

Prediction of treatment resistance in obsessive compulsive disorder patients based on EEG complexity as a biomarker

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ARTICLE INFO

Article history:

Accepted 25 November 2019

Available online 13 January 2020

Keywords:

EEG

Obsessive-compulsive disorder

Approximate entropy (ApEn)

Classification

HIGHLIGHTS

- EEG beta band complexity could be a biomarker for treatment resistance in OCD.
- EEG beta band complexity was lower in treatment-resistant OCD patients.
- Severity of illness as measured by Yale-Brown Obsessive Compulsive Scale was inversely correlated with approximate entropy (ApEn) complexity values.

ABSTRACT

Objective: This study aimed to identify an Electroencephalography (EEG) complexity biomarker that could predict treatment resistance in Obsessive compulsive disorder (OCD) patients. Additionally, the statistical differences between EEG complexity values in treatment-resistant and treatment-responsive patients were determined. Moreover, the existence of correlations between EEG complexity and Yale-Brown Obsessive Compulsive Scale (YBOCS) score were evaluated.

Methods: EEG data for 29 treatment-resistant and 28 treatment-responsive OCD patients were retrospectively evaluated. Approximate entropy (ApEn) method was used to extract the EEG complexity from both whole EEG data and filtered EEG data, according to 4 common frequency bands, namely delta, theta, alpha, and beta. The random forests method was used to classify ApEn complexity.

Results: ApEn complexity extracted from beta band EEG segments discriminated treatment-responsive and treatment-resistant OCD patients with an accuracy of 89.66% (sensitivity: 89.44%; specificity: 90.64%). Beta band EEG complexity was lower in the treatment-resistant patients and the severity of OCD, as measured by YBOCS score, was inversely correlated with complexity values.

Conclusions: The results indicate that, EEG complexity could be considered a biomarker for predicting treatment response in OCD patients.

Significance: The prediction of treatment response in OCD patients might help clinicians devise and administer individualized treatment plans.

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1. Introduction

Obsessive compulsive disorder (OCD) is a disabling psychiatric disorder with a life-time prevalence of 2.3% (Rusico et al., 2010). The disorder is characterized by obsessions in the form of recurrent

intrusive thoughts, urges, or impulses that cause distress or anxiety, and compulsions in the form of repetitive behaviors performed to suppress the anxiety or relieve stress associated with obsessions (DSM-5). The mainstay of the pharmacological treatment of OCD is clomipramine or selective serotonin reuptake inhibitors (SSRIs), which yield a response in about 50% of patients (Bystritsky, 2006; Jenike, 2004; Pallanti et al., 2002). Psychological interventions, such as cognitive behavioral therapy (CBT) together with exposure and/or response prevention, can—in some patients—be more effective than pharmacological interventions; however, few

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trials have compared the efficacy of psychological interventions and medications for the treatment of OCD (Skapinakis et al., 2016).

Despite the availability of several treatment options, clinicians frequently encounter treatment-resistant OCD patients—those that do not respond adequately to medications or CBT. Numerous factors might contribute to treatment resistance in OCD patients, including disease severity, medical or psychiatric comorbidities, lack of treatment compliance, and exposure to chronic stressors (Pallanti and Quercioli, 2006).

Storch et al. (2008) reported that the clinical indicator of treatment-resistance OCD included significantly more obsessions, compulsions, and internalizing symptoms, together with profound social dysfunction. A review by Knopp et al. (2013) reported that the factors associated with treatment outcome in OCD patients based on clinical profiles include demographic, interpersonal, symptom-specific, psychological/psychosocial and treatment-specific variables. More specifically treatment resistance was potentially associated with increased anxiety, increased OCD symptom severity, category of OCD symptom subtypes especially hoarding symptoms as well as non-clinical variables that were unemployment and being single.

In addition to clinical profiles, individualized treatment plans based on brain activity, the development of novel pharmacological and non-pharmacological treatment guidelines, and timely treatment of treatment-resistant patients have become an important issue. Nonetheless, there are limited number of studies investigating biomarkers of treatment response in OCD patients (Maron and Nutt, 2015; Fullana and Simpson, 2016). For instance, there are several pharmacogenetic studies investigating the relationship between antidepressant treatment response and genetic factors in OCD. A review paper by Maron and Nutt (2015) reported that the genes related to serotonin, glutamate, dopamine systems and neurotrophic factors have been identified as potential predictors of treatment response. Additionally, a few studies have explored blood-based predictors of treatment response in OCD. Whole-blood serotonin concentration, platelet serotonin transporter, 5-HT_{2A} receptor binding characteristics and platelet IP₃ content are peripheral serotonergic parameters identified as potential predictors of antidepressant treatment response in OCD.

There are also multiple studies utilizing neuroimaging technologies to predict treatment response in OCD patients. For instance, Brody et al. (1998) investigated PET scans in OCD patients prior to CBT or fluoxetine treatment, and observed that a high level of left orbitofrontal cortex activity prior to CBT treatment and low-level left orbitofrontal cortex activity prior to fluoxetine treatment were associated with treatment response.

MRI findings in OCD patients indicate that there is a positive correlation between volume of gray matter in the subgenual anterior cingulate (Hoexter et al., 2013) and a negative correlation between cortical thickness in the rostral anterior cingulate cortex (Fullana et al., 2014) and the degree of treatment response. Other researchers used functional neuroimaging techniques to investigate activity in the anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC) in OCD patients, observing that—in general—as metabolic activity before treatment decreased the response to medication increased (Ball et al., 2014; Shin et al., 2013). Banks et al. (2015) noted that OCD patients that responded to anterior cingulotomy had more connectivity between the right ACC and subcortical brain regions before surgery than those that did not respond.

The literature includes several studies that used EEG or quantitative EEG (qEEG) for predicting treatment resistance in OCD patients; however, the findings are inconsistent. For instance, 2 subgroups of OCD patients were described using qEEG data: those with increased prefrontal theta power, and those with increased alpha and beta power (Prichep et al., 1993). Interestingly Prichep

et al. (1993) and Hansen et al. (2003) reported that the increased theta power subgroup did not respond to treatment, whereas the increased alpha and beta power subgroup did respond to pharmacological treatment.

Koprivova et al. (2013) explored predictors of treatment response and EEG correlates of clinical symptoms and reported that high delta, low alpha, and low beta2 power were associated with a lower rate of response to independent component neurofeedback treatment in OCD patients. Krause et al. (2016) obtained EEG recordings in OCD patients before standardized treatment with sertraline and CBT, and based on low-resolution brain electromagnetic tomography (LORETA) analysis reported that treatment responders had significantly lower activity in the beta1, beta2, and beta3 bands, and lower activity in the alpha2 band, as compared to non-responders.

Considering the cost-effective and non-invasive nature of EEG, its use to identify potential predictors of treatment resistance in OCD patients could ultimately help to devise individualized treatment plans and improve our understanding of OCD. On the other hand, given the heterogeneity of earlier studies and their inconsistent findings, we think more consistent EEG biomarkers are needed. In this regard, advanced signal processing methods might help in identifying new biomarkers and subtypes for prediction of treatment resistance in OCD patients. Interpreting EEG signals in terms of the power spectrum in different frequency bands is a very common approach (Pogarell et al., 2006; Moretti et al., 2004; Hansen et al., 2003; Tot et al., 2002; Sponheim et al., 2000; Kuskowski et al., 1993; Prichep et al., 1993). The primary shortcoming of using the power spectrum of oscillations to identify OCD subgroups, as did Hansen et al. (2003) and Prichep et al. (1993), is that these measures indicate only the general power of the corresponding oscillations and do not provide additional data related to signal characteristics. Considering the complex, irregular, and possibly nonlinear and nonstationary nature of EEG signals, analysis of nonlinear complexity features is considered a potential approach for improving the characterization of these signals.

In the context of mental disorders, the primary aim of using EEG complexity measures has been to investigate the existence of abnormal brain activity in patients with Alzheimer disease, schizophrenia, autism spectrum disorders, and mood disorders (Fernandez et al., 2013; Takahashi, 2013). While interpretation of EEG complexity varies based on physiological parameters and the research question under consideration, studies have shown that those with mental disorders are often associated with low or high complexity, as compared to healthy controls (Catarino et al., 2011; Fernandez et al., 2011, 2010a, 2010b; Mendez et al., 2012; Stam, 2005). These types of studies show that EEG complexity could be used as a biomarker for differentiating controls, and patients with OCD (Aydin et al., 2015), depression (Sabeti et al., 2009), schizophrenia (Sabeti et al., 2009; Li et al., 2008) and autism spectrum disorders (Catarino et al., 2011).

The primary aim of the present study was to determine the efficacy of a nonlinear complexity measure, namely approximate entropy (ApEn), as a biomarker for predicting treatment resistance in OCD patients. ApEn is a nonlinear complexity index that is robust to noise and provides stable results, even when using short data segments, rendering it a potential feature for characterization of EEG signals (Sun et al., 2017; Pincus, 1995). In the first part of the study the ability of the ApEn complexity extracted from whole EEG data (0.01–62.5 Hz) and EEG data filtered using 4 common frequency bands, namely delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), and beta (12–24 Hz), to differentiate between treatment-resistant and treatment-responsive OCD patients has been investigated. The frequency band with the highest discrimination ability (as measured by classification accuracy) was then further investi-

gated to determine the most discriminative channels. Additionally, the most discriminative channel and band combinations was investigated. In the next part of the study the complexity differences between the treatment-resistant and treatment-responsive OCD patients were compared. Additionally, the correlation between EEG complexity and the severity of OCD (as measured by the Yale Brown Obsessive Compulsive Scale [YBOCS] score) was investigated.

2. Methods

2.1. Patients

The study included OCD patients diagnosed at Uskudar University Outpatient Clinic, Istanbul, Turkey, between December 2015 and December 2017. OCD was diagnosed by 2 psychiatrists via the Structured Clinical Interview for DSM-5 (SCID-5) (Elbir et al., 2019). All the patients were medication free for at least 2 weeks prior to EEG acquisition. Treatment response was evaluated retrospectively.

The treatment-responsive group included 29 patients (15 male and 14 females) aged 18–48 (mean age: 29 years) and the treatment-resistant group included 28 patients (9 male and 19 female) aged 19–65 years (mean age: 31 years). There weren't any significant differences in age or gender between the 2 groups ($p > 0.6$). The mean initial YBOCS score in the treatment-responsive group was 24, versus 28 in the treatment-resistant group ($p < 0.05$). The cutoff YBOCS score for inclusion in the study was 16.

Treatment resistance was defined as a lack of meaningful improvement in OCD symptoms (defined as a <35% decrease in the YBOCS score) after pharmacotherapy that included adequate trials (3 months of the maximum recommended dose by the US FDA) of ≥ 3 SSRIs, augmentation of SSRI treatment with a neuroleptic (Bloch et al., 2006), with a benzodiazepine (Starcevic et al., 2016), and ≥ 20 sessions of CBT (exposure and response prevention) (Rauch et al., 1994). OCD treatment was generally initiated with SSRIs, and based on response the clinician could switch to another SSRI or clomipramine. Inadequate response to SSRIs and clomipramine prompted augmentation strategies, using neuroleptics, benzodiazepine, and CBT.

In the treatment-responsive group 9 patients were treated with medications only, and 19 patients were treated with medications and CBT. As 1 of the patients was pregnant and treated with CBT, her treatment was switched to medications when she could no longer go to CBT.

2.2. EEG data

EEG was recorded at 125 Hz during 3 min with patients at rest with eyes closed, and using 19 electrodes (Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T7, T8, P7, P8, Fz, Cz, and Pz) placed on the scalp based on the international 10–20 system. Brain Vision Analyzer v.2.1.2 software was used (<https://www.brainproducts.com>) for preprocessing and data analysis. Prior to artefact rejection processing, EEG data were filtered between 0.01 Hz and 62.5 Hz, and a notch filter (50 Hz) was used to remove electricity network artefacts. Eye movement artefacts were rejected automatically using Ocular Correction ICA (Makeig et al., 1995) and other types of artefacts, such as muscle artefacts, were rejected using raw data inspection. Then, data were exported to a text file in the ASCII format using the generic data export tool in Brain Vision Analyzer software.

2.3. Feature extraction

ApEn is a measure of complexity/irregularity/disorder in time series data. Higher ApEn values correspond to higher complexity/greater irregularity and, conversely, lower ApEn values indicate the existence of repetitive patterns in time series data (Pincus, 1995).

Originally, ApEn is calculated by assuming we have EEG time series from a single channel with N data points, and $X = [X_1, X_2, X_3, \dots, X_N]$, a sequence of vectors (V), are constructed as follows;

$$V = [v_1, v_2, v_3, \dots, v_M] \quad (1)$$

$$v_i = [X_i, X_{i+1}, X_{i+2}, \dots, X_{i+(m-1)}] \quad (2)$$

For $i = 1, 2, 3, \dots, M$, where M is $N-(m-1)$, that is the number of vectors and m is the length of the vectors; however, we previously determined that when ApEn is used as a feature for classification of physiological signals, such as EEG and ECG, using a sequence of vectors reconstructed in state space using time delay embedding instead of the original version described above provides better separability, as described earlier (Balli and Palaniappan, 2010; Dyson et al., 2008; Takens, 1981). In this case, vector V is defined as;

$$V = [v_1, v_2, v_3, \dots, v_M] \quad (3)$$

$$v_i = [X_i, X_{i+1\tau}, X_{i+2\tau}, \dots, X_{i+(m-1)\tau}] \quad (4)$$

For $i = 1, 2, 3, \dots, M$, where M is $N-(m-1)\tau$, that is the total number of embedded vectors in state space, m is the length of the vector (referred to as the embedding dimension in the context of time delay embedding) and τ is time lag.

The remainder of the ApEn estimation procedure for both the original and modified versions described above is the same, where for each of the vectors v_i , the correlation integral (C_i^m) that enumerates the number of vectors v_j ($i \neq j$) that are closer to v_i than a tolerance value r , is calculated as;

$$C_i^m = \sum_{j=1}^M \frac{\Theta(r - \|v_i - v_j\|)}{M} \quad (5)$$

where $M = N-(m-1)\tau$ is the number of embedded vectors, $\|v_i - v_j\|$ is the Euclidean distance between vectors v_i and v_j , $\Theta(x) = 0$ for $x > 0$, and $\Theta(x) = 1$ for $x \leq 0$.

Finally, ApEn is calculated as;

$$ApEn(m, \tau, r) = \Phi^m(r) - \Phi^{m+1}(r) \quad (6)$$

$$\Phi^m(r) = \frac{1}{M} \sum_{i=1}^M \ln[C_i^m(r)] \quad (7)$$

ApEn measures the likelihood that vectors that are close to each other for m observations remain close for $m + 1$ observations. Greater likelihood of remaining close, which can also be defined as regularity, yields smaller ApEn values and vice versa.

The 3 input parameters, m (length of vector), τ (time lag), and r (tolerance of comparison), must be fixed to estimate ApEn. Most published studies suggest that τ can be estimated using first zero crossing of the autocorrelation function and m can be estimated using the false nearest neighbors method (Stam, 2005); however, earlier research has shown that different values of m and τ can lead to greater separability of ApEn complexity features in EEG data (Balli and Palaniappan, 2010; Dyson et al., 2008); thus, in the present study ApEn values were extracted for m values starting from 2 to 5 and τ values starting from 1 to 10 to determine if ApEn with different parameter settings resulted in greater classification accuracy. Originally ApEn is estimated using an r value that is 0.1–0.25 times standard deviation of time series data (Pincus, 2006, 1995;

Abásolo et al., 2005); however, earlier studies show that using a fixed r value will increase the discrimination rate for classification of mental task EEG using ApEn as a feature (Dyson et al., 2008). Thus, in the present study fixed r values starting from 0.1 to 1.0 with increments of 0.1 were used. Note that the r value range was tested based on classification results where the discrimination ability of ApEn would reach a plateau or decrease with higher values of r , indicating that increasing the r value would not improve classification accuracy. Accordingly, the ApEn features were extracted for 4 length of vector values (m) \times 10 time lags (τ) \times 10 tolerance of comparison (r) values, resulting in 400 different parameter combinations. Each feature set extracted with different parameter settings was classified and the parameter set leading to highest classification accuracy was selected as optimal.

2.4. Feature selection and classification

Filter and wrapper methods are the standard approaches for feature selection (Blum and Langley, 1997). Using the filter method, the optimal feature subset is selected independent of the classification algorithm. The statistical characteristics of the training data, such as distances between classes or the variance of features within the same class, are used to select the features. On the other hand, the wrapper method utilizes a predetermined classification algorithm for evaluating performance of feature combinations, so as to determine the optimal feature subset.

In the present study a wrapper-based approach known as the sequential floating forward selection (SFFS) algorithm along with a Random Forests (RF) classifier was used. The SFFS method is a combination of sequential forward selection (SFS) and sequential backward selection (SBS) algorithms.

The SFS algorithm is an iterative algorithm that starts with an empty optimal feature subset. In the first iteration each feature in the candidate feature set is evaluated based on its classification accuracy and the feature that yields the highest accuracy is included in the optimal feature subset. In the second iteration the combination of features in the optimal feature subset with each feature in the candidate feature set is evaluated, and the feature that yields the highest classification accuracy is added to the optimal feature subset. This process of evaluating the combinations of each feature in a candidate feature set with the optimal feature subset and adding the best feature to the optimal feature subset is repeated until the maximum number of features is reached.

Conversely, the SBS algorithm starts with an optimal feature subset that contains a complete candidate feature set. Each feature in the candidate feature set is evaluated and the least significant feature whose removal yields the least decrease or most improvement to classification performance is removed from the candidate feature set. This process of removing features from a candidate feature set is repeated until the desired number of features is reached.

The problem with both algorithms is that they result in a nested feature subset, which in the case of SFS added features have no chance of removal and in the case of SBS the removed features have no chance of being used in later iterations; thus, solutions may get stuck in a local minimum, leading to a suboptimal feature subset (Pudil et al., 1994). The SFFS method overcomes the problem of being stuck in a local minimum by combining the SFS and SBS methods. The optimal feature subset is created by iterating through growing (SFS) and pruning steps (SBS), respectively.

For the growing step the most significant feature (leading to highest classification accuracy) is added to the optimal feature subset. The pruning step is performed only if the size of the optimal feature subset is > 2 . During the pruning step the least significant feature is removed from the optimal feature subset and added back to the candidate feature set if its removal improves classification performance. This step is repeated while the optimal feature sub-

set size is > 2 and removal of the least significant feature improves the classification accuracy of the optimal feature subset. The inclusion and pruning steps are repeated until the maximum number of features or maximum number of iterations is reached. In the present study the maximum number of iterations was 100.

The RF method was used in the present study for classification of EEG complexity features. RF is composed of many independent decision trees. The RF classifier is known to run efficiently on large datasets; RF can handle a large number of input features and has its own internal feature selection/rating structure with which decision boundaries are created by growing decision trees using features with higher ratings (Breimann, 2001). In the present study the RF algorithm was trained and tested using 10-fold cross validation. In each fold the RF algorithm steps were as follows;

- (1) The training data were used to create a new data set with bootstrapping. In bootstrapping typically 2/3 of the training data are used (in-bag samples).
- (2) The bootstrapped data set was used to create a decision tree.
- (3) Each split of the decision tree was determined using a randomly selected subset of attributes/features in the bootstrapped dataset.
- (4) The remaining 1/3 of unused training data (out-of-bag samples) were used to test the performance of the decision tree.
- (5) Steps 1, 2, 3, and 4 were repeated k times to create a random forest with k trees.

The size of the attribute subset that is used while creating the decision tree needs to be optimized, which is achieved by minimizing the overall error rate of the decision trees tested with out-of-bag samples; therefore, steps 1, 2, 3, 4, and 5 are repeated by changing the size of attribute subset. The number of decision trees used for RF in the present study was 100. It was confirmed that the classification accuracy would not improve by increasing the number of trees in RF. Fig. A.1 in Appendix A shows the flow diagram of RF classification process.

2.5. ApEn parameter settings and analysis procedure

ApEn complexity features were extracted from whole EEG data, as well as EEG data filtered using 4 common frequency bands, namely delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), and beta (12–24 Hz). ApEn complexity features were extracted from EEG data using a window of 125 samples (1-s segments) with no overlap. The present study's dataset was composed of 29 treatment-responsive and 28 treatment-resistant OCD patients' EEG recordings. There were 3 min of EEG recordings for each patient, resulting in a 19-channels \times 180-s feature vector per patient for each frequency band.

ApEn parameters were selected using an exhaustive search approach, in which length of vectors (m), time lag (τ), and tolerance of comparison (r) parameter combinations yielding the highest classification accuracy were selected as optimal. The classification accuracy of ApEn versus r and τ parameters for whole data and individual frequency bands are presented in Fig. 1. Only the results for $m = 2$ are shown, as this setting provided the highest classification accuracy with respect to parameter m . The graphs in the figure show that as the value of r increased the classification accuracy would either reach a plateau or decrease, indicating that increasing the r value would not further improve the classification accuracy of the ApEn feature.

Parameters (resulting in the highest classification accuracy) for the ApEn complexity features extracted from the beta band EEG segments were selected as $m = 2$, $\tau = 5$, and $r = 0.7$. Parameters for ApEn extracted from whole data, alpha, delta, and theta bands were selected as $m = 2$, $\tau = 1$, and $r = 0.4$. It should be noted that the

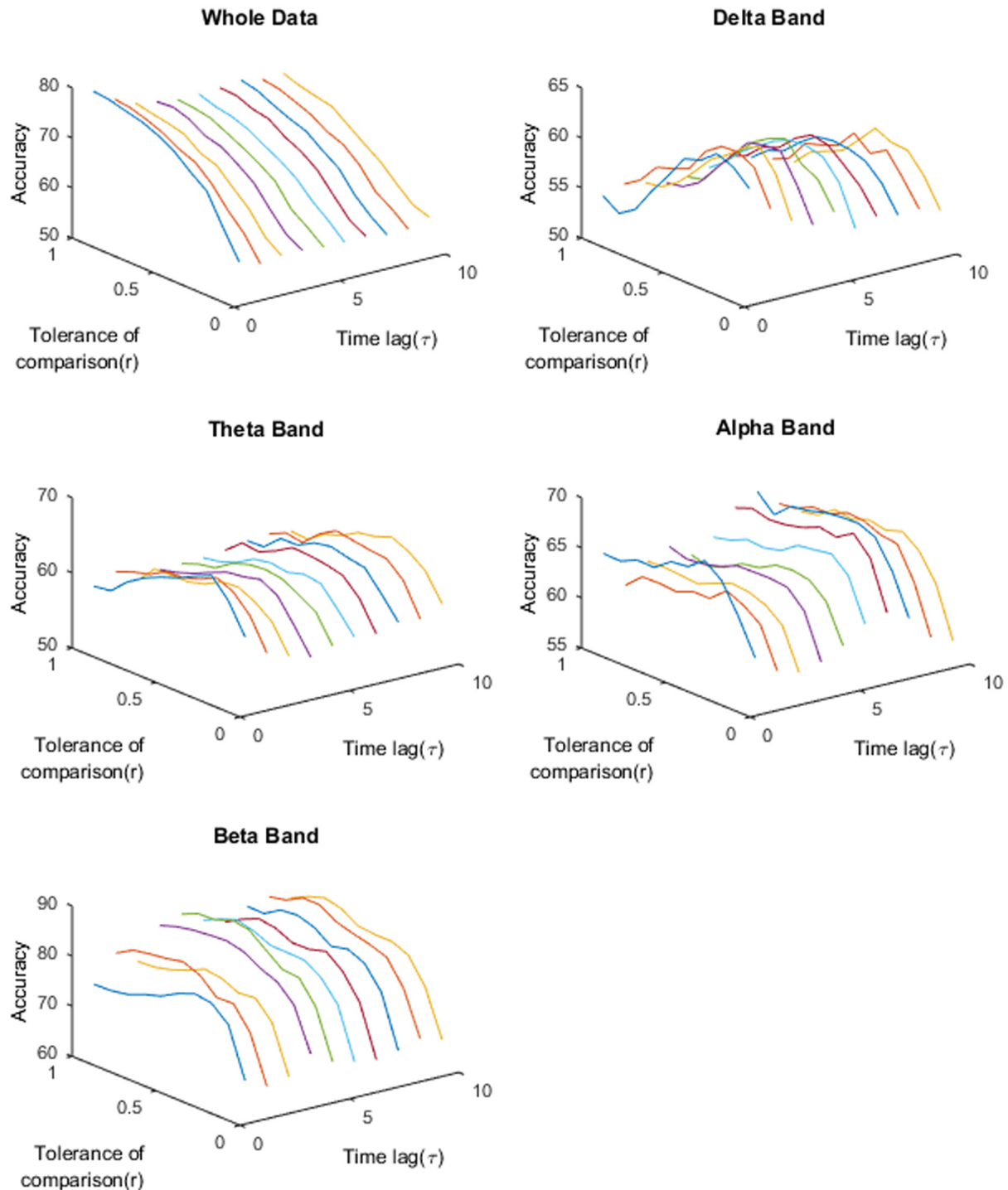


Fig. 1. Classification accuracy of approximate entropy (ApEn) versus r and τ parameters for whole data and individual frequency bands for $m = 2$.

parameter selection process was not a part of the cross validation process. Feature vectors extracted with different parameter settings were used individually to train and test the RF classifier, and the parameter settings that yielded the highest classification accuracy were selected as optimal.

3. Results

Accuracy, sensitivity, and specificity of classification (between treatment-responsive and treatment-resistant OCD patients)

according to each frequency band are given in the Table 1. The greatest ability to discriminate between treatment-responsive and treatment-resistant OCD patients (89.66%) was obtained from beta band EEG segments (sensitivity: 89.44%; specificity: 90.64%). Note that these classification results were obtained using all features from each band (without feature selection).

The SFFS method was used to determine the most discriminative channels in whole EEG data and each frequency band. In all cases, using all 19 channels provided the highest classification accuracy, indicating that all features had a positive contribution to the classification process. Next, features extracted from whole

Table 1

The accuracy, sensitivity, and specificity of classification based on whole electroencephalography (EEG) data and each frequency band (without feature selection).

Frequency Band	Accuracy	Sensitivity	Specificity
Whole EEG	77.52%	77.58%	74.55%
Delta Band	68.14%	69.23%	62.54%
Theta Band	73.91%	74.06%	63.73%
Alpha Band	73.65%	73.79%	68.75%
Beta Band	89.66%	89.44%	90.64%

EEG data and all bands were grouped together, and the SFFS feature selection algorithm was applied to identify the most discriminative channel and band combinations that could improve the classification accuracy, as compared to individual EEG frequency bands. There were 19 channels \times 5 frequency ranges (4 bands + whole data) for a total of 95 features. Among the 95 features, 14 features were selected as the most discriminative feature combination, yielding an accuracy of 91.55% (sensitivity: 91.58%; specificity: 91.36%). The number of selected features was chosen based on the convergence of classification accuracy with the increasing number of features. The selected features were, as follows: Beta band channels Fp2, T8, O1, T7, Fp1, C4, O2, F7, Fz, P8, P7, and F4; alpha band channels Fp1 and P8. These findings show that beta band features were selected predominantly as the most discriminative features, which is in agreement with the classification results based on individual frequency bands showing that the beta band provided the highest classification accuracy, as compared to whole EEG, delta, theta, and alpha bands.

In the second part of this study the 2 patient groups were compared in terms of ApEn complexity values extracted from the beta band. A channel-wise comparison was performed first, which showed that ApEn complexity values differed significantly between the treatment-responsive and treatment-resistant patients in all channels, except for channel F8 (Mann-Whitney U-test, $p < 0.05$).

Fig. 2 shows the topographic plot of the averaged ApEn complexity values in the 2 groups over each channel in the beta band. The plot shows that beta band complexity (irregularity) was higher in the EEG segments in the treatment-responsive group than in the treatment-resistant group.

Figs. 3 and 4 show the topographic plots of ApEn features extracted from the beta band averaged over all samples for each channel and each patient. Apart from a few exceptions, the general trend in the plots follow Fig. 2; the complexity values in the treatment-responsive group were higher than in the treatment-resistant group.

Finally, the relationship between YBOCS score and ApEn complexity values was investigated using Pearson's correlation analy-

sis. The relationship was investigated without taking group data into account. The linear models showed that the trend was for a negative correlation in all channels; ApEn complexity decreased as YBOCS score increased. Moreover, this trend was statistically significant ($p < 0.05$) in channels Fp2 ($r = -0.287$), C4 ($r = -0.294$), P3 ($r = -0.306$), P4 ($r = -0.300$), O1 ($r = -0.289$), F7 ($r = -0.331$), F8 ($r = -0.313$), and Pz ($r = -0.208$), indicating that there was a negative correlation between YBOCS score and ApEn complexity values.

4. Discussion

The present study explored the use of ApEn complexity as a biomarker for identifying treatment-resistant OCD patients. Additionally, differences in EEG complexity between treatment-responsive and treatment-resistant OCD patients were investigated. Lastly, the correlation between ApEn complexity and YBOCS score was investigated in all patients. The findings indicate that ApEn complexity/irregularity extracted from EEG beta band segments could be considered a promising method for discriminating between treatment-responsive and treatment-resistant OCD patients. Feature selection using complexity features extracted from whole data and each frequency range (delta, theta, alpha, and beta) was consistent with the classification accuracy based on individual frequency bands, where features extracted from the beta band were the most discriminative. Further analysis based on the complexity values extracted from EEG beta band segments showed that the complexity was higher in the treatment-responsive OCD patients than in the treatment-resistant OCD patients (lower entropy). Moreover, the severity of OCD based on YBOCS score was inversely correlated with ApEn complexity values; YBOCS score increased as the complexity decreased.

These present study's findings have a number of implications. First, the lower complexity in treatment resistant patients indicates the existence of similar patterns in EEG segments. The complexity was lower in all brain regions, including the frontal temporal and central regions. Current theories on neuropsychology of OCD point to abnormalities in the frontostriatal networks (Menzies et al., 2008). Earlier studies indicate that the severity of mental diseases generally increases as ApEn complexity decreases (Pincus et al., 2006; Abásolo et al., 2005). As the relationship between ApEn and frontostriatal dysfunction remains to be fully elucidated, future studies should evaluate this relationship. In addition, it was observed that patients with OCD have lower permutation entropy values than healthy controls (Aydin et al., 2015). In total, these earlier findings, as well as the present findings, suggest that OCD patients not only have lower complexity,

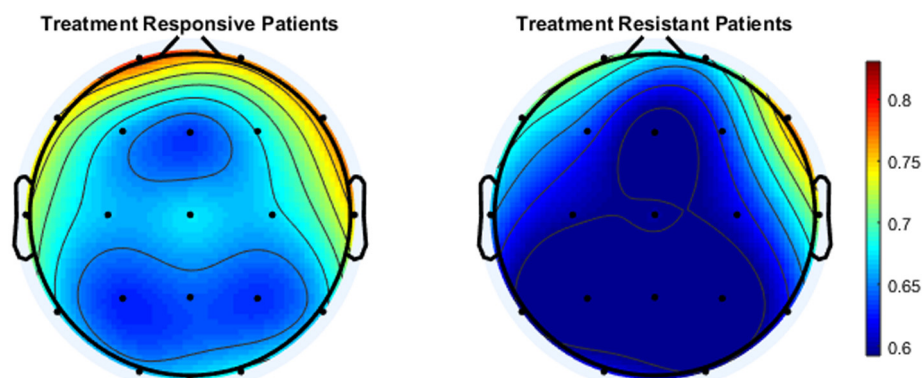


Fig. 2. Topographic plot of the averaged approximate entropy (ApEn) complexity values extracted from electroencephalography (EEG) beta band segments in the treatment-responsive and treatment-resistant obsessive compulsive disorder (OCD) patients.

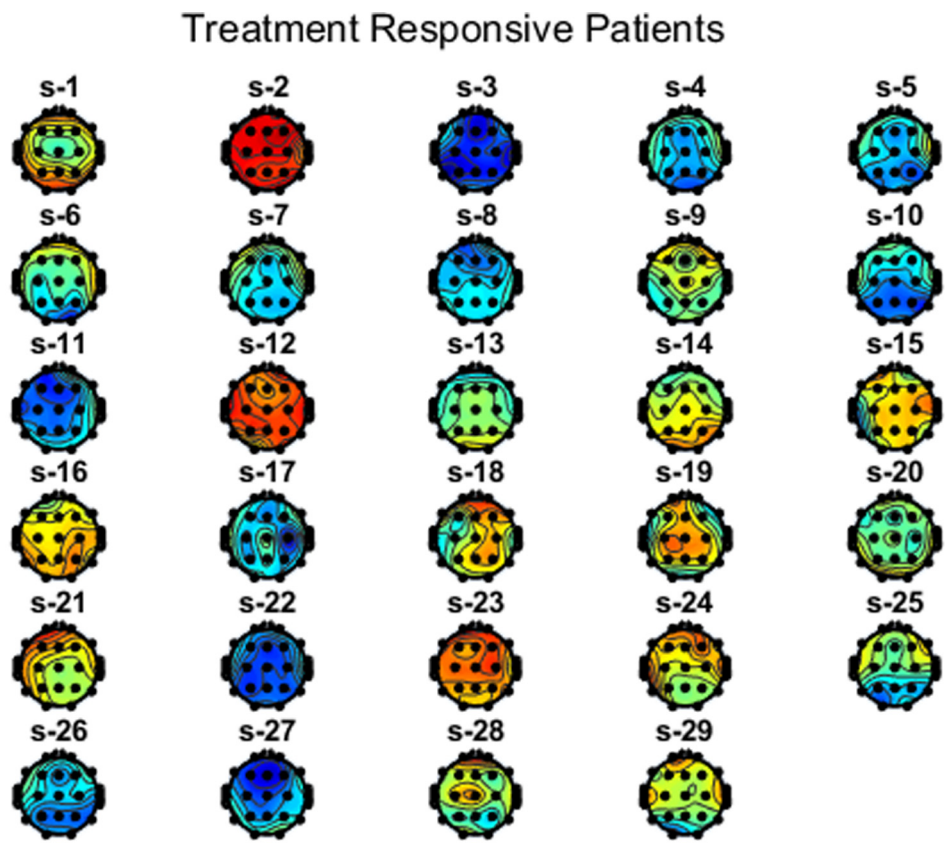


Fig. 3. Topographic plot of the approximate entropy (ApEn) complexity values extracted from the treatment-responsive obsessive compulsive disorder (OCD) patients.

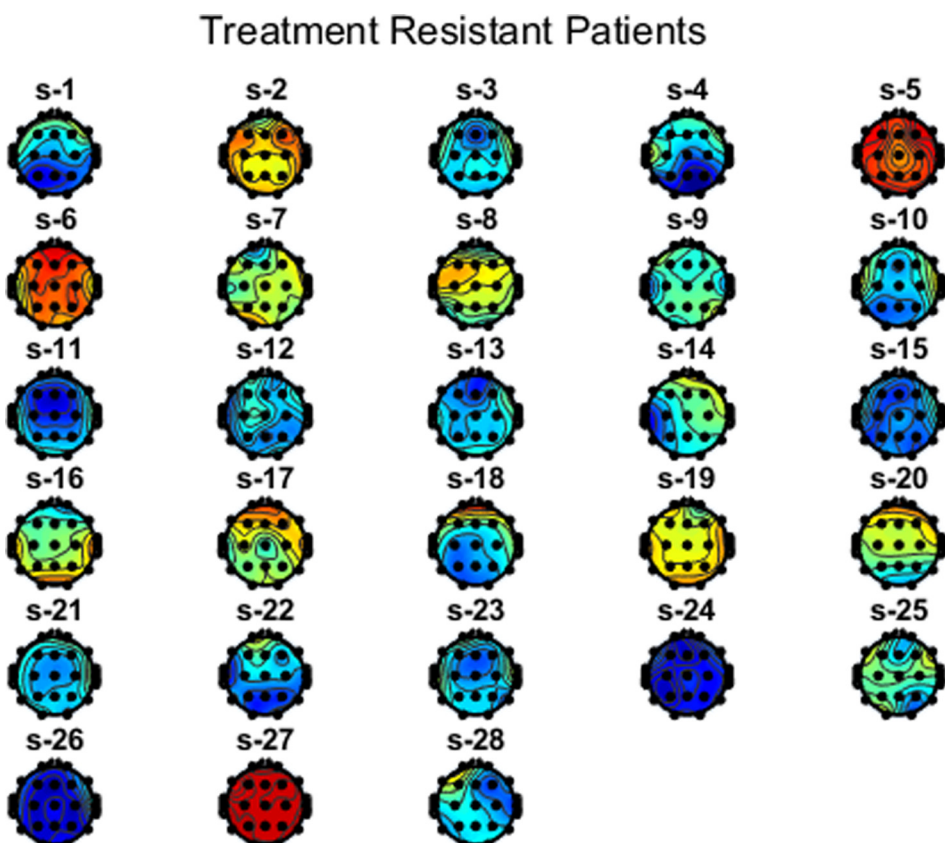


Fig. 4. Topographic plot of the approximate entropy (ApEn) complexity values extracted from the treatment-resistant obsessive compulsive disorder (OCD) patients.

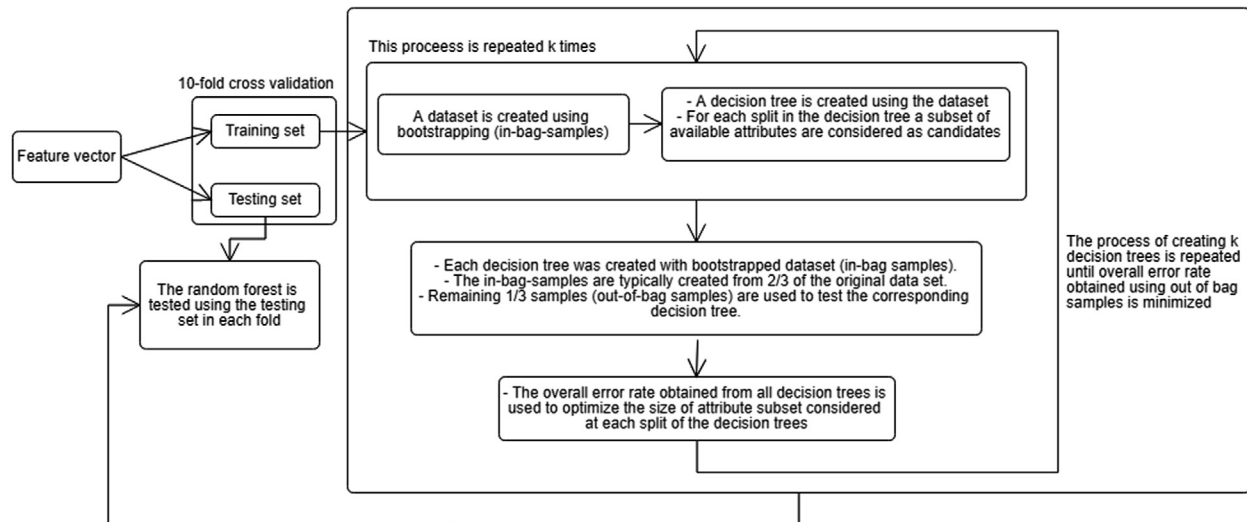


Fig. A.1. Flow diagram of random forests (RF) classification.

but also that the degree of complexity is correlated with greater frontostriatal alterations, leading to treatment resistance and an increase in the severity of OCD.

The second implication of the present findings is related to predicting which OCD patients will and will not respond to treatment. As described in the introduction, it has been reported that EEG could be used to predict treatment response; however, most of these earlier studies measured the power spectrum (Koprivova et al., 2013; Hansen et al., 2003; Prichet et al., 1993) and studied only a single treatment modality (SSRI or neurofeedback). In the present study the non-response criteria was stricter –patients were determined to be non-responders after a long follow-up and trial of several treatment options. In addition, in contrast to those earlier studies, the present study used a nonlinear complexity measure (ApEn) that quantifies the existence of similar patterns in EEG segments. The present findings clearly show that signal complexity is reduced in OCD treatment non-responders. The classification performance of signal complexity was sufficiently high as to justify its use in clinical practice if confirmed by additional research. EEG complexity might be used confidently in the future to predict and manage treatment resistance in OCD patients. For instance, patients with decreased complexity might be managed more aggressively and could be referred for neuromodulation treatments, such as transcranial magnetic stimulation (TMS) (Carmi et al., 2019), early in the course of the disease, or psychosurgery (Tastevin et al., 2019) could be considered before sequential trials of several medications.

The present study has some limitations; the parameters of APEN method were selected using an exhaustive search approach where feature vectors, created with all possible parameter combinations, were trained and tested and the parameter set leading to the highest classification accuracy was selected as optimal. However, parameter selection itself was not a part of the cross validation process. Thus, the optimal parameters for APEN method needs to be validated by different datasets. Furthermore, treatment resistance was evaluated retrospectively. Prospective follow-up studies might provide more useful data concerning the efficacy of EEG complexity for predicting treatment resistance in OCD patients. In addition, whether or not the response to other treatments, such as TMS, could be predicted was not investigated. The sample size was limited, as only 28 OCD patients with treatment-resistance were identified. Finally, the treatment-resistant group had significantly higher YBOCS scores at the time

of EEG recording than did the treatment-responsive group ($p < 0.05$); this difference in the severity of OCD might account for some of the observed group differences in EEG-based measurements. The present findings, although promising, should be confirmed by other studies.

Conflict of interest

The authors declare there are no conflicts of interest – financial or otherwise – related to the material presented herein.

Appendix A

See Fig. A.1.

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