Detrended Fluctuation Analysis for Major Depressive Disorder

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***Abstract*— Clinical utility of Electroencephalography (EEG) based diagnostic studies is less clear for major depressive disorder (MDD). In this paper, a novel machine learning (ML) scheme was presented to discriminate the MDD patients and healthy controls. The proposed method inherently involved feature extraction, selection, classification and validation. The EEG data acquisition involved eyes closed (EC) and eyes open (EO) conditions. At feature extraction stage, the de-trended fluctuation analysis (DFA) was performed, based on the EEG data, to achieve scaling exponents. The DFA was performed to analyzes the presence or absence of long-range temporal correlations (LRTC) in the recorded EEG data. The scaling exponents were used as input features to our proposed system. At feature selection stage, 3 different techniques were used for comparison purposes. Logistic regression (LR) classifier was employed. The method was validated by a 10-fold cross-validation. As results, we have observed that the effect of 3 different reference montages on the computed features. The proposed method employed 3 different types of feature selection techniques for comparison purposes as well. The results show that the DFA analysis performed better in LE data compared with the IR and AR data. In addition, during Wilcoxon ranking, the AR performed better than LE and IR. Based on the results, it was concluded that the DFA provided useful information to discriminate the MDD patients and with further validation can be employed in clinics for diagnosis of MDD.**

I. Introduction

Major Depressive Disorder (MDD) is a mental illness. It is recurrent, chronic and progressive. The diagnosis of MDD is a challenge especially at initial stages. Both the MDD and the bipolar disorder (BD) can be misdiagnosed because of the sharing of common clinical symptoms [1]. Hence, it can be concluded that the treatment success for MDD is based on an early diagnosis and robust treatment management. There is a need to provide objective scientific evidence about the MDD to be diagnosed correctly.

It is commonly known that the electrophysiological techniques have been used to elucidate the nature of brain dysfunctions. Electroencephalogram (EEG) is a standard non-invasive modality to measure voltage differences between sensing electrodes and a reference, placed over human scalp. Placement of electrodes may follow 10-20 electrode placement standard [2].

In this paper, the EEG data are considered as time-series and analyzed with detrended fluctuation analysis (DFA) [3] to compute long-range temporal correlations (LRTC). The DFA is a method to quantify the correlation property in a non-stationary time series data such as EEG data by computing a scaling exponent based on a modified root mean square analysis of a random walk [4]. In this paper, the LRTCs were quantified as scaling exponents for the MDD patients and the control groups separately. Furthermore, these scaling coefficients are utilized as features for training and testing machine learning (ML) models.

In the literature, the DFA is applied for various purposes, for example, the analysis of sleep studies using polysomnography data [5]. Another example is the analysis of heart rate variability (HRV) during sleep and sleep apnea study [6]. In addition, the depth of anesthesia is quantified based on DFA [7]. Moreover, mental diseases such as Alzheimer [8] and depression [4, 9, 10] are also analyzed using DFA. However, during the analysis no machine learning techniques are used. In a recent study [11], automation is provided with the support vector machine (SVM). However, the study participants are not the MDD patients. Based on our literature survey, we have identified that there is no study which have employed ML techniques to make the process automated for MDD. Therefore, in this study we have employed ML techniques to discriminate the MDD patients and controls groups based on the scaling exponents.

In brief, the technique proposed in this paper is based on feature extraction, feature selection, classification and 10-fold cross validation. The feature extraction involves scaling exponents (self-similarity parameters) computed by DFA. Feature selection included 3 different methods to show their individual performance in the ML process. The classification model selected is logistic regression classifier [12]. It is famous for applications with dichotomous outcomes. Finally, the 10-fold cross-validation provides sufficient evidence of the robustness of the selected features and data points in this scenario. A detailed description is provided in the section IV.

The paper is organized as follows. The section II describes DFA theoretically. Section III explains the process of study participant recruitment, the experiment design, data acquisition process and data analysis. Section IV shows the results. Finally, in section V, the results are discussed and also conclude the paper with some future suggestions.

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II. DETRENDED FLUCTUATION ANALYSIS

The detrended fluctuation analysis (DFA) was first introduced by Peng [3], in his seminal work, he applied the DFA for the analysis of the healthy and severe heart disease. He proved that the method was capable to identify the cross-over behavior due to differencing in scaling over short versus long time scale. We have described the DFA algorithm in a flow chart form to develop better understanding as shown in Figure 1.

According to the figure, the scaling exponents were achieved by following the process step-by-step. The EEG data recorded during EC and EO conditions were integrated and time segmented where each time segment was termed as boxes. For each time segmented EEG data were fitted with a straight line and local trend was determined. Moreover, the local fluctuations were determined based on the equation (1). Mathematically, the DFA is described in equation (1).

$$F(n) = \sqrt{\frac{1}{N}\sum_{k=1}^{N}[y(k) - y_n(k)]^2} \qquad (1)$$

The values computed with equation (1) were repeated for each different time scales or boxes. Finally, the values ln(F(n)) vs. ln(n) were plotted and their slopes were computed to achieve scaling exponents which were utilized as features during our proposed data analysis schemes.

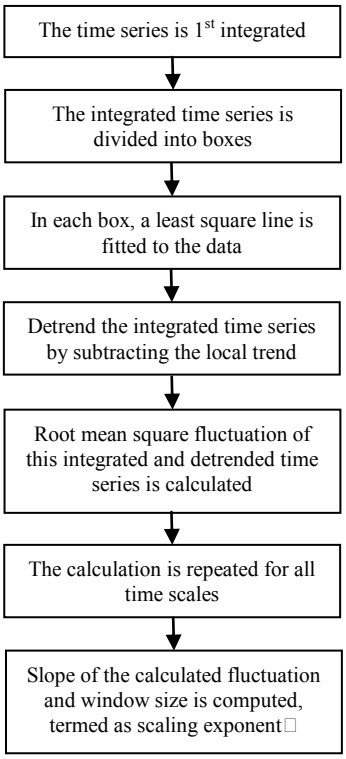

Figure 1. De-trended Fluctuation Analysis

III. MATERIAL AND METHOD

A. Participants

EEG data acquisition involved two different study groups recruited from Hospital Universiti Sains Malaysia (HUMS). First group included 33 MDD patients (mean age= 40.33±12.861, female participants = 17). The second group included 30 well-matched healthy controls (mean age= 38.27±15.64, female participants = 9). The MDD patients have fulfilled the international diagnostic and statistical manual of depression-IV (DSM-IV) [13]. In addition, the clinical questionnaire named Beck depression inventory-II (BDI-II) [14] was administered to quantify the disease severity. This self-assessment questionnaire assigned numerical scores to the disease according to the severity, i.e., higher the number higher the disease condition. The healthy controls were screened for any psychiatric illness and were found without any such symptoms.

Moreover, the study experiment design was approved by the ethics committee, HUSM. All the participants were well-informed about the experiment design before its commencement. The consent forms were signed by all participants. In this experiment, the participations were on the voluntary basis. The participants were allowed to leave the experiment any time without any justification.

B. EEG Data Acquisition

The EEG data acquisition scheme is described in Figure 2. Initially, the participants were asked to sit in a comfortable chair under quiet environment in a semi-recumbent position. A wearable cap with 24 electrodes is used. Out of those 24 electrodes, 19 electrodes were used for EEG data acquisition, 3 were used for ECG and 2 for reference purpose. The placement of EEG electrodes follows 10-20 electrode place standard. According to Figure 2, the frontal region consists of electrodes Fp1, Fp2, F7, F3, Fz, F4, and F8. The central region includes electrodes Cz, C3, and C4. Temporal region consists of electrodes T3, T4, T5, and T6. The parietal and occipital regions comprise electrodes Pz, P3, P4 and O1, O2, respectively.

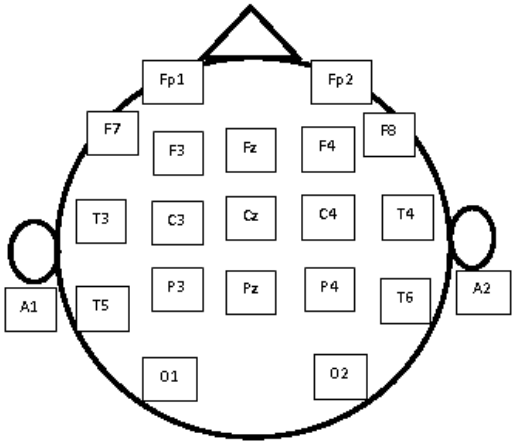

Figure 2. The 10-20 locations for 19 EEG channels

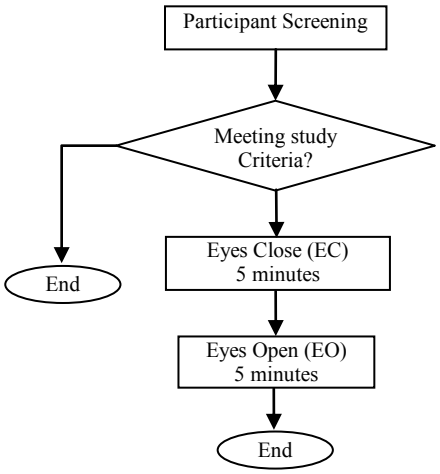

Figure 3. Experiment Design for Data Acquisition

In this study, only EEG data were used for analysis. Brain master discovery software was used to preprocess and storage of the datasets on computer disk. The EEG data from the scalp was amplified by Brain master 24 E amplifier. For this purpose, the sampling rate was set at 256 Hz, and a bandpass filter within the range 0.5-70 Hz was applied. An additional 50 Hz notch filter for power line noise filtration was also used. The duration of EO and EC sessions was five (5) minutes each.

C. EEG Artifact Removal

The EEG data were confounded with artifacts such as eye blinks, movements and muscular activates, e.g., heart beats. The data confounded with these artifacts may not truly represent the underlying brain activities and therefore required to clean the data from these artifacts. In this paper, EEG data cleaning involved surrogate filtering technique implemented in the standard brain electric source analysis (BESA) software [15]. The Surrogate filtering technique effectively modeled eye blinks, movements, and muscular activities. The model learning was based on EEG data and then can be applied to whole recording.

D. Proposed Data Analysis

The proposed EEG data analysis scheme inherently involved feature extraction, feature selection, classification and 10-fold cross validation. The application of cross-validation involved 100 times Monte-Carlo iterations to 10-fold cross validation. This provides enough statistical data to plot the box plots for classifier performances such as accuracies, sensitivities, and specificities. Finally, the median values were used as results shown in tabular form. For feature extraction, the DFA was performed on epochs of 1 minute of EEG data both in the EC and EO conditions. As a result scaling exponents were achieved for the MDD patients and control groups. At feature selection stage, 3 different techniques were applied to determine which one was better suited to this scenario. In general, the features were ranked according to 3 criteria: receiver operating characteristics (roc), Wilcoxon and t-test. The ranked features were arranged in a descending order according to the given ranks.

Table 1: Accuracies for EEG dataset during EC and EO conditions

		ROC	Wilcoxon	t-test	FPR	FNR
LE	Accuracy	**87.2%**	**87.8%**	85.8%	0.062	0.20
	Sensitivity	80%	80%	78.3%		
	Specificity	93.8%	93.8%	93.8%		
AR	Accuracy	85%	85.6%	**86.3%**	0.076	0.21
	Sensitivity	78%	78.3%	78.3%		
	Specificity	92%	92.6%	92.6%		
IR	Accuracy	85.5%	85.12%	85.89 %	0.094	0.20
	Sensitivity	80%	80.83%	78.3%		
	Specificity	89.5%	89.5%	92.6%		

The top-ranked features were sub-grouped as top 5, 10 and 15 features. Each subgroup was utilized during training and testing process. Our proposed data analysis scheme was repeated for each feature subgroup and each of the feature selection criteria. We have reported only the results with maximum accuracies.

In addition, the proposed scheme was repeated for 3 different EEG references: link-ear (LE), average reference (AR), and infinity reference (IR). The EEG data were recorded with LE as reference. Later on, the EEG data were re-referenced to AR and IR. We did not find any literature on the effect of different EEG references on DFA of EEG resting conditions: EC and EO. The performance metrics computed from the confusion matrix were presented by equations (2-6). Classifier sensitivity corresponds to the percentage of true cases (TP) which are correctly classified as cases equation (2). The classifier specificity refers to the percentage of true non-cases (TN) which are correctly classified as non-cases equation (3). The classification accuracy is the percentage of correctly classified cases and non-case among all the example points equation (4).

$$Sensitivity = \frac{TP}{TP + FN} \quad (2)$$

$$Specificity = \frac{TN}{TN + FP} \quad (3)$$

$$Accuracy = \frac{TP + TN}{TP + TN + FP + FN} \quad (4)$$

$$FPR = 1 - Specificity \quad (5)$$

$$FNR = 1 - Sensitivity \quad (6)$$

IV. RESULTS

Table 1 shows results of the proposed data analysis scheme for EC and EO EEG data. These results showed the discrimination ability of scaling exponents derived from the EEG data acquired from the MDD patients and controls groups. The more the performance, the more efficient is the scheme. The results were computed by each EEG reference and different feature selection criteria.

According to the table, for the LE EEG data, the Wilcoxon ranking features performed better (*accuracy=87.8%*) than the t-test and roc criteria. However, the 3 methods have the same specificities. For AR EEG data, the maximum efficiency is provided by t-test (*accuracy = 86.3%*). Moreover, for IR EEG data again the t-test provided highest efficiencies i.e., (*accuracy = 85.89%*).

V. Discussion and Conclusion

MDD has been misdiagnosed as bipolar disorder due to subjective assessments during 1st visit of the MDD patients. In this paper, we have presented discrimination of the MDD patients from healthy controls based on objective measures of brain activity, i.e., the EEG data. In addition, our proposed scheme utilizes incorporation of ML concepts with an added advantage of automating the process of identification of useful patterns that can be utilized for discrimination of the MDD patients and control groups. Hence, the diagnosis is made possible based on EEG data only.

The study provides a proof that the automatic diagnosis of MDD may be possible based on the EEG data acquired from the MDD patients during resting states. In the literature, the DFA is applied for various purposes, for example, the analysis of sleep studies using polysomnography data [5]. Another example is the analysis of heart rate variability (HRV) during sleep and sleep apnea study [6]. In addition, the depth of anesthesia is quantified based on DFA [7]. Moreover, mental diseases such as Alzheimer [8] and depression [4, 9, 10] are also analyzed using DFA. However, during the analysis no machine learning techniques are used. In a recent study [11], automation is provided with the support vector machine (SVM). However, the study participants are not the MDD patients. Based on our literature survey, we have identified that there is no study which have employed ML techniques to make the process automated for MDD. Therefore, in this study we have employed ML techniques to discriminate the MDD patients and controls groups based on the scaling exponents.

To remove the likelihood that the resulting classifier models are concluded due to noise present in the EEG data, we have adopted the following precautions. First, during preprocessing, the artifacts are carefully removed and tested by plotting their histograms plots to check the presence of any kind of outliers and found the data to be suitable for classification purposes. Second, we have selected equal sample sizes in both the groups. In addition to this the gender distribution is equal among the groups as well. This is eliminating the gender biases from the final results. Third, the logistic regression classifier model is relatively simpler than the support vector machine classifier. The incorporation of the classifier with 3 different structures has proved the validity of our data also. Fourth, the over-fitting may happen; therefore, we have incorporated 100-time permutation test with 10-fold cross-validation to improve the robustness of the underlying models. □

The study is confounded with few limitations. First, the MDD patients are asked to be medication free at least 2 weeks before the first EEG recording. However, the effect of mediation cannot be ruled out completely. Second, since the patients are out-patients, variable such as sleep patterns, appetite, and lifestyle could not be controlled. The small sample size poses a constraint that the results should not be generalized to a wider population. □

In conclusions, a novel data analysis scheme based on scaling exponents acquired from DFA of EC and EO data is presented. The objective was to discriminate the study participants into the MDD patients and healthy controls. Based on the result we may conclude that the numerical feature values or scaling exponents can be applied as discriminants of clinically diagnosed MDD patients. Different feature selection criteria were applied. It is concluded that the AR with t-test performed better than other schemes. For other selection criteria, the results are comparable and can be concluded that the difference between references has a slight effect on the analysis based on DFA. The features presented in the study have the capability to discriminate the MDD patients and healthy controls with statistical significance.

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