Analyzing epileptogenic brain connectivity networks using clinical EEG data

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***Abstract*—Epileptogenic brain connectivity networks are altered compared to normal ones. Here, we have investigated the properties of epileptogenic networks by applying graph theoretical, statistical and machine learning approaches to the resting state electroencephalography (EEG) recordings obtained from 30 normal volunteers and 51 patients suffering from generalized epilepsy. In the case of epileptic patients, we have found that the brain networks behave like random networks. There is some loss in node connectivity. Hub nodes are more affected during epilepsy. Hence, the epileptogenic networks show less clustering coefficient than normal ones. In addition, we have identified 11 specific regions of brains and ten most significant connections among them as an epileptogenic signature by feature extraction. The ten most significant features are used to classify 81 sample data sets into two classes, *i.e.*, epileptogenic and normal, with 79.01% accuracy. The highly probable eleven regions of human brain according to the positions of electrodes and connections among them may lead to a progress in the clinical treatment of epileptic patients.**

***Keywords*—brain network, graph theory, epilepsy, EEG, feature extraction and classification.**

I. Introduction

Brain is one of the most complex and important organs of human body. It serves as the centre of the nervous system and is composed of neurons, glia and blood vessels. Neurons form the functional units of a brain. They are electrically excitable and transmit information through electrical and chemical signals. Understanding a brain's functionality employs mathematical, physical and computational models and principles.

The brain's functional organisation can be represented as a graph to establish relationship among its different areas [19]. The principle aim is to explain how the network changes from healthy to a diseased state and how it modulates brain functionality. All communication between nerve cells is carried out along physico-chemical connections, that send signal in the form of potential action. A network representation in a biological system treats individual components or neurons as network nodes and the interaction among them as network edges. Due to biological and technical complexities, the communication between different brain regions is also plotted, rather than each neuron, to form the so called brain network.

Though human brain is an organised structure, the anatomical and functional networks are highly plastic in nature [20]. This is the main bottleneck in the study of human brain network. It has a tendency to maximise functional motifs and minimise structural motifs [21]. As a result the networks change according to maturity and learning, as well as show individual variability [5]. Thus forming a uniform network is a daunting task.

Epilepsy is characterized by epileptic seizures that tend to recur with no immediate underlying cause. During an episode of epileptic seizure, neurons fire in an abnormal, excessive and asynchronized manner. During these episodes, functional brain network changes. This condition is observed only during the occurrence of seizure. However, it is absent before the onset or after the occurrence. Graph theoretical analysis [16] of an epileptogenic network may show deviation from normal. It may be associated with cognitive and behavioural alterations in individuals.

A number of epilepsy related researches have been carried out on human brain. Most of them consider the brain connectivity network as a graph due to its simplicity [11], [1], [22]. Graph theoretical analyzes help in visualising the brain functional networks as simple graph connections depicted by nodes and edges. Network studies show that the brain network is highly organised. They form network hubs. Besides, they are characterised by small world network and scale free properties. Thus, they maintain an optimal balance between wiring cost and efficiency. Previous investigations [14] have shown that small world network efficiencies are associated with intelligence of a person. Moreover, they show enhanced degree centralities in the frontal and parietal cortex [26]. Neuronal disorders may bring an alteration in any of the nodes or edges. Thus, it may affect the hub nodes. Consequently, they disrupt the whole network [24]. Previous studies have shown that in the case of epilepsy the brain network becomes more random. Subsequently, the network shows decrease in efficiency with the increase in age of an individual [10].

Previous findings on epileptic EEG data have found that enhancement in epileptic activities of patients happens because of sleep disorders [28]. Sleep disruption due to sleep apnoea, increases seizure frequency of some patients. Thus, the treatments of sleep disorders may reduce the frequency of recurrent epilepsy [27]. Other findings indicated that small world properties have been somehow preserved within the same individual groups, but they differ among different indi-

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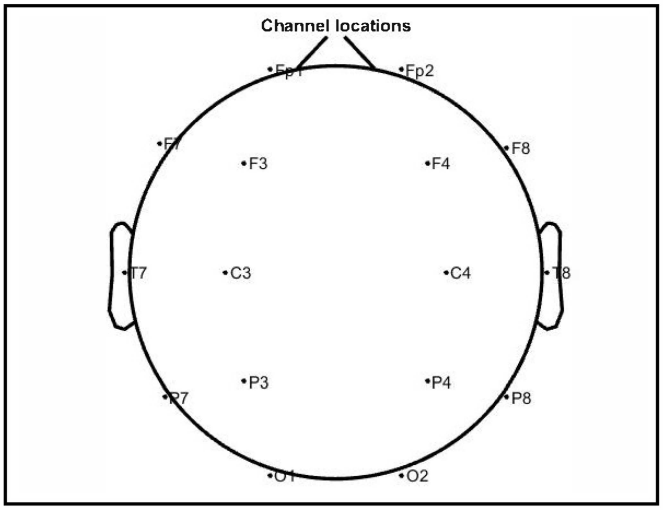

Fig. 1. Locations of electrode on the scalp.

vidual groups based on age, gender, education, intelligence and other related criteria [24], [13]. Besides, these investigations support the increase of local clustering and path length with the enhancement of the severity of the disease [23], [25].

All these studies made overall inferences based on neuronal networks of whole human brain. None of them pin-pointed the highly probable regions and connections in the brain network of an epileptic patient for clinical purposes. In this article, we pin-point ten significant epileptogenic features among eleven subareas of human brain according to node placement. We focused on EEG analysis of 51 patients suffering from epilepsy and 30 normal volunteers. Here, we have calculated the graph connectivity, graph energy, graph density, network efficiency, average clustering coefficient, rich club index and small world properties for both epileptic and normal brain networks. Our results show that epileptogenic brain networks behave like the random networks. Besides, some loss in node connectivity can be found. Compared to normal ones, epileptogenic networks show reduced clustering coefficient. Subsequently, the hub nodes are more affected during epilepsy. Moreover, we have extracted 10 most significant features to classify the 81 sample data sets into two classes, i.e., epileptogenic and normal ones, with 79.01% accuracy and ROC area scores of 0.871 for both the classes.

II. DATA

We have collected EEG data from 30 healthy volunteers with no history of epilepsy or other major neurological disorders and 51 patients suffering from generalized epilepsy. Among the healthy volunteers, 15 are female with mean age of 16.87 years and 15 are male with mean age of 17.67 years. Patient data of 26 females with mean age of 15.21 years and 25 males with average age of 13.46 are considered.

III. DATA ACQUISITION AND PRE-PROCESSING

All EEG data have been recorded using 16 channel Recorders & Medicare Systems Pvt. Ltd. (RMS) computerised EEG machine for an interval of 20-30 minutes. Electrode locations are according to internationally accepted Modified Combinatorial Nomenclature (MCN) system (Figure 1). In the MNC system, letters and numbers are used to identify the lobes and the hemisphere locations respectively. The letters FP, F, T, P, and O stand for frontal polar, frontal, temporal, parietal and occipital lobes respectively. Here, odd numbers refer to the electrodes positioned on the left hemisphere and even numbers refer to the electrodes on the right hemisphere. We have illustrated electrode positions with corresponding hemisphere, brain regions, anatomy and functionalities in Table I. Subsequently, a brief description of individuals selected for the study can be found in Table II.

All participants have been asked to relax and lay motionless as far as possible with open eyes. Besides, they have been requested to try to think nothing in particular. Thus, data was recorded at a probable no-thinking state of awake patients during the whole procedure. A series of activation procedures, like hyperventilation, photic stimulation and eye closure have been used to induce normal/abnormal EEG.

Data pre-processing have been done using EEGLAB toolbox version 13 [6] implemented in MATLAB R2015a. The raw EEG data was filtered to remove sinusoidal noise using an EEGLAB plugin, called CleanLine. Moreover, the slow sleep waves of adults (also found in babies), i.e., delta waves (<4 Hz) have been filtered out using Finite Impulse Response (FIR) filter. Thus, we have filtered the data within a range of 4-60 Hz to remove the sleep waves. Subsequently, the data was manually inspected to remove noise if present. In addition, Independent Component Analysis (ICA) [12] has been performed by applying the Runica algorithm. ICA is a signal processing method for separating a multivariate signal into its additive independent non-Gaussian subcomponents. It is a special case of blind source separation. Here, neural networks are used to separate the maximum likely component from a number of noisy components. Finally, the data was manually inspected until all the artefacts were removed.

IV. METHODOLOGY

A. Formation of brain connectivity network

Dependency between two variables can be estimated by correlation. Pearson's correlation coefficient is a familiar measure to identify the linear correlation between two electrode positions, considered as vertices. It can be represented by Equation 1.

$$\rho(x,y) = \frac{cov(x,y)}{\sigma_x \sigma_y} \tag{1}$$

Here, $\rho(x,y)$ is the correlation coefficient, $cov(x,y)$ is the covariance, and σ_x and σ_y are the standard deviations of x and y respectively.

We have created a correlation matrix **M** of order 16. The diagonal elements of **M** are 1. The off-diagonal elements of **M** represent correlation coefficients of the corresponding vertex pairs. The values of the correlation coefficients lie between -1 to +1. Here, a value of -1 represents a direct negative

TABLE I
IMPORTANCE OF DIFFERENT AREAS MARKED BY THE ELECTRODE CHANNELS

Electrode name	**Hemisphere**	**Brain regions**	**Anatomy**	**Function**
FP1	Left	Frontal Polar	Prefrontal cortex	Cognitive functions
FP2	Right	Frontal Polar	Prefrontal cortex	Cognitive functions
F3	Left	Frontal	Premotor cortex	Movement
F4	Right	Frontal	Premotor cortex	Movement
F7	Left	Frontal	Prefrontal cortex	Cognitive functions
F8	Right	Frontal	Prefrontal cortex	Cognitive functions
T7	Left	Temporal	Medial temporal lobe	Speech and vision
T8	Right	Temporal	Medial temporal lobe	Speech and vision
C3	Left	Central	Motor areas	Locomotion and movement
C4	Right	Central	Motor areas	Locomotion and movement
P3	Left	Parietal	Somatosensory cortical area	Sensory functions
P4	Right	Parietal	Somatosensory cortical area	Sensory functions
P7	Left	Parietal	Inferior parietal lobule	Auditory functions
P8	Right	Parietal	Inferior parietal lobule	Auditory functions
O1	Left	Occipital	Occipital lobe	Visual functions
O2	Right	Occipital	Occipital lobe	Visual functions

TABLE II
DESCRIPTION OF INDIVIDUALS SELECTED

Age group	**Normal Individuals**		**Epileptic Patients**	
	Male	Female	Male	Female
Child (<13yrs)	6	7	15	13
Teenage (13-18yrs)	4	4	6	8
Adult (18-55yrs)	5	4	4	5
Total	15	15	25	26

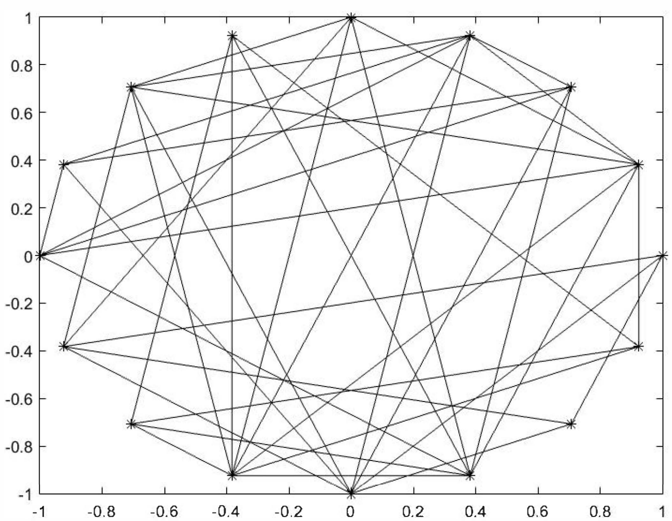

Fig. 2. Visualization of a brain connectivity network using EEG data.

correlation, whereas a value of 0 represents no correlation. On the other hand, a value of +1 represents a direct positive correlation. Subsequently, we have created a p-value matrix $\mathbf{P}$ of order 16 to check the null hypothesis. The p values lie in a range of 0 to 1. We have set a cut-off value 0.05 as such a small p-value indicates higher correlation between a pair of nodes. Thereafter, we have compared all off-diagonal elements of $\mathbf{M}$ with corresponding elements of $\mathbf{P}$. If an element of $\mathbf{M}$ has p-value less than 0.05, we have considered an edge between two vertices corresponding to the same entry of $\mathbf{M}$. In the same manner, if there is an edge, we have assigned 1 to the corresponding entry of an adjacency matrix $\mathbf{A}$ of order 16. The entries of $\mathbf{A}$ become 0 if there is no edge. Thus, we have created brain connectivity networks for both epileptic and normal individuals. A graph plotted from such an adjacency matrix is shown in Figure 2.

B. Graph theoretical and statistical method

Here, we have calculated algebraic connectivity to measure the robustness of a graph [9]. The term robustness indicates the ability of the network to perform even if it is subjected to failures or attacks. However, the algebraic connectivity of a graph is the second smallest Eigen value of the Laplacian matrix ($\mathbf{L}_{n\times n}$) as follows.

$$\mathbf{L} = \mathbf{D} - \mathbf{A} \tag{2}$$

Here, the term $\mathbf{D}$ is a degree matrix of order 16 whose diagonal elements represent the degree of corresponding vertices and off diagonal elements are zeros. The term $\mathbf{A}$ is the adjacency matrix, and n (=16) is the measure of vertices. The value of algebraic connectivity greater than zero represents a connected graph and vice versa.

Graph energy is calculated using MATLAB. Graph energy can be defined as the sum of the absolute values of the real components of the Eigen values of an adjacency matrix.

On the other hand, the graph density is a measure of the denseness or sparseness of a graph. In this scenario, a value of graph density close to 1 indicates that the numbers of the edges of a graph are very close to the maximum numbers of possible edges. For an undirected graph, the graph density (δ) is calculated using the following equation.

$$\delta = \frac{2 \mid e \mid}{\mid v \mid (\mid v \mid -1)} \tag{3}$$

Here, the term $\mid e \mid$ is the number of edges and $\mid v \mid$ is the number of vertices of a graph.

We have calculated the efficiency of a network to measure how efficiently a network exchanges information. Global efficiency quantifies the efficiency to exchange the information at the global level, while local efficiency quantifies information exchange at a small scale. We have used the following equations to calculate the two types of network efficiencies.

$$\varphi_{global}(G) = \frac{\varphi(G)}{\varphi(G^{ideal})} \tag{4}$$

$$\varphi_{local}(G) = \frac{1}{n}\sum_{i \in G}^{n} \varphi(G_i) \tag{5}$$

Here, $\varphi_{global}(G)$ and $\varphi_{local}(G)$ denote global efficiency and local efficiency of a network G respectively. The term n represents the total number of nodes in the network, whereas i represents any node of the graph. Besides, the term G_i is a local sub graph consisting the immediate neighbours nodes of node i. Subsequently, the term G^{ideal} refers to the maximum number of possible networks. On the other hand, the term $\varphi(G)$ is a measure of the average efficiency of the network following the equation below.

$$\varphi(G) = \frac{2}{n(n-1)} \sum_{i<j \in G}^{n} \frac{1}{\varepsilon(i,j)} \tag{6}$$

Here, the term $\varepsilon(i,j)$ denotes a shortest path between a node i and a neighboring node j.

The local clustering coefficient of a node of a graph is a measurement of the closeness of the node to its neighbours. For an undirected graph, the local clustering coefficient ϑ_i of a node i is calculated as follows.

$$\vartheta_i = \frac{2\mathscr{E}_i}{\mathscr{K}_i(\mathscr{K}_i - 1)} \tag{7}$$

Here, $\mathscr{K}_i$ is the number of neighbours of i, whereas $\mathscr{E}_i$ is the number of connected pairs between all neighbours of i. Thus, the clustering coefficient of a node i is the ratio of the number of connected neighbours of i to the total number of possible connections. The average network clustering coefficient is the average of all the local clustering coefficient of nodes present in the network. Its value lies in a range of 0 to 1. Consequently, the value 1 signifies that all the nodes are connected to its neighbours, whereas the value 0 means that no edges are present between neighbouring nodes.

Rich club coefficient measures how the nodes are connected to each other. A network that displays a relatively high rich club coefficient has many connections among nodes of high degree. Thus, the rich club coefficient value ($\gamma(k)$) , where k is the degree of the node, has been calculated following the Equation 8.

$$\gamma(k) = \frac{2e_{>k}}{n_{>k}(n_{>k} - 1)} \tag{8}$$

Here, $e_{>k}$ is the number of edges between the nodes of degree greater than or equal to k and $n_{>k}$ is the number of nodes with degree greater than or equal to k.

Finally, small world network is a type of mathematical graph where most of the nodes are not neighbours to one another. However, each node can be reached from the other nodes through alternative paths. Here, we have calculated the small world network index (τ) value using the following equation.

$$\tau = \frac{\psi}{\omega} > 1 \tag{9}$$

Here the term ψ is defined as follows.

$$\psi = \frac{c_{real}}{c_{random}} \tag{10}$$

Here c_{real} is a measure of the clustering coefficient as calculated from the graph and c_{random} is the clustering coefficient of a random graph. The term ω is defined in Equation 11.

$$\omega = \frac{l_{real}}{l_{random}} \tag{11}$$

Here l_{real} and l_{random} refers to path length of a real and random graph respectively.

C. Feature extraction and classification

In this article, we have used minimum Redundancy Maximum Relevance (mRMR) feature selection algorithm [17]. Our aim was to find significant features that differentiate epileptogenic and normal brain connectivity networks. Here, every 16×16 adjacency matrix is symmetric and diagonal elements are zero. In this fashion, maximum $\frac{16\times15}{2}$(=120) features and 2 classes (epileptogenic and normal) can be considered as inputs to the mRMR feature selection algorithm. We have used Mutual Information Difference (MID) [17] feature selection scheme to extract 10 most significant features for classification of epileptogenic and normal data. Besides, logistic regression techniques [8] with ridge parameter of 10^{-8} coefficients are used to classify the epileptogenic and normal data by applying 5-fold cross-validation test mode [7] for feature extraction and classification.

Figure 3 illustrates the pipeline of the used methodology in a single summarized manner.

V. RESULTS

A. Graph theoretical analysis

The results (Figure 4, Table III) shows the mean (Φ) values of algebraic connectivity of epileptic and normal brain networks are 0.65309 and 0.847284314 respectively. Besides the standard deviation (SD) values for epileptic and normal brain networks are 0.375687043 and 0.38013226 respectively. We have found the graph energy values for epileptic patients and normal individuals are (Φ= 29.20349 and SD = 0.674442) and (Φ= 28.93389 and SD = 0.638983) respectively. The global efficiencies of the networks in the case of both normal (Φ=0.651) and epilepsy (Φ=0.656) remain almost same but the local efficiencies of the networks vary. Subsequently, the graph density values for normal and epileptogenic networks are (Φ=

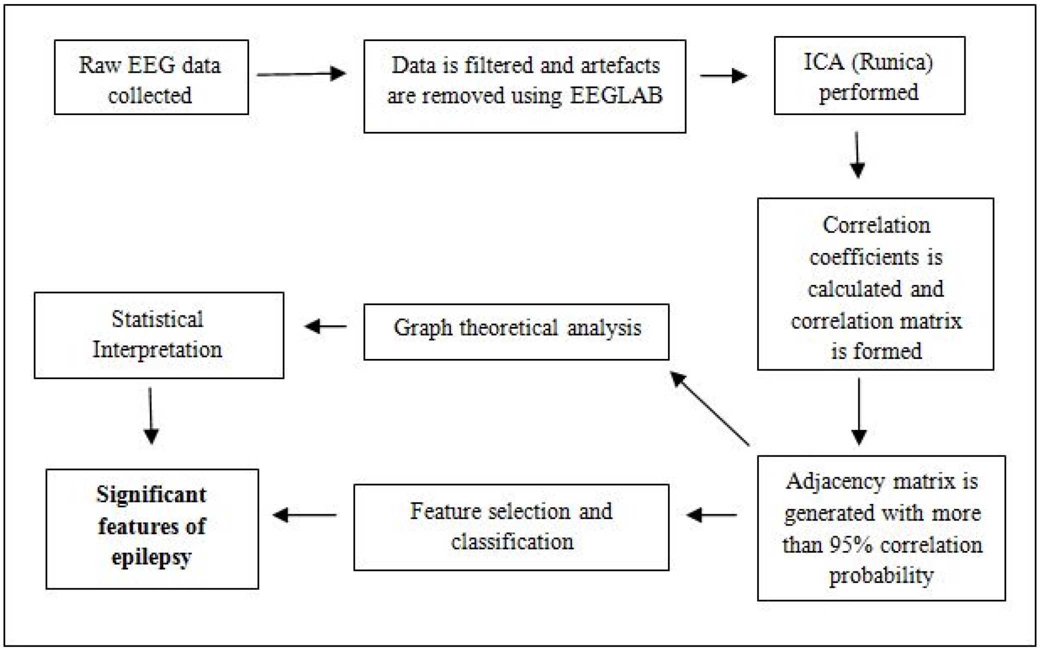

Fig. 3. Pipeline for analysis.

0.8289 and SD= 0.0686) and (Φ= 0.8071 and SD= 0.0925) respectively. Again, the average clustering coefficient values are (Φ=0.7527 and SD= 0.1001) and (Φ= 0.7005 and SD= 0.1028) for normal and epileptogenic networks respectively. On the other hand, the rich club coefficient values reduce in the case of patients (Φ= 0.404 and SD = 0.04625) when compared with normal individuals (Φ= 0.4144 and SD = 0.0342). We have also calculated the small world index values for normal individuals and patients, (Φ=1.63799; SD= 0.4575326) and (Φ=1.54271; SD= 0.31686) respectively.

B. *Features and classification*

We have found 10 significant features (Table IV) that can be used to classify epileptogenic and normal data. Two short distant connections (C3-F3 and O2-O1) as well as a very long distant connection (P4-FP1) were found more in epileptogenic patients than normal ones. On the other hand, four medium distant connections (P7-O2, F8-C3, F8-F3 and T7-O1) and three long distant connections (T7-O2, P8-C3 and T8-F3) are less frequent in epileptic patients than normal volunteers. The classification results shows 64 instances among total 81 samples are correctly classified with 79.01% accuracy. 20.98% instances are wrongly classified. 43 instances out of 51 epileptic samples and 21 instances out of 30 normal samples are classified correctly. The ROC area scores for epileptogenic and normal classes are 0.871 and 0.871 respectively.

VI. Discussions

Our analysis shows (Table IV) that loss of long/medium distance connections and formation of short distance connections are frequent in the case of epilepsy. As a result, we found a significant enhancement in average algebraic network connectivity in the case of epileptogenic networks (0.8473) than the normal individuals (0.6531). Moreover, brain connectivity network becomes more random in the case of epileptic patients [4], [3].

Energy of a graph measures randomness. Our result shows enhancement of graph energy in case of epilepsy. If energy increases, the graph becomes unstable. As stated earlier, epileptogenic networks are random than normal ones. Thus, the corresponding graphs become unstable. Besides, it is suggested that the epileptogenic networks are prone to external attacks due to unstability [18]. Consequently, the robustness of the epileptogenic network decreases. Our results follow these kinds of previous findings [18]. However, the density of an epileptogenic graph decreases compared to a normal graph. In addition to that, the rich club coefficient value also drops for epilepsy. These findings indicate loss of hub node connectivity in the case of epileptogenic networks. Though the rich club coefficient values for epilepsy are less than the normal ones, the difference is very small. From this finding, we can conclude that epilepsy is localized to some regions of the brain. It does not affect the overall connectivity of the network.

It is clear from our analysis that the small world index value for epilepsy decreases compared to normal individuals. The small world index value is characterized by long path lengths and high clustering coefficients [2]. Interestingly, our analysis also shows reduction of clustering coefficient in the case of epilepsy.

Hub nodes are economically very important, because they integrate and distribute information due to their high connectivity with other nodes in a network. Our analysis confirms

TABLE III
AVERAGE VALUES (Φ) AND STANDARD DEVIATIONS (SD) OF DATA OBTAINED FOR BOTH NORMAL INDIVIDUALS AND PATIENTS

Parameters	Normal Individuals		Epileptic Patients	
	Average	Standard Deviation	Average	Standard Deviation
Average Connectivity	0.6531	0.3757	0.8473	0.3801
Average Density	0.8289	0.0686	0.8071	0.0925
Average Energy	28.9339	0.639	29.2035	0.6744
Clustering Coefficient	0.7527	0.1001	0.7005	0.1028
Network Efficiency	0.8951	0.0441	0.8712	0.0654
Rich Club Coefficient	0.4144	0.0343	0.4036	0.0462
Small World Index	1.638	0.4575	1.5427	0.3169

TABLE IV
THE TOP 10 MOST SIGNIFICANT FEATURES SELECTED BY MRMR FEATURE SELECTION ALGORITHM USING MID SCHEME

Connection Type	Participating Nodes	Epileptogenic	Normal	Found in epilepsy patients:
Short	C3-F3	39.21%	0.06%	More
Medium	P7-O2	25%	60%	Less
Very long	P4-FP1	78%	50%	More
Short	O2-O1	72%	43%	More
Medium	F8-C3	29.41%	60%	Less
Long	T7-O2	21.56%	46.66%	Less
Medium	F8-F3	33.33%	63.33%	Less
Long	P8-C3	37.25%	63.33%	Less
Long	T8-F3	21.56%	46.66%	Less
Medium	T7-O1	19.60%	40%	Less

that rich club coefficients decrease in case of epilepsy. Thus, the edges originating from hubs get disrupted. Subsequently, metabolic rate of the brain gets affected.

Our graph theoretical and statistical analysis on epileptogenic network show that there is randomization in the network as well as loss in network edges. Moreover, we have extracted ten most significant features that distinguish epileptogenic network from the normal ones. The features reveal that the epileptogenic sample has more short distant connections between central motor area and frontal premotor cortex in the left hemisphere, and occipital lobe of the left and right hemisphere than the normal sample. Due to this locomotion, movement and visual functionality are somehow altered during epilepsy. This property may lead to uncontrollable jerking of hands and legs as well as a staring spell during epileptic seizure. On the other hand, our analysis shows formation of a very long distant connection between right parietal somatosensory region and left prefrontal cortex is more frequent in epileptogenic sample than the normal ones. Probably, such a phenomenon causes an alteration of sensory and cognitive functions of the epileptic patient which affect consciousness/awareness. However, we have found less connections between right prefrontal cortex and left frontal cortex in the case of epileptogenic sample compared to normal individuals. This finding is supported by an the previous investigation [15] which states that epileptic patients show reduction of connectivity within frontal lobes. Besides, the connections between left parietal and right occipital, right frontal and left central, left temporal and right occipital, right parietal and left central, right temporal and left frontal, and left temporal and left occipital have been found less in epileptic patients than the normal volunteers.

VII. Future Scope

Though our results have extracted some significant features of epileptic patients, our sample size is small to predict other relevant features. Thus, the accuracy of our classification technique applied to the samples is 79.01%. In future, we aim to collect more samples in order to increase our classification accuracy. Besides, we will consider different demographic information such as age and gender for our future study. In addition, graph theoretical measures can be considered as striking features to distinguish normal individuals and patients. Subsequently, we can analyze the results with the comparison among different classification algorithms. This will help to identify the key significant features of epilepsy. Here, we have pin-pointed certain key regions of brain and connections among them as epileptic signatures. Hence, we also intend to focus on these key regions of brain by considering the neuronal connections among them and analysis of those networks.

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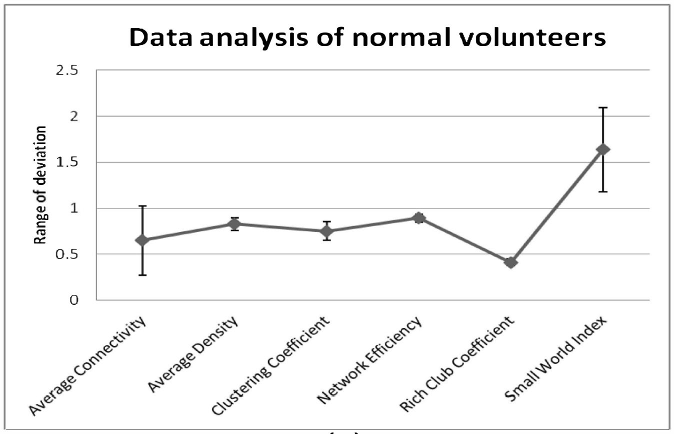
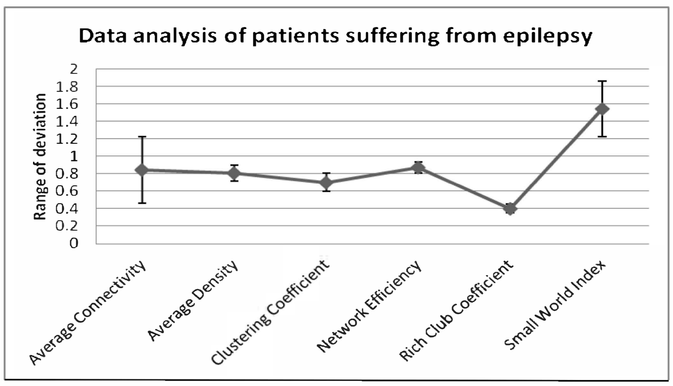


(a)



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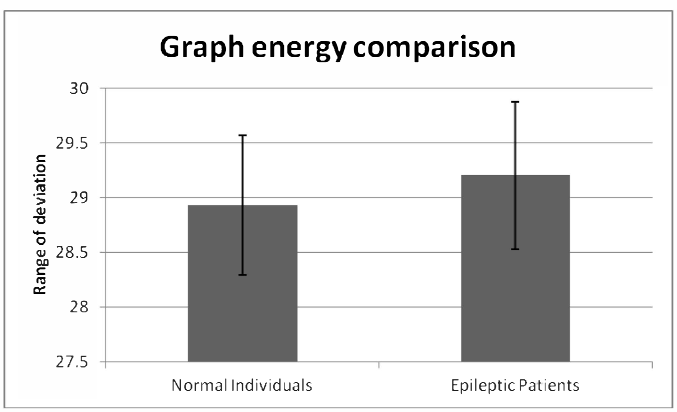

(c)

Fig. 4. Comparative analysis of the brain connectivity networks: (a) Statistical data analysis of normal individuals; (b) Statistical data analysis of patients suffering from epilepsy; (c) Comparison of average graph energy of the networks for both patients and normal individuals.

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