Diagnosis of Pediatrics Epilepsy Based on Graph analysis of Scalp EEG Applying Mutual Information

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***Abstract*:** Epilepsy is a brain disorder that causes seizures, affecting nearly half a million children in the US alone. In this study, we aimed to use a nonlinear driven method to characterize scalp EEG recordings of pediatric epilepsy patients (PE: n=7) compared to pediatric control subjects (PC: n=7) in a clinical environment. A time-varying approach was used to construct functional connectivity networks (FCNs) of all subjects. Next, the FCNs are mapped into the form of undirected graphs that are subjected to the extraction of graph theory-based features. An unsupervised clustering technique based on K-mean is used to delineate the PE from the PC group. Our findings show a statistically significant difference in the mean FCNs between PC and PE groups ($t(340)=-15.9899$, $p<< 0.0001$). Performance results showed an accuracy of 92.5% with a sensitivity of 90% and a specificity of 95.3%. This approach can help improve and validate the early diagnosis of PE by applying non-invasive scalp EEG signals.

Keywords—: *Interictal Epilepsy EEG; Functional connectivity; entropy, Mutual Information; Graph theory; Clustering.*

1. INTRODUCTION

Epilepsy is the fourth most common neurological disorder characterized by recurrent unprovoked epileptic seizures that affect individuals from all walks of life [1-3]. According to the US Centers for Disease Control and Prevention (CDC), there are 3.4 million people living with epilepsy (PLWE) nationwide, including nearly 3 million adults and half a million children [4]. Although recent scientific endeavors on epilepsy have uncovered important and clinically relevant mechanisms to help in the diagnosis and prognosis of the disease, a large percentage of PLWE continue to suffer the consequences of uncontrolled seizures, which include psychosocial stigma and death [2]. Therefore, to prescribe a broad-spectrum anti-seizure medicine for PLWE and subsequently improve their quality of life and avoid harm, it is vital to have an on-time and accurate diagnosis [5, 6].

Since its discovery in 1929 by the German psychiatrist Hans Berger [7], electroencephalography (EEG) has played a central role in the diagnosis and management of patients with seizure disorders [8]. Since the 1950s, scalp EEG has been extensively used as a convenient and relatively inexpensive way for carrying out non-invasive brain investigations in PLWE [9]. By the turn of the century, this diagnostic tool has gained significant prominence for examining brain functions in PLWE while simultaneously providing high temporal resolution data with negligible side effects [8, 9].

It is notable that the benign EEG variants (i.e., certain rhythmic and epileptiform spikes without known clinical importance) sometimes occur in healthy subjects which can lead to numerous sources of misdiagnosis [10]. To tackle this issue, interictal EEG data is the most frequent recording type in clinical practice, which can help both in the diagnosis and treatment stages with high predictive values in terms of sensitivity of specificity [11]. In fact, medical practitioners rely heavily on EEG patterns to identify, quantify, classify, and localize epileptic seizures, which are largely based on the monitored spikes in EEG recordings [12]. Additionally, the connectivity pattern of the brain networks for disease differentiation would be useful to explore the brain model when the patient is diagnosed with epilepsy assuming that connectivity features of a healthy brain would instinctively be different from the PLWE's brain [13-15]. Since the connectivity network of the brain can be considered as a graph, several attributes of EEG data can be obtained using specific graph

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characteristics for further investigation [11, 13]. Taken together, comparing extracted EEG data (including connectivity patterns) from PLWEs and healthy controls using robust statistical methods could lead to enhanced diagnosis and better treatment planning.

Almost all biological systems including brain activity recorded through EEG signals show considerably complex nonlinear behavior, which may be directly assessed using non-linear analytical methods [16, 17]. A nonlinear component is apparent in all analyzed EEG records which directs the analysis more towards modeling the brain as a complex model, and consequently, can be used to extract the higher order information through nonlinear operators [18]. An analytical approach that can identify and quantify any characteristic of this nonlinear change may better reflect the dynamic structure of the EEG, measure the irregularity/complexity of a signal, and consequently classify PLWE versus healthy controls [19]. Several classification techniques have been proposed in the literature [20]. For example, our research team [21] and others [22] employed different types of Artificial Neural networks (ANN) to classify patients with epilepsy versus healthy controls. Although ANN is a promising tool for automatic on-line seizure detection, the ultimately goal is in designing an optimal network [20]. On the other hand, in order to extract associative features from EEG signals without the need for any prior information, the EEG signals can be grouped by a clustering algorithm such as K-means, which is a well-known clustering algorithm that requires no prior training part or defining parameters to categorize the graph and the associations of data points with clusters [23]. Therefore, in this study, we used K-means to categorize the graph-based extracted features of each calculated connectivity matrix. Moreover, we used a probabilistic approach to label each subject into the epileptic or healthy control group.

2. MATERIALS AND METHODOLOGY

2.1. EEG data source and preparation

Multichannel scalp EEG recordings from 14 pediatric patients, 7 pediatric epilepsy (PE) patients, and 7 pediatric control (PC) group were included in this study. The scalp EEG signals were recorded using XLTEK Networks ver. 3.0.5 equipment and referential montage following 10-20 electrode placement system with a varying sampling rate of 200 Hz and 512 Hz, indistinctly for PC and PE subjects. The studied EEG data were collected from the 19 electrodes: C3, C4, O1, O2, Cz, Fa3, F4, F7, F8, Fzrat1, Fp2, P3, P4, Pz, T3, T4, T5, and T6. We selected 10-second segments free of artifacts from all EEG recordings. To avoid any bias, care was given to the initial selection of EEG segments from the patients with epilepsy ensuring that they do not contain ictal activity. A total of 134 EEG segments from the study subjects were considered. The demographic characteristics of the study subjects are presented in Table 1. The study flowchart of the algorithm is shown in Figure 1, which was implemented using MATLAB software environment. The study was approved by the Institutional Review Board (Protocol number: IRB-052708-03) and parental written informed consent was obtained prior to participation.

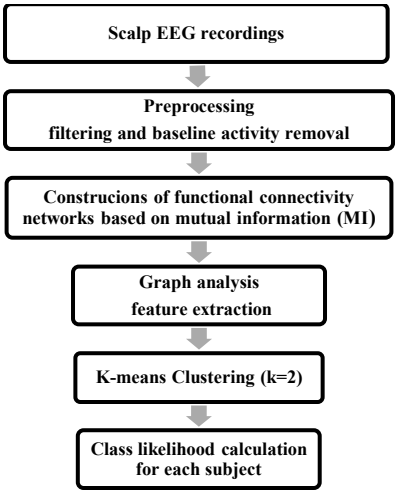

Figure 1. Study flowchart

Table 1. Demographic characteristics of study subjects (patients and controls are labeled as "P" and "C" respectively)

ID	Age	Gender	Diagnosis	Sampling rate (Hz)
P1	10	F	L.T. lobe dysplasia	200
P2	7	F	L. F. region	512
P3	7	M	L.F. Posterior frontal lobe	512
P4	14	M	Generalized	512
P5	4	M	R. Fronto-centro-temporal	512
P6	2	F	L.T. (posterior)	512
P7	8	M	R. Parietal	200
C1	12	M	-	200
C2	15	F	-	512
C3	12	M	-	200
C4	15	F	-	512
C5	10	M	-	512
C6	18	F	-	512
C7	8	M	-	200

T: Temporal lobe, F: Frontal lobe, R: Right, L: Left

2.2. Preprocessing

Evidence indicates that EEG signals are easily contaminated by undesired noise [24]. To tackle this issue, prior to segmentation, the EEG data were preprocessed to attenuate the effect of unwanted sources and to maximize brain-related activities.

Therefore, all EEG signals were preprocessed with a 4th order Butterworth zero-phase digital band-pass filter with a range of [0.5 70] Hz passing frequency and with the digital infinite impulse response (IIR) notch filter with 60 Hz notch frequency to remove power line noise. For all EEG data, the baseline of signals was also removed.

2.3. Functional connectivity networks construction based on mutual information (MI)

Mutual information (*MI*) is an information-theoretic and non-parametric approach that measures the generalized interdependence, both linear and nonlinear, between two random variables. Consider discrete random variables X and Y with sets of values $\mathcal{X}$ and $\mathcal{Y}$ respectively. According to [17] the entropy $H(X)$ of a random single variable X is defined by:

$$H(X) = -\sum_{X\epsilon\mathcal{X}} p(x)\log_a p(x)$$

where $p(x) = \Pr\{X = x\}, x \epsilon \mathcal{X}$ is the probability distribution function (PDF). The entropy is measured in bits (or Shannon) if the logarithm is to the base $a = 2$, while the entropy is measured in natural units $(nats)$ if the logarithm is to the base e. The $MI\ (X;Y^{\tau})$ defined as the average amount of shared information in the variables X and Y^{τ} will be formulated as follows:

$$MI\ (X;Y^{\tau}) = -\sum_{x_t\epsilon\mathcal{X}}\sum_{y_t^{\tau}\epsilon\mathcal{Y}} p(x_t, y_{t-\tau})\log_a \frac{p(x_t, y_{-\tau})}{p(x_t)p(y_{t-\tau})}$$

The term x_t defines a time series of the variable X recorded at discrete time t, and $y_{t-\tau}$ is the signal displaced by lag τ. Furthermore, $p(x_t, y_t)$ is the joint probability distribution function (*PDF*) associated with the two variables. *MI* always appears to be non-negative and zero if and only if X and Y are stochastically independent. We assume $p(y_{t-\tau}) = p(y_t)$, to mean that time shifting does not change the individual *PDF*, only the joint *PDF*. The *MI* can capture higher correlation when two time series are coupled in terms of the entire *PDF* and the selection of different sampling bins has a great influence on the accuracy of *MI* [25]. The logarithm with base e and 11 bins were adopted for the purpose of this study.

To select the maximum value of $MI\ (X;Y^{\tau})$ over the lag as the strength of FC of each pair, the *MI* between x_t and y_t as expressed in [17] is defined as

$$MI = \max_{\tau} MI(X,Y)$$

where MI is the value between the range of zero and *1,* i.e., normalized [26]. Thus, we obtained a symmetric adjacency matrix to show the mutual connectivity among all electrodes of one EEG segment:

$$MI_{N\times N} = \begin{bmatrix} MI_{1,1} & \cdots & MI_{1,N} \\ \vdots & \ddots & \vdots \\ MI_{N,1} & \cdots & MI_{N,N} \end{bmatrix}$$

with $MI_{i,j}$ defining the *MI* between channels i and j. A high value for *MI* is hypothesized as the more powerful functional connectivity between electrodes. After calculating the connectivity strength for each EEG segment, we computed average connectivity matrices for each group.

2.4 Parameters Selection and Statistical Evaluation

There is a possibility that, during applying a nonlinear approach, the linear correlation in the data leads to false results. Therefore, it is important to evaluate the data compatibility to avert potential bogus results. To avoid this likelihood and to assure the implication of the findings, one of the best statistical approaches is surrogate data testing, which is widely used in the literature for this purpose [27, 28]. We used the surrogate data testing technique to suggest an algorithm to choose the proper parameters, choosing the number of bins, and evaluate the significance of the connectivity matrices.

The method works based on generating surrogate time series with some similarities with original data and tests for the null hypothesis of similarity between two connectivity matrices generated from surrogate and original signals. Rejection of the null hypothesis is an indication that the test result shows a signification difference between connectivity matrices of surrogate and original data.

To generate surrogate data, the Iterative Amplitude Adjusted Fourier Transform (iAAFT) was used. We calculated surrogates for each EEG segment based on the 95% confidence intervals that we need for the test. In line with the literature [2], for the level of significance (α), the minimum number of surrogate time series (M), can be obtained from the below equation:

$$M = \frac{2K}{\alpha} - 1$$

where K is a positive integer mostly chosen as 1 in order to minimize the computational effort of generating surrogates. Therefore, for a two-sided test with a 95% confidence interval, the critical threshold for significance level (α) will be set at 0.05, which requires 39 surrogate time series.

We calculated connectivity matrices for the original data and all generated surrogates. Next, using a non-parametric statistical hypothesis test, namely the

Wilcoxon Rank Sum test, each surrogate connectivity matrix was tested against the original connectivity matrix. The original connectivity matrix is considered to be significant if the rejection rate of the null hypothesis was more than 60%. Selecting different sampling bins has a great influence on the accuracy of *MI* [25], therefore, to get significant results for all connectivity matrices of all segments, the surrogate data set was performed for a different number of bins. In this study, we took the logarithm with base e, and 10 bins were adopted.

2.5. Graph analysis and feature extraction

Graph theory is a well-established mathematical procedure to model any complex system as a group of nodes (vertices) and links (edges) between pairs of nodes as well as anatomical connections in the brain [29]. For this study, the results of connectivity matrices obtained from the *MI* method are visualized in the constructed head map plots (i.e., undirected graphs). In the context of FCNs, vertices that are shown as nodes provide the strength of connectivity through edges. In the mapping of these FCNs, the hypothesis is to test for the existence of statistically significant differences among the functional connectivity matrices of epileptic patients from that of control subjects and consequently determine whether the hypothesized alteration could be used to distinguish patients with epilepsy from healthy control subjects. For this purpose, as shown in Table 2 [15], we extracted a set of 6 features from the graph obtained from each segment.

Table 2. Extracted features from functional connectivity network

Feature	Description
LD	Link density of the graph
AD	Average neighbor degree of a node
RCM	Rich club metric
SM	S-metric of graph
AC	Algebraic connectivity of the graph
GR	Graph radius

2.5. K-means clustering

All extracted features corresponding to 134 segments are fed to the *k-means* clustering algorithm. This clustering method is unsupervised without any training, and each segment was categorized into one of the two groups that later were labeled as PE or PC group (K=2; the number of groups). Based on the findings obtained from each EEG segment, the probability of assigning to each group was calculated for each subject using below equation:

$$P_{sx} = \frac{N_{sx}}{T_{sx}}$$

where P_{sx} is a calculated probability for each subject that illustrates the degree of belonging of subject s, and x could be E for epileptic patients or C for control. Term N_{sx} is the number of segments from the given subject clustered in group x, and T_{sx} is the total number of segments for the corresponding subject. The probability threshold that determines subjects positions in the groups (either healthy or epileptics) was considered as 50%, as shown in Table 3 in the results section.

3. RESULT AND DISCUSSIONS

Figure 2 displays the constructed undirected FCNs averaged for PE and PC groups based on selected thresholds. In contrast to PC, higher and stronger connections were observed in PE head map plots under two pre-defined thresholds (20% and 25%).

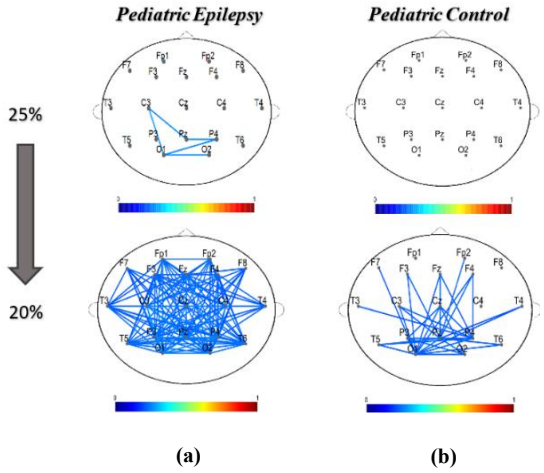

Figure 2. Graph representation. Graph representation of average of FCNs for (a) pediatric epilepsy (PE) and (b) pediatric control (PC) for selected thresholds.

To validate the hypothesis of the proposed method, a two-sided two sample student t-test was performed to examine whether there is a significant difference between the undirected mean FCNs of the PE and PC groups. The *Null* hypothesis of the mean difference in functional connectivity of epileptic and healthy groups was rejected, resulting in a statistically significant difference in the mean FCNs ($t(340) = -15.99,\ p = 2.61e^{-43}$) between PE and PC groups.

As shown in Figure 3, the number of connections between the two groups based on different thresholds is compared. The alteration in the form of the increasing number of connections in epileptic patients

validates the hypothesis that abnormal networks will show more activation in all regions of the brain.

Table 3 shows the results of clustering and calculated class likelihood for each group. The suggested algorithm has shown the ability of detecting epileptic segments with high accuracy of 92.5%, sensitivity of 95.3%, and specificity of 90%. The experiment is iterated 1000 times to assure the consistency of the results and obtained accuracies. Based on our results, increasing the EEG segments may improve the accuracy of the final clustering results. Compared with the method applied in the previous study [11], although fewer features were considered, higher accuracy and sensitivity were achieved.

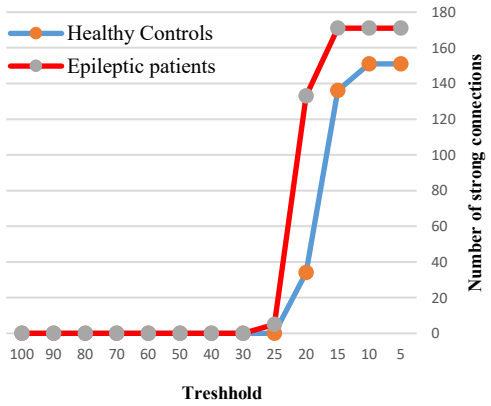

Figure 3. The quantification comparison for average connectivity matrices based on pre-defined thresholds.

Table 3. Table 3. Resulted Classification Probabilities of Study Subjects

Subject ID	#Of segments	P_{sC}	P_{sE}	Subject labeled as
P1	10	0%	100%	Epileptic
P2	10	0%	100%	Epileptic
P3	10	10%	90%	Epileptic
P4	10	0%	100%	Epileptic
P5	10	0%	100%	Epileptic
P6	10	0%	100%	Epileptic
P7	10	60%	40%	Healthy
C1	10	90%	10%	Healthy
C2	10	100%	0%	Healthy
C3	10	90%	10%	Healthy
C4	10	100%	0%	Healthy
C5	4	100%	0%	Healthy
C6	10	100%	0%	Healthy
C7	10	90%	10%	Healthy
Accuracy	**92.5%**			
Specificity	**90%**			
Sensitivity	**95.3%**			

4. CONCLUSION

The method applied in this study has a promising clinical implication. Using scalp EEG, the delineation between the PE and PC groups is hypothesized to be related to their different brain wiring patterns. The implemented algorithm was based on constructing FCNs of the brain using *MI*- an information theoretic approach- between the electrodes and analyzing graph theoretical based features to identify the connectivity pattern differences among these two groups. Since the brain connectivity networks of the PE group (vs PC) demonstrate stronger connections, the results strongly support the hypothesis that abnormal networks will exhibit more activation in all regions of the brain. Our findings support the algorithm that uses the *k-means* clustering method for classification. Such a method facilitates the screening process of potential epileptic patients since it does not require any training. Altogether, the fully automated approach that was applied in the current study can provide clinicians with a validation tool to improve early and on-time diagnosis of pediatric epileptic patients, as a vulnerable population. Future studies with large samples of pediatric and adult patients are warranted to add statistical meaningfulness in the results using the same approach.

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