in the feature set.

The PSO algorithm employed 3 steps that were iterated until a stopping criterion was met:

1. Initialize:
   - The swarm is composed of $\mathbf{n}$ particles $\mathbf{S = \{X_1, X_2, \ldots, X_n\}}$.
   - The position of particle $\mathbf{i}$ in the swarm is represented by the vector $\mathbf{X_i = [x_{i1}, x_{i2}, x_{i3}, \ldots, x_{iD}]}$, where $\mathbf{D}$ is the dimensionality of the search space.
   - For each of $\mathbf{n}$ particles:
     - Initialize position of a particle: $\mathbf{x_i(0), i = 1, \ldots, n}$
     - Initialize particle's best position: $\mathbf{p_i(0) = x_i(0)}$
     - Calculate fitness $\mathbf{f(\cdot)}$ of each particle and initialize global fitness:
       $\mathbf{g = argmax\ \{f(x_1(0), x_2(0), \ldots, x_n(0))\}}$, where $\mathbf{f(\cdot)}$ represents the fitness function.

2. Repeat the following steps until the stopping criterion is met:
   For each of **n** particles:

   - Update velocity of particle **i**:
     $\mathbf{v_i(t+1) = w \cdot v_i(t) + c_1 \cdot R_1 \cdot (p_i - x_i(t)) + c_2 \cdot R_2 \cdot (g - x_i(t))}$, where **t** and **t + 1** indicate successive iterations of the algorithm, the rest of parameters are explained below.
   - Update position of particle **i**: $\mathbf{x_i(t+1) = x_i(t) + v_i(t+1)}$
   - Calculate fitness of particle **i:** $\mathbf{f(x_i(t+1))}$
   - Update individual and global fitness:
     If $\mathbf{f(x_i(t+1)) > f(p_i)}$, $\mathbf{pi = f(x_i(t+1))}$
     If $\mathbf{f(x_i(t+1)) > f(g)}$, $\mathbf{g = f(x_i(t+1))}$

3. After the stopping criterion was met, the optimal solution was represented by particle **g**, which represented the best fitness in the population.

In the present study, the stopping criterion was reaching the maximum of 180 iterations. This value was selected based on examination of the convergence of the feature weights represented by each particle.

The velocity update formula, $\mathbf{v_i(t+1) = w \cdot v_i(t) + c_1 \cdot R_1 \cdot (p_i - x_i(t)) + c_2 \cdot R_2 \cdot (g - x_i(t))}$, has a set of parameters that needs to be fixed. The inertia weight (**w**) keeps the particle from changing its original direction. $\mathbf{c_1 \cdot R_1 \cdot (p_i - x_i(t))}$ is the cognitive component representing a particle's memory, which causes the particle to return to regions of the search space in which particle fitness was the highest. $\mathbf{c_2 \cdot R_2 \cdot (g - x_i(t))}$ is the social component representing a particle's interaction with other particles, causing the particle to move to regions of the search space in which global fitness is highest. Parameters $\mathbf{c_1}$ and $\mathbf{c_2}$ control the step size of a particle toward the best individual fitness and best global fitness, respectively. Clerc[33] recently reported some general directives for choosing a good combination of parameters, as follows: Swarm size: $\mathbf{n} = 20$ particles; cognitive parameter: $\mathbf{c_1}$ [0,1], with a preference for 0.7; social parameter: $\mathbf{c_2} \sim 1.5$, with a preference for 1.43. Nevertheless, different parameter values can generate better or worse outcomes depending on the problem; therefore, the best solution is to perform sensitivity analysis in the context of the problem description.[26] Parameters $\mathbf{R_1}$ and $\mathbf{R_2}$ are 2 diagonal matrices of random numbers with a uniform distribution between 0 and 1. These parameters help a particle move toward the optimal solution in a semirandom manner. The values of parameters $\mathbf{R_1}$ and $\mathbf{R_2}$ in the present study were 0.7 and 0.8, respectively.[33-35]

Artificial Neural Networks

The ANN model used in the present study was composed of an input layer with 19 nodes, a hidden layer with 20 nodes, and an output layer with 1 node. The neural network model was constructed with a 19-node input layer because the band power features were computed using qEEG signals recorded from 19 electrode locations. Because of its nonlinear structure, the logsig transfer function was employed in the hidden layer and the purelin transfer function was employed in the output layer. The trainlm training function was used to train the model. Trainlm is a training function that uses Levenberg-Marquardt optimization to update the weight and bias values in the neural network model. The classification accuracy of the neural network model was tested using 5-fold, 7-fold, and 10-fold cross validation, and 7-fold cross-validation was subsequently used, as it provided the highest classification accuracy.

Table 1. Descriptive Statistics for Patients' Gender.[a]

	Nonresponsive	Responsive	Total
Age, years, mean (SD)	35.07 (11.41)	30.86 (10.46)	
Gender			
Male	8	18	26
Female	7	17	24
Total	15	35	50

[a] $P = .23$ and $P = .9$ for age and gender differences, respectively.

Results

There was no significant difference in age ($P = .232$) or gender ($P = .902$) between the patients who did and did not respond to rTMS (Table 1).

Repeated-measures analysis of variance of the responders' and nonresponders' delta, theta, alpha, and beta band power values, with electrode locations as the within-participant factor and treatment response as the between-participant factor, showed that there were no significant differences ($P > 0.05$) between the 2 patient groups. According to the independent samples t-test used to compare pairwise electrodes in the responders' and nonresponders' delta, theta, alpha, and beta band power data, there were no significant differences ($P > .05$).

The present study investigated the ability to predict response to rTMS treatment in OCD patients based on qEEG band power features (extracted from the delta, theta, alpha, and beta bands), which were considered biomarkers. ANN and PSO were used for feature selection/weighting and classification. The correct prediction rate and confusion matrices for each frequency band are given in Table 2. The highest prediction rate of 80% was obtained using theta band power features. The confusion matrices of all the frequency bands indicated that the majority of prediction errors were caused by misclassification of treatment nonresponders as responders, which is a common problem when analyzing classes with an imbalanced sample size and decision boundaries tend to be biased toward the majority class.[36]

Table 3 shows the feature weights estimated using the PSO algorithm and ANN classifier; weights for 12 of the 19 features

Table 2. Correct Prediction Rate Along With Confusion Matrices for Each Frequency Band.

Frequency Band	PSO + ANN Accuracy (%)			
Delta	68.0		Not responsive (actual)	Responsive (actual)
		Not responsive (predicted)	2	3
		Responsive (predicted)	13	32
Theta	80.0		Not responsive (actual)	Responsive (actual)
		Not responsive (predicted)	10	5
		Responsive (predicted)	5	30
Alpha	74.0		Not responsive (actual)	Responsive (actual)
		Not responsive (Predicted)	6	4
		Responsive (predicted)	9	31
Beta	68.0		Not responsive (actual)	Responsive (actual)
		Not responsive (predicted)	2	3
		Responsive (predicted)	13	32

Abbreviations: PSO, particle swarm optimization; ANN, artificial neural network.

Table 3. Feature Weights Estimated by Particle Swarm Optimization.

Selected Channels	Feature Weights
C3	0.054
O2	0.226
Fp2	0.478
F4	0.682
F3	0.774
Fp1	0.792
Pz	0.825
Fz	0.972
O1	1
F7	1
C4	1
Cz	1

are given, as the weights for the other 7 features were <0.05, which led to the conclusion that these features were irrelevant for the classification task.

Figure 1 shows the absolute band power features averaged over channels for the 2 patient groups. The plots in the figure show that the mean delta, theta, and alpha band power values were higher in the treatment responders than in the nonresponders.

Discussion

The present study aimed to determine if OCD patient response to rTMS can be predicted via qEEG data subjected to machine learning methods. The findings showed that among the 4 qEEG bands analyzed, theta band power was able to differentiate treatment responders from nonresponders. The responders had higher theta band power at all electrodes than did the nonresponders. The findings also show that qEEG could be helpful for predicting treatment response for OCD patients.

The present findings are important in the following 2 ways. First, treatment resistance is a critical issue in psychiatry and, in particular, OCD is associated with a high rate of treatment resistance.[37] Although the definition of treatment resistance varies, studies report that $>50\%$ of OCD patients may not respond to treatment.[38] Some patients need to try several courses of different antidepressant and antipsychotic medications before a satisfactory treatment response is achieved. Beyond pharmacological therapies, neuromodulation can also be used to treat OCD; however, as with pharmacological treatments, a significant percentage of patients do not respond to rTMS (30% in the present study). Use of biomarkers, such as qEEG absolute power, might help clinicians tailor the treatment of OCD to yield the most optimal outcome possible; such an approach is consistent with the emerging concept of personalized medicine.[39] Second, theta power might be positively correlated with the level of response to rTMS. Increased theta power has been reported in a number of neuropsychiatric disorders; in particular, ADHD is frequently associated with increased theta and decreased beta power.[40] The same finding in OCD patients (as reported herein) indicate that responders to rTMS might have a lower resting arousal level than non-responders. Interestingly, an earlier study also reported that lower resting arousal predicted better response to antidepressants in OCD patients.[19]

The present study has some limitations, including a small OCD patient sample that included only 15 nonresponders to rTMS (primarily due to the retrospective study design). In addition, treatment response was defined by clinicians and a formal symptom measurement scale such as the YBOCS was not used; however, it should be noted that patient files were independently evaluated by 2 psychiatrists to confirm nonresponder status. Lastly, rTMS and qEEG results were evaluated retrospectively. Based on these limitations, the present findings should be evaluated cautiously and considered preliminary. Additional larger-scale studies that employ a prospective design, and document pretreatment and posttreatment

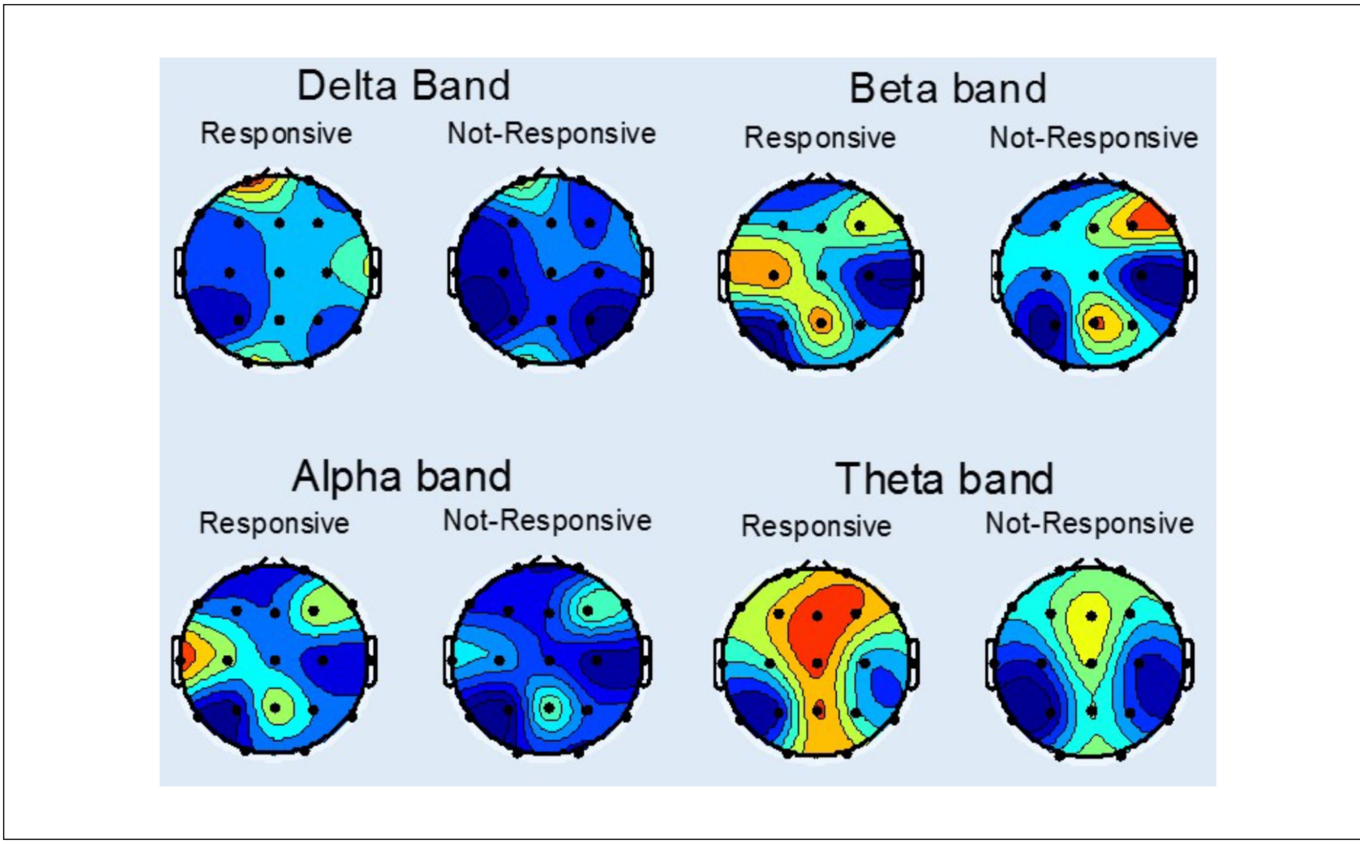

Figure 1. Topographic plots of mean delta, theta, alpha, and beta band absolute band power in the treatment responders and non-responders.

symptom scores are required to further elucidate the ability of qEEG to predict the response of OCD patients to rTMS.

Author Contributions

SZM contributed to conception and design; contributed to acquisition and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. BM contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. TE contributed to analysis; drafted manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. TBA contributed to analysis and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. MKA contributed to conception; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. KNT contributed to conception; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. SY contributed to analysis; drafted manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

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