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Characterization of fibromyalgia using sleep EEG signals with nonlinear dynamical features

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ABSTRACT

Fibromyalgia is an intense musculoskeletal pain causing sleep, fatigue, and mood problems. Sleep studies have suggested that 70%–80% of fibromyalgia patients complain of non-restorative sleep. The abnormalities in sleep have been implicated as both a cause and effect of the disease. In this paper, the electroencephalogram (EEG) signals of sleep stages 2 and 3 are used to classify the normal and fibromyalgia classes automatically. We have used various nonlinear parameters, namely sample entropy (SampEn), fractal dimension (FD), higher order spectra (HOS), largest Lyapunov exponent (LLE), Kolmogorov complexity (KC), Hurst exponent (HE), energy, and power in various frequency bands from the EEG signals. Then these features are subjected to Student's t-test to select the clinically significant features, and are classified using the support vector machine (SVM) classifier. Our proposed method can classify normal and fibromyalgia subjects using the stage 2 sleep EEG signals with an accuracy of 96.15%, sensitivity and specificity of 96.88% and 95.65%, respectively. Performance of the developed system can be improved further by adding more subjects in each class, and can be employed for clinical use.

1. Introduction

Fibromyalgia is a complex, poorly understood clinical syndrome with a prevalence of 2% in the general population [1] and sleep disturbances are one of the characteristic features of fibromyalgia. 70%–80% of patients suffering from fibromyalgia complain of non-restorative sleep [2]. The abnormalities in sleep have been implicated as both cause and effect of the disease. Studies have shown abnormalities including prolonged sleep latency [3,4], increased proportion of stage 1 non–rapid eye movement (NREM) sleep [5,6], reduction in slow wave sleep [4,7], reduction in rapid eye movement (REM) sleep percentages [4], as well as an increased number of arousals [6] and restless leg movements [8]. Not all studies have replicated these results, and data on decreased sleep efficiency and association with obstructive sleep apnoea have been conflicting [9,10]. Moreover, no studies have been conducted on the Indian population.

Currently, the gold standard to diagnose sleep disorder is an overnight polysomnogram (PSG) [11]. PSG is a comprehensive sleep study which includes the recording of electroencephalography (EEG) which is a record of brainwave activity, electromyography (EMG) which records leg movements made during sleep, electro-oculography (EOG) which records eye movement, and also breathing rate, heart rate, oxygen level in the blood, and snoring and other noises made during sleep [12].

There are a number of studies. qEEG analysis based on linear and nonlinear techniques yield subtle information that are not forthcoming with the visual reading that is usually employed in clinical practice. Rosenfeld et al. observed that a qEEG delta to alpha frequency power ratio when less than or equal to 1 was 95% sensitive for fibromyalgia [13].

There are a few studies supporting the view that disordered sleep physiology is the root cause of generalized myalgia and musculoskeletal pain. In general, disturbances to slow wave sleep produce increased sensitivity to pain [14]. It has been shown that symptoms of fibromyalgia can be reproduced in healthy volunteers subjected to deprivation of slow wave sleep [14,15]. Sleep is affected by pain, but sleep deprivation also lowers the threshold for pain as evidenced by studies in young healthy individuals who were deprived of slow-wave sleep. This view gained further momentum when it was observed that

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by pharmacologically increasing the duration of slow-wave sleep with an endogenous neuropeptide, sodium oxybate, which is a potent GABA-B agonist, daytime pain and fatigue experienced by fibromyalgia patients was greatly diminished, and their quality of life measures improved [16]. Nonquantitative methods have shown that there are correlations between symptoms of fibromyalgia and different subtypes of sleep alpha activity [17]. Phasic alpha as compared with tonic alpha intrusions have better correlations with increased pain after sleep and reports of poor sleep.

Our study aims to identify and characterize the alterations in the EEG signals of a homogenous population of fibromyalgia patients. Hence, characterization of fibromyalgia using sleep EEG signals is a novel component of this paper as it differs from the norm because these changes are non-specific.

Nonlinear techniques are helpful to extract subtle information from EEG signals. Frequency domain (linear analytic) techniques can be used to detect the rhythmic oscillations in the time series, but are unable to provide nonlinear information in the same spectrum [19]. Biological systems can be represented in an effective way using nonlinear techniques. The EEG signals are nonlinear in nature. Hence, nonlinear methods can capture subtle information present in the EEG signal effectively. The various nonlinear parameters such as largest Lyapunov exponent (LLE), fractal dimension (FD), higher order spectra (HOS), Hurst exponent (H), entropies including sample entropy (SampEn), and recurrence quantification analysis (RQA) can be extracted from the EEG signals to detect information relevant to fibromyalgia. Nonlinear signal processing techniques have been used on EEG signals to find unseen signatures [20–22] in various pathological states. To the best of our knowledge, these nonlinear parameters have not been characterized in fibromyalgia, and our study aims to also explore this venue. Accurate characterization of EEG signals may be helpful in both the diagnosis and monitoring of therapeutic responses in fibromyalgia.

Fig. 1 shows a sample of the eight different channels of control and fibromyalgia EEG signals acquired during stage 2 sleep. Likewise, Fig. 2 is an example of the various EEG channels of the two classes of EEG signals obtained during stage 3 sleep.

2. Study protocol

This study was conducted at the outpatient Department of Neurology, Government Medical College, Thiruvananthapuram, India between April 2017 and April 2018. Consecutive patients attending our neurology clinic meeting the revised 2016 American College of Rheumatology (ACR) criteria for fibromyalgia were selected as cases, and healthy volunteers (age and sex matched) were used as controls. Institutional ethical committee clearance was obtained prior to the study (IEC.No.06/09/2017). Detailed informed written consents were obtained from the patients and controls prior to their inclusion in the study. The exclusion criteria are given below:

a. Patients and controls with coexisting epilepsy, taking anti-seizure medications, and other diseases that could affect the EEG and sleep and thus interfere with the effects of fibromyalgia.
b. Patients already on pharmacologic treatment for fibromyalgia.
c. Patients not providing consent.

Fibromyalgia patients were identified in accordance with the revised 2016 ACR criteria and detailed clinical examination. Smoking, alcohol and caffeine were not allowed for at least 24 h prior to polysomnography. Overnight polysomnography starting at their usual bedtimes was performed in our laboratory. EEG leads were placed in accordance with standard recommendations from the American Academy of Sleep Medicine (AASM)-2013, using NIKOLET V44 (NATUS neurology, USA) with 512 Hz sampling rate. The EEG was analysed using visual analysis techniques (AASM-2013) to determine the stage of sleep. The analyses of non–rapid eye movement (non-REM) sleep were performed in the frequency domain, and with nonlinear techniques. Healthy age and sex matched volunteers were used as controls. Data was obtained from a total of 16 patients and 16 controls. There were 12 females and 4 males among both cases and control. The data description used in this study is shown in Table 1.

The eight channels used are F4-M1,C4-M1,O2-M1,F3-M2,C3-M2,O1-M2,E1-M2 and E2-M1(according to AASM 2012 recommendations). E1-M2 and E2-M1 are used for electrooculography but since there are no eye movements during stage 2 and stage 3 NREM sleep,it picks up only EEG signals during these two stages of sleep.

3. Methodology

A computer-aided detection (CAD) system is proposed in this study to automatically differentiate control and fibromyalgia using EEG signals. Firstly, the signals obtained are pre-processed to remove noise and artefacts from the signals. Then, significant features and information are extracted from the pre-processed signals. These features are subjected to a feature ranking technique, to rank the features according to their level of significance. Finally, the ranked features are input to the classifier. Fig. 3 is an illustration of the proposed CAD system.

3.1. Pre-processing

Extrinsic as well as intrinsic artifacts may contaminate eeg signal. Extrinsic artifacts like lead impedance artifact were eliminated using 60 Hz notch filter. Electrode artifacts were eliminated by meticulous care in application of electrodes. Intrinsic artifacts like movement, pulse and bruxism were minimised by proper recording techniques and patient education. The low pass filter was set at 35 Hz and high pass filter set at 1 Hz. Finally only eeg segments free of obvious artifacts were used for analysis. Eight channels of EEG signals collected from stage 2 and 3 sleep cycles were used in this study. The EEG signals acquired in each channel are of different sample sizes. Hence, 5000 samples are taken from the middle of the EEG signal in each channel.

3.2. Features extraction

Seven different nonlinear feature extractors and the extraction of four frequency wave bands were employed in this work. These nonlinear features may be useful in the representation of important and subtle details in the physiological signals [40,41]. Furthermore, the extraction of these nonlinear features has been extensively employed to analyse the characteristics of EEG signals. Several feature representations, namely the sample entropy (SampEnt) [23], fractal dimension (FD) [24], higher order spectra (HOS) [25], largest Lyapunov exponent (LLE) [26],Kolmogorov complexity (KC) [27], Hurst exponent (HE) [28], energy, and power frequency bands [29] were implemented.

SampEnt: This entropy is a measure of chaos present in the signals [23]. It is suitable for a small dataset and short-length signals.

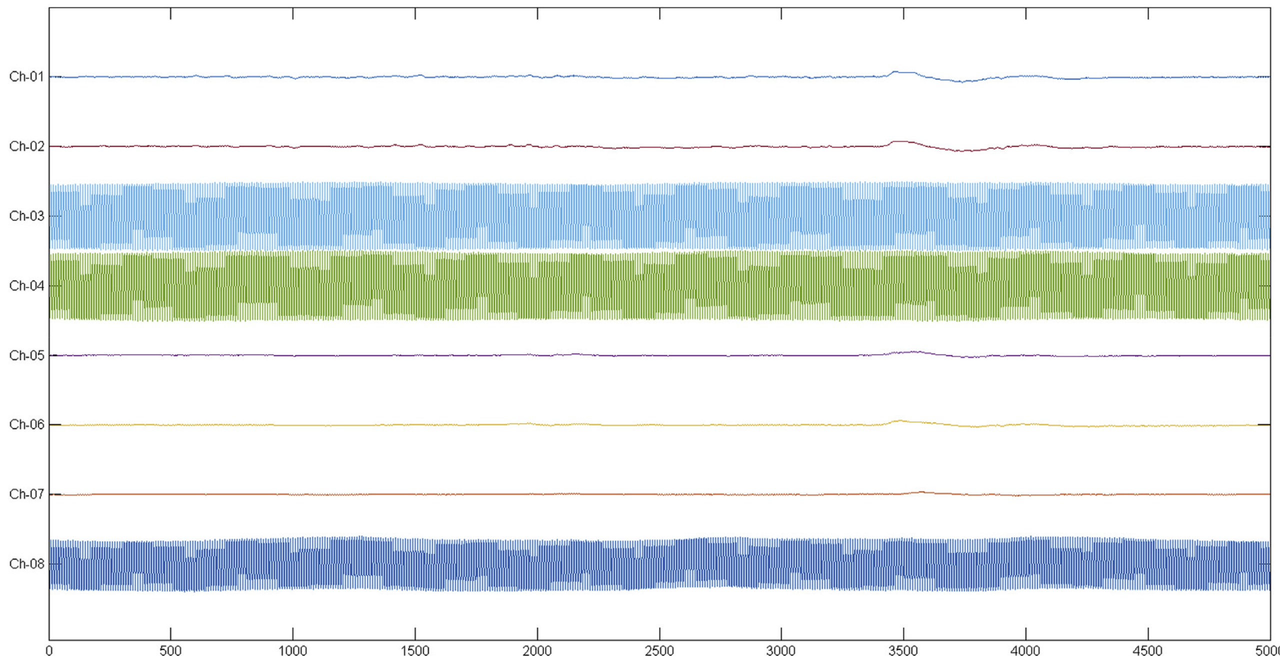
FD: It measures the complexity of the signals and discloses homogenous patterns in the signals. The higher the FD values, the more complex the signals are [24].

HOS: It is an extension of second-order measures that represent the moments and cumulants of the signals [25]. The following parameters including the phase entropy (EntPh), bispectrum entropy 1 (Ent1), bispectrum entropy 2 (Ent2), and bispectrum entropy 3 (Ent3) are employed to analyse the nonlinearity of the signals [42,43]. It has shown good results for many biomedical applications [40,41].

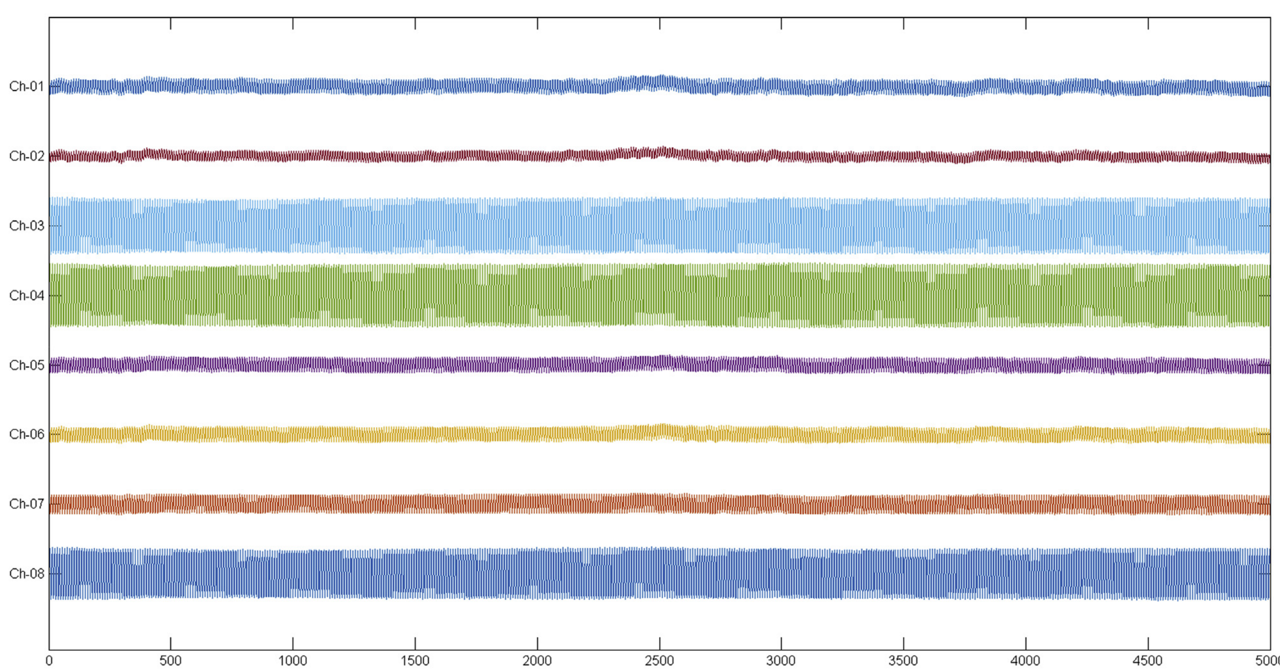
LLE: It estimates the degree of chaos in the signals [26]. The higher the LLE values, the more complex and complicated are the EEG signals.

KC: This feature estimates the complexity of the signals [27]. The more random the signals, the higher the values of the KC features.

HE: It is a parameter that predicts the recurrence of information in the EEG signals [28]. The higher the value of the Hurst exponent, the less complicated the signal is.

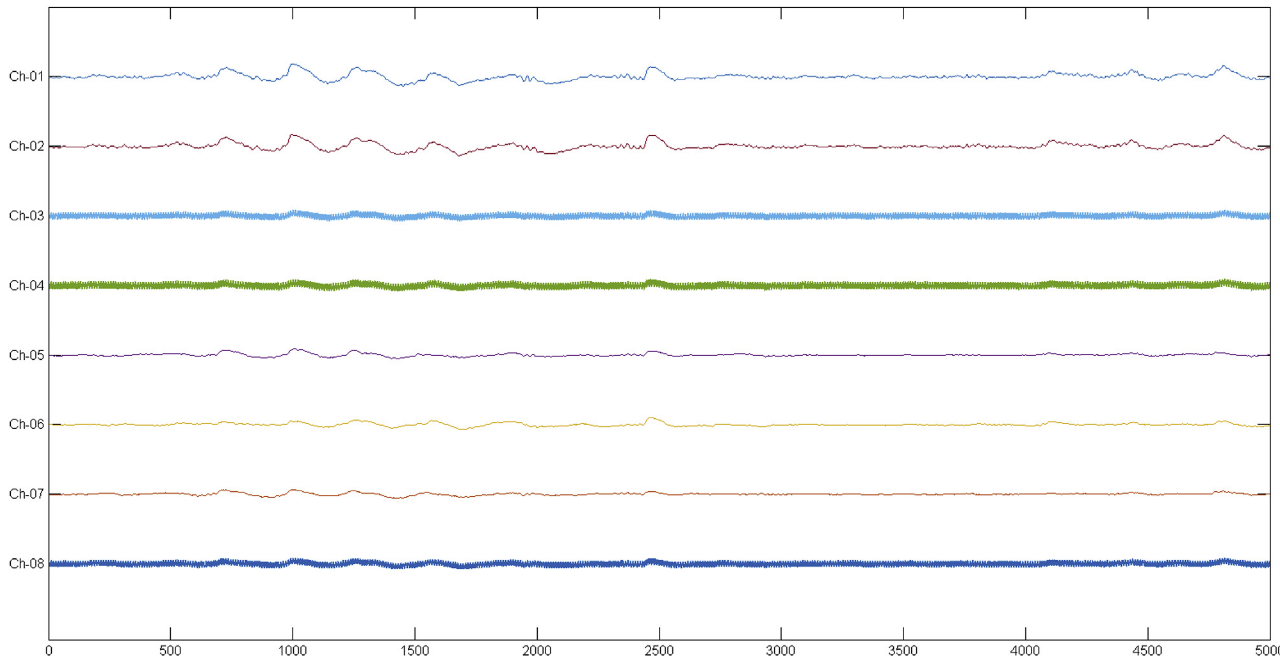


(a)

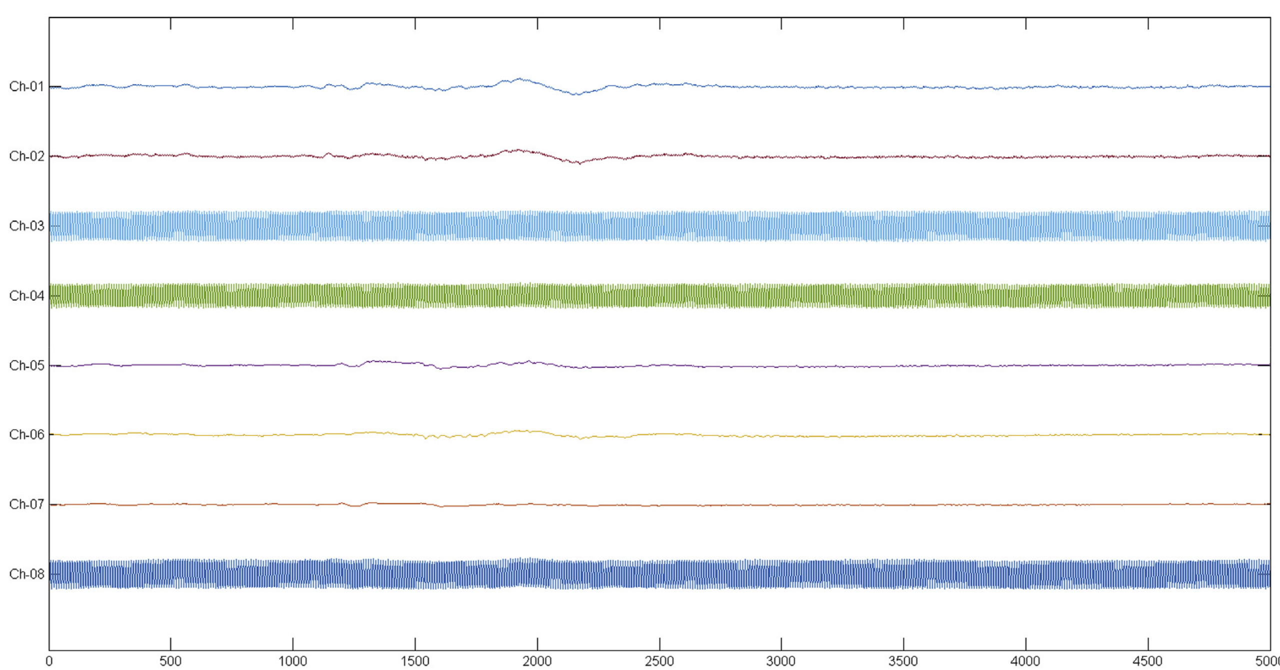


(b)

Fig. 1. An example of eight different channels of (a) control and (b) fibromyalgia stage 2 sleep EEG signals. Note: X-axis indicates samples and Y-axis: different channels.



(a)



(b)

Fig. 2. An example of eight different channels of control (a) and fibromyalgia (b) stage 3 sleep EEG signals. Note: X-axis indicates samples and Y-axis: different channels.

Table 1
Details of the data used for this study.

Item	Number	Mean (standard deviation)		p-value
Types		Control	Fibromyalgia	
Age	16	45.19(4.475)	46.81(4.820)	0.331
BMI	16	23.76(2.149)	23.743(2.707)	

Energy: It is an estimation of the uniformity of the signals. A higher energy value refers to a greater sum of the squares of the signal's details.

Power (Theta, Delta, Beta, and Alpha): The power spectrum of these four waveform features - alpha, beta, delta, and theta wave bands, were extracted to obtain information from each of the frequency bands of the signals [29]. The delta band is < 4 Hz, theta band is 4–7 Hz, alpha band is 8–13 Hz, and beta band is 14–30 Hz [30]. Thus, various details in the EEG data will be acquired in the four different frequency bands.

In total, we extracted the 14 following features from each channel: SampEnt (1), FD (1), HOS(4), LLE(1), KC(1), HE(1), energy(1), and power frequency bands(4). From *eight* channels, we have extracted $14 \times 8 = 112$ features to yield optimum performance.

3.3. Features ranking

Student's t-test [31] is a statistical test that can be utilized to arrange the extracted features correspondingly to their level of significance. The higher the t-value of the feature, the more significant it is. Also, the p-value is inversely proportional to the t-value. The feature was considered to be statistically significant if the p-value is less than 0.05. Both the t-value and p-values of the extracted features were recorded in this study.

3.4. Classification

The support vector machine (SVM) [32] classifier was employed in this study. It is a straightforward classifier that separates the two classes (control and fibromyalgia) using a separating hyperplane. The nonlinear polynomial 3 kernel is used as the nonlinear separating boundary in this work. In this work, polynomial 3 kernel performed better for our dataset. The choice of kernel function depends purely on the extracted features. The SVM classifier is adopted in this study as it can generalize better, and it is suitable for use with smaller datasets. Furthermore, a ten-fold cross-validation [33] is implemented in this work to avoid the overfitting problem. We have obtained high accuracy of 96.15%, sensitivity and specificity of 96.88% and 95.65%, respectively using sleep stage 2 EEG signals. This clearly illustrates that, we have obtained high performance in each fold of the ten-fold cross validation and hence there is no overfit problem.

Two different sets of EEG signals were used. The first set of EEG signals was obtained during stage 2 sleep and the second set was collected during stage 3 sleep.

4. Results

The extracted features of stage 2 and 3 of sleep stages is shown Tables 3 and 5 respectively. The averaged results of using stage 2 and stage 3 sleep EEG signals are tabulated in Tables 2 and 4 respectively. The performance of the proposed algorithm is evaluated based on parameters, namely the sensitivity, specificity, positive predictive values (PPV), and accuracy.

Table 2
Results of classification obtained for stage 2 sleep data using the SVM classifier.

Features used	TP	TN	FP	FN	Accuracy	PPV	Sensitivity	Specificity
28	31	44	2	1	96.15%	93.94%	96.88%	95.65%

TP: true positive; TN: true negative; FP: false positive; FN: false negative.

Table 3
Extracted features obtained using stage 2 sleep EEG signals.

Features	Control		Fibromyalgia		p-value	t-value
	mean	SD	Mean	SD		
Ch5_LLE	0.6474	0.2262	0.4614	0.2572	0.0016	3.2981
Ch6_LLE	0.7205	0.1955	0.5566	0.2364	0.0020	3.2300
Ch5_SampEnt	0.2773	0.1625	0.4584	0.2883	0.0024	3.2144
Ch6_KC	0.5023	0.3173	0.2885	0.2744	0.0022	3.1730
Ch5_KC	0.5075	0.3168	0.2936	0.2789	0.0024	3.1496
Ch6_SampEnt	0.3057	0.2036	0.4916	0.2911	0.0030	3.1188
Ch5_Theta	0.1193	0.2553	0.0098	0.0242	0.0059	2.8896
Ch6_Theta	0.1144	0.2459	0.0097	0.0233	0.0062	2.8688
Ch5_Delta	0.1108	0.2423	0.0083	0.0199	0.0065	2.8535
Ch6_Delta	0.1091	0.2397	0.0085	0.0200	0.0068	2.8334
Ch6_Energy	0.1358	0.2840	0.0154	0.0410	0.0068	2.8321
Ch5_Energy	0.1274	0.2670	0.0147	0.0392	0.0070	2.8199
Ch6_Alpha	0.1289	0.2723	0.0146	0.0398	0.0073	2.8030
Ch5_Alpha	0.1215	0.2568	0.0139	0.0378	0.0074	2.7993
Ch5_EntPh	0.8279	0.2494	0.9410	0.1249	0.0103	2.6382
Ch6_EntPh	0.8267	0.2509	0.9399	0.1316	0.0116	2.5897
Ch5_Beta	0.0810	0.2035	0.0043	0.0095	0.0141	2.5538
Ch6_Beta	0.0876	0.2202	0.0049	0.0105	0.0144	2.5452
Ch4_FD	0.5242	0.2872	0.3607	0.2794	0.0143	2.5133
Ch1_KC	0.5041	0.2941	0.3357	0.2917	0.0149	2.5003
Ch5_HE	0.3740	0.2346	0.5250	0.2882	0.0172	2.4530
Ch6_HE	0.3685	0.2491	0.5269	0.3075	0.0189	2.4148
Ch8_Ent1	0.4484	0.2077	0.5572	0.2127	0.0283	2.2433
Ch1_LLE	0.6651	0.2090	0.5447	0.2500	0.0292	2.2356
Ch8_HE	0.7714	0.1146	0.6906	0.1850	0.0332	2.1941
Ch3_HE	0.8716	0.1318	0.7648	0.2752	0.0478	2.0398
Ch6_Ent3	0.1294	0.1207	0.2205	0.2333	0.0487	2.0289
Ch2_HE	0.8685	0.1145	0.7684	0.2640	0.0505	2.0176

*ChN_HE: Hurst exponent feature extracted from N^{th} Channel of the EEG.

In stage 2 sleep (Table 2), it is noted that out of 32 fibromyalgia EEG datasets, one of the datasets were wrongly classified as the control class. Also, two of the control EEG signals were misclassified as fibromyalgia EEG signals. A total of 28 features were required to obtain the best classification accuracy of 96.15%, with a sensitivity and specificity of 96.88% and 95.65%, respectively.

In sleep stage 3 (Table 4), *three* out of 29 fibromyalgia EEG signals were classified wrongly, and seven out of 37 control EEG signals were grouped under the fibromyalgia class. A total of 12 features fed to a sensitivity and specificity of 89.66% and 81.08%, respectively.

Tables 3 and 5 represent the features that were fed to the classifier to characterize the control and fibromyalgia classes with their mean and standard deviation (SD) values arranged according to the statistical significance (p-value and t-value) for sleep stages 2 and 3, respectively. The clinically significant features in both tables have p-values less than 0.05. Fig. 4 provides the unique bispectrum plots for normal subjects and fibromyalgia patients for sleep stages 2 and 3. These plots can be used for visual identification of normal and fibromyalgia classes. Most

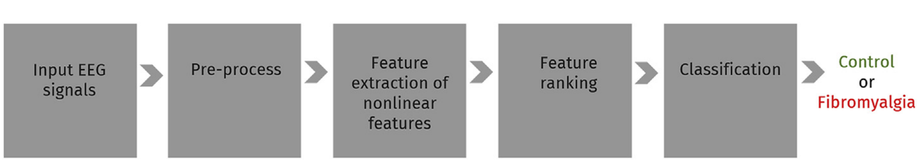


Fig. 3. The flowchart of the proposed algorithm to automatically differentiate control or fibromyalgia classes.

Table 4
Results of classification obtained for stage 3 sleep data using the SVM classifier.

Features used	TP	TN	FP	FN	Accuracy	PPV	Sensitivity	Specificity
12	26	30	7	3	84.85%	78.79%	89.66%	81.08%

TP: true positive; TN: true negative; FP: false positive; FN: false negative.

Table 5
Extracted features obtained using stage 3 sleep EEG signals.

Features	Control		Fibromyalgia		p-value	t-value
	mean	SD	Mean	SD		
Ch5_SampEnt	0.3448	0.1924	0.5462	0.2683	0.0013	3.4118
Ch5_Energy	0.1823	0.3106	0.0090	0.0232	0.0017	3.3815
Ch6_Energy	0.1887	0.3217	0.0093	0.0220	0.0017	3.3812
Ch6_Alpha	0.1721	0.2994	0.0094	0.0231	0.0022	3.2946
Ch5_Alpha	0.1551	0.2713	0.0086	0.0232	0.0024	3.2687
Ch5_Theta	0.1361	0.2439	0.0057	0.0129	0.0025	3.2490
Ch5_EntPh	0.8349	0.2430	0.9699	0.0667	0.0024	3.2268
Ch6_Theta	0.1322	0.2390	0.0055	0.0114	0.0027	3.2195
Ch5_Delta	0.1247	0.2324	0.0048	0.0105	0.0034	3.1347
Ch5_LLE	0.5994	0.2869	0.3894	0.2594	0.0028	3.1138
Ch6_Delta	0.1208	0.2276	0.0048	0.0094	0.0038	3.0973
Ch5_KC	0.4805	0.3824	0.2382	0.2509	0.0029	3.0964

of the features in both classes of sleep stage 2 and 3 overlap. Hence, it does not show a clear separation in the feature graph (t values are low). However, using the SVM classifier with nonlinear kernel functions helps to yield high classification accuracy.

5. Discussion

Based on the classification results, it is observed that the classification accuracy using EEG signals from stage 2 sleep performs better. This observation argues against the hypothesis that it is the alpha-intrusions or disruption of slow wave sleep which is responsible for the symptoms of fibromyalgia, as more subtle micro architectural distortions of sleep occur in the 2nd stage of NREM sleep as compared to NREM stage 3. These observations might indicate that the sleep disturbances occur as secondary phenomenon to the generalized pain experienced by these patients, with lesser effects of the pain on sleep as the patient moves into deeper stages of sleep.

Measures of entropy generally tend to be higher in signals from healthy biological systems with a decrease in entropy for pathological states. The LLE, KC, FD, energy and power features are higher for the control class as compared to the fibromyalgia class. This suggests that the normal EEG signals are more complex, and reveals a greater variability as compared with the fibromyalgia EEG signals. Fig. 4 exhibits the various bispectrum plots of control and fibromyalgia using

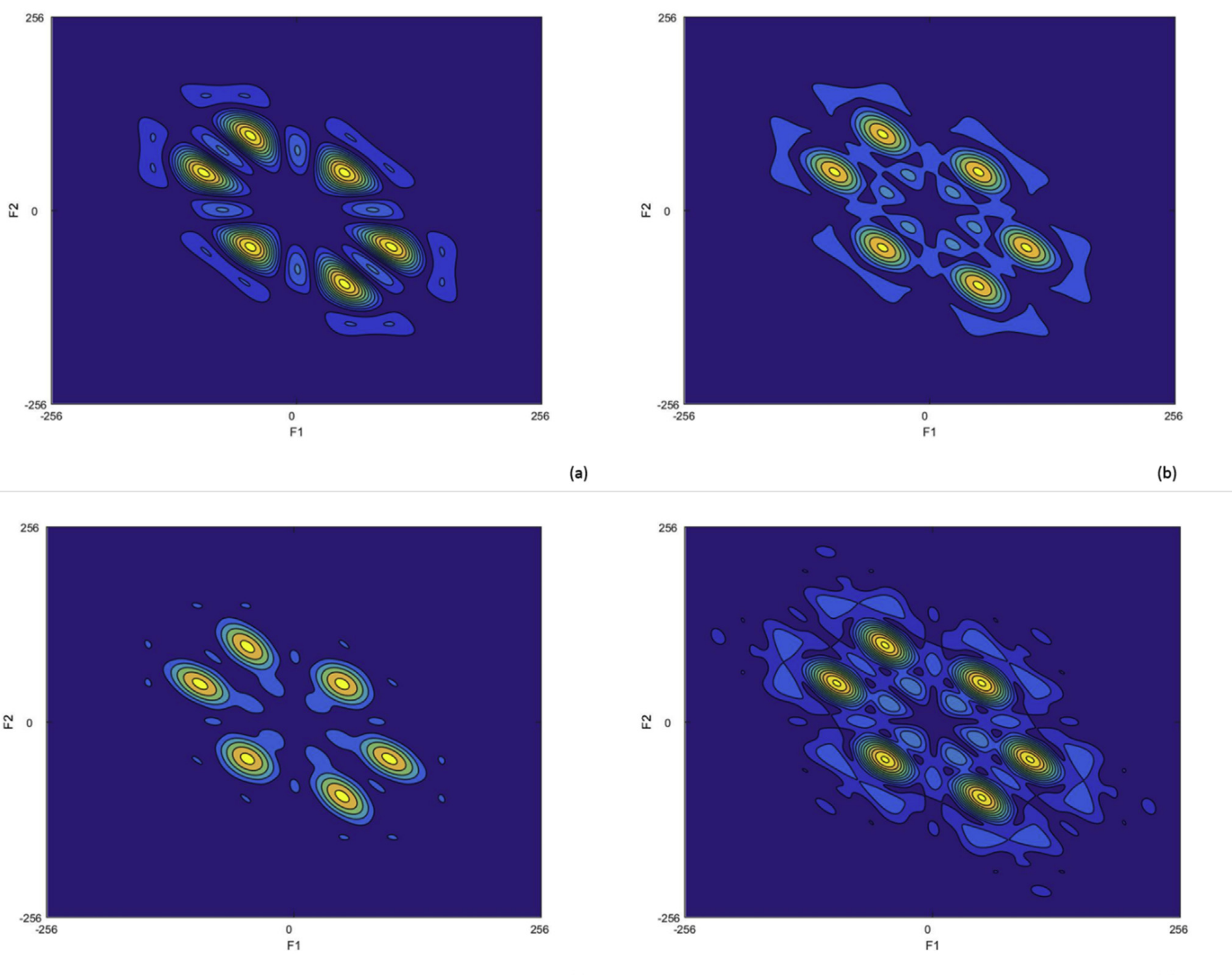


Fig. 4. An example of the various bispectrum plots obtained from (a) control and (b) fibromyalgia stage 2 sleep data and (c) control, and (d) fibromyalgia stage 3 sleep data.

both the data collected in stages 2 and 3 sleep. These plots are unique and display different characteristics. It can also be noted that the fibromyalgia bispectrum plots in the two different sleep cycles exhibit more patterns and greater magnitude as compared to the control class. We have extracted bispectrum entropies from these plots and classified them into two classes. Hence, these features have contributed to the classification of normal versus fibromyalgia with high accuracy.

In this work, we have used machine learning methods for the automated classification of control and fibromyalgia classes. We have extracted the features from the EEG signals and fed those features to the SVM classifier for automated classification. To the best of our knowledge, this is the first paper which addresses the characterization of fibromyalgia using sleep EEG signals and machine learning techniques. The performance of the system depends on the discriminating ability of the features. In the future, we intend to use deep learning for classification of normal versus fibromyalgia classes using more data. Hence, we need not extract the features, as the deep learning model itself will extract the features automatically and perform the classification [34–39]. Various state-of-art techniques, such as convolutional neural networks, long short-term memory, autoencoders, and deep neural networks can be used in our future work.

6. Conclusion

A novel method is employed to automatically distinguish between fibromyalgia and healthy classes using EEG signals from stage 2 and stage 3 NREM sleep. We have used various nonlinear parameters from the EEG signals. These features, namely entropies, LLE, KC, FD, energy and power features, are higher for the control class as compared to the fibromyalgia class. This indicates that the normal EEG signals are more complex, and reveal greater variability than the fibromyalgia EEG signals. Also, we have proposed unique bispectrum plots for the two classes (normal and fibromyalgia) in sleep stage 2 and stage 3. Our results indicate that EEG signals obtained from sleep stage 2 has yielded higher performance than sleep stage 3 in discerning the two classes. Future studies should be done to determine whether these alterations in EEG detected by nonlinear analysis are truly specific for fibromyalgia, or just a reflection of the non-specific disturbance in sleep. For this we will need to study and compare fibromyalgia patients with other pain, depression, and anxiety matched patients with chronic pain disorder.

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