Connectivity Dynamics of Interictal Epileptiform Activity

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Abstract— Patterns of interictal epileptiform activities, such as sharp waves, spikes, spike-wave complexes and polyspike-wave complexes are explored in the recorded electroencephalograms (EEG) to gauge the different functional connectivity dynamics and to assess how they could be affected by the type of a seizure. Connectivity measures were represented by the phase synchronization among scalp electrodes that were obtained by adopting a nonlinear data-driven method. These interictal epileptic activities were investigated using a graph theory analysis. The connectivity maps were compared by considering the number of connections in four main brain regions (anterior region, posterior region, left hemisphere and right hemisphere). Results revealed interesting and different network topology for the connectivity maps. Besides, a relationship between the connectivity patterns of the recorded epileptic activities and the types of seizures was observed. This relationship was statistically confirmed by analysis of variance (ANOVA) that denoted a significant difference among connectivity patterns of sharp waves and spike activities, which were seen in focal epilepsy, in contrast to the spike-wave and polyspike-wave complexes that were associated with generalized epilepsy (P-value ≤ 0). These results augment the prospects for diagnosis and enhance the recognition of the disease type via EEG-based connectivity maps.

Keywords —Connectivity maps, Electroencephalography, Focal epilepsy, Generalized epilepsy, Graph theory analysis, Interictal epileptiform discharges, Nonlinear connectivity analysis, Recurrence based phase synchrony.

I. INTRODUCTION

Epilepsy is a prevalent neurological disorder. Epileptic patients experience unprovoked and recurring seizures. Although there are many symptoms and types of seizures, epileptic seizures are often characterized as generalized or focal. The disease includes recurrent seizure attacks induced with the outbreak of abnormal synchronous neuronal activity [1]. In focal epilepsy, the unusual electrical discharges engage partial brain modules, normally in one of the hemispheres, whereas a generalized seizure starts from both hemispheres simultaneously and affects a larger area of the brain [1]. In addition to seizure attacks, which are the main characteristic of epilepsy, interictal epileptiform discharges are another non-trivial disease symptom that inherits some attributes of the disorder [2].

The high temporal resolution, noninvasive property and inexpensive but high electrophysiological monitoring quality of scalp EEG have made the EEG-based recording modality become the primary clinical evidence for disease detection [3], [4]. Despite the fact that neurons of epileptic focus are responsible for ictal events, there are recent claims that contribute to the role of an epileptic network in the behavior of a disordered brain [5], [6]. The properties of abnormal brain networks have been widely explored using interictal EEG intervals, but few studies address the connectivity attributes of interictal epileptiform waves. In [7] and [8], the effect of only one category of interictal epileptic activities was investigated while in this study, we have collected a variety of interictal epileptic waveforms and compared and assessed the connectivity maps of these different categories.

Phase synchronization (PS) is a proper metric to evaluate the functional relation between brain modules. Many connectivity measures have been proposed in the literature to express the dependence among electrodes in time/frequency domain as well as on utilizing data-driven analysis [9], [10]. PS-based metrics are proved to be more suitable for analyzing the functional connectivity networks since such measures highlight the synchrony of cortical modules rather than the signal amplitude relations [11]. The synchronization metrics can be realized using linear measurements like coherence, or nonlinear methods which can be adopted instead [12]. Since the complex and nonlinear nature of brain signals can be well explained as chaotic oscillators [13], applying recurrence-based methods to the chaotic systems can well estimate the PS [5].

Brain connectivity maps can be represented by applying modern science network [6], which combines graph theory with dynamical systems and statistics [14]. A healthy brain has adapted an optimized combination of local information processing with efficient global data transfer between modules. This attribute that is known as small-world network topology will be damaged when the brain is engaged with an abnormality like epilepsy [15]. In this study, we have investigated the network anomalies caused by epileptic
interictal activities.

In this research, we have utilized a nonlinear recurrence-based method that uses the time series to estimate the PS among electrodes as a connectivity metric. In section II, the characteristics of data are presented. Section III explains the applied method. Connectivity maps are then explored in section IV on how they were affected by the type of seizure under consideration.

II. MATERIAL

The scalp EEG signals of four adult individuals, diagnosed as epileptic, were collected. Data was recorded at Baptist Hospital of Miami. Recorded EEG data included nineteen electrodes (Fp1, F7, T3, T5, O1, F3, C3, P3, Fz, Cz, Pz, Fp2, F8, T4, T6, O2, F4, C4, and P4) based on 10-20 international system. EEG signals were digitized by a sampling frequency of 200 Hz. The study process was approved by the Institutional Review Board of Florida International University (protocol number: IRB-150247). EEG data included both ictal and interictal events, but only interictal parts were utilized in this study. Table I represents the demographic information of participants. 43 files that contained different spike types were separated and used in this research.

III. METHODOLOGY

A. Preprocessing and artifact rejection

We preprocessed data before segmentation to maximize brain-related activities rather than the unwanted noise. All EEG signals were processed with a 4th order Butterworth bandpass filter with a passing frequency range of [0.5 36] Hz. The band-pass filter with zero phase characteristics was applied to eliminate the distortion effect of the filter on signals [16]. We applied the 36Hz as high cut-off frequency since the role of brain activities higher than 36Hz was minimal in the final connectivity maps and the epileptiform discharge was thus emphasized. Signal baselines were also removed for all EEG data sets.

We re-referenced data sets to average montage to minimize the volume conduction problem [17]. The recorded data were processed using both the principal component analysis (PCA) and independent component analysis (ICA) to remove various artifact contaminations with the use of EEGLAB software [18].

B. Segmentation

Extracted files included sharp waves, spikes, spike-wave complexes (complex spike) and polyspike-wave complexes (repetitive spikes). We considered sharp waves and spikes in one category and referred to them as spikes in this manuscript. Therefore, three major groups of the spike, complex spike, and repetitive spike represented the different interictal epileptiform discharges in this research endeavor. The filtered, artifact-free EEG data was subdivided into one-second segments. The one-second segment length was chosen because we wanted to focus only on the dynamics of the interictal discharge, by eliminating the EEG propagation of the background activity. Fig.1 illustrates sample data segments of a spike, a complex spike, and a repetitive spike. The peak of the spike was positioned in the middle of the segment for spikes and sharp waves, while for the complex and repetitive spikes, the peak of the first spike was placed in the first 20% portion of the one-second EEG segment [2].

C. Functional connectivity maps

Considering the brain as a nonlinear chaotic system, the behavior of brain dynamics can be investigated in a reconstructed multi-dimensional space which we refer to here as the phase space [10], [19]. The signal trajectory in the phase space can be simply rebuilt using the time delay theorem as expressed in [20]. As per this theory, the signal $X = \{x_1, x_2, \ldots, x_N\}$ with $N$ items, reconstructed into the trajectory, $y_i$, in phase space using (1).

$$y_i^T = [x_k x_{k+t} x_{k+2t} \ldots x_{k+(m-1)t}]$$

where $m \geq 1$, $t \geq 1$, $i = 1, \ldots, N$, and $k = 1, \ldots, N = (m-1)t$

Where $m$ is the embedding dimension, $t$ denotes time delay, and $y_i$ is one point of the trajectory. The trajectory preserves the topological properties of the original signal; therefore the spike activities were reflected in these constructed paths [21].

The brain signal trajectories, like other chaotic dynamics, have recursive behavior, meaning it returns to its

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Type of spike</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>F</td>
<td>Spike</td>
<td>Focal epilepsy(LH)</td>
</tr>
<tr>
<td>P2</td>
<td>F</td>
<td>Spike</td>
<td>Focal epilepsy(RH)</td>
</tr>
<tr>
<td>P3</td>
<td>F</td>
<td>Complex</td>
<td>Generalized epilepsy</td>
</tr>
<tr>
<td>P4</td>
<td>M</td>
<td>Complex &amp; Repetitive</td>
<td>Generalized epilepsy</td>
</tr>
</tbody>
</table>

Fig. 1. Samples of EEG segments used for connectivity analysis. (a) Spike (b) Spike-wave complexes (Complex spike) (c) Poly spike-wave complexes (Repetitive spike)

TABLE I: DEMOGRAPHIC INFORMATION OF PATIENTS
neighborhood after a while thus establishing a recurrence. The amount and pattern of recurrences explain the signal behavior [21]. Since a direct investigation of trajectory behavior in a phase space is not feasible, recurrence maps are developed to assess such behavior [19]. Calculation of recurrence is consequently formulated as in (2).

\[ R_{i,j} = \Theta(\varepsilon - \| y_i - y_j \|) \] (2)

Based on this relation, the recurrence between points \( i \) and \( j \) \((R_{i,j})\) is said to occur when the Euclidean distance between these two points in the trajectory is less than the threshold \( \varepsilon \). The function \( \Theta \) is a Heaviside step function making the resulted value, 0 (for no recurrence), or 1 (when recurrence occurs). Calculation of recurrence for all points of the trajectory leads to the matrix of recurrence plot (RP).

The RPs diagonal and vertical lengths can be utilized to calculate the probability of recurrence for each electrode. This likelihood of recurrence can be designated as a generalized trajectory leads to the matrix of recurrence plot (RP).

The connectivity matrices were computed for all 43 segments, and the average matrix of the three categories (spikes, complex spikes, and repetitive spikes) was obtained. In fact, two electrodes are considered connected, if the CPR value is high (closer to 1) and they are not connected if the value of PS is small (around 0) [20].

In our study, the connectivity procedure was implemented using MATLAB software. We have considered two electrodes connected if the value of PS was higher than or equal to 0.7. This threshold is selected based on the comparison of the resulted connectivity matrices.

### D. Proper choice of parameters and statistical evaluation

When applying nonlinear methods, data compatibility needs to be examined since linear correlation in the data may lead to false results [1]. The surrogate data testing method is a reliable statistical method that helps to evaluate the significance of results [1]. This process works based on generating surrogates with some similarities with the original data. The resulting metric (connectivity matrix in this study) of the original data and surrogates are statistically tested with the null hypothesis of similarity. If the test result shows a significant difference between the connectivity matrices of original and surrogate data (rejecting the null hypothesis), the result from original data is validated [1]. We used the surrogate data testing to choose the proper parameters and evaluate the significance of connectivity matrices.

The Iterative Amplitude Adjusted Fourier Transform (iAAFT) is a popular method to create a surrogate data [1], [22]. The number of surrogates calculated for each EEG segment depends on the confidence we need for the test. In this study, we implemented 39 surrogates because according to the literature [1], for a level of significance, the minimum number of surrogates \((M)\), can be obtained from (6).

\[ M = \frac{2K}{\alpha} - 1 \] (6)

Where \( K \) is an integer, which is commonly chosen to be 1 for simplicity. Therefore, for a two-sided test with a 95% confidence interval, at least 39 surrogates are needed [1].

The connectivity matrices were calculated for the original data and all created surrogates. Then, each surrogate connectivity matrix was tested against the original matrix using Wilcoxon rank sum test. If the rejection rate of null hypothesis was more than 60%, the initial connectivity matrix is considered to be significant.

To find a set of parameters that lead to significant results, surrogate data test was performed for a different combination of parameter values (time lag range of \([2\text{~to~}13]\) and dimension range of \([3\text{~to~}10]\)). This procedure helps to find a set of parameters that lead to significant results. The parameters were chosen in a way that connectivity matrices for all segments of data be significant. Based on test results, the time lag of 3 and embedding dimension of 6 were selected for spikes and complex spikes and time lag of 2 with dimension 3 were used for repetitive spike group. For the recurrence threshold \((\varepsilon)\), the variable value of 10% of average space diameter is calculated [19].

### IV. RESULTS AND DISCUSSION

The connectivity matrices were computed for all 43 segments, and the average matrix of the three categories (spikes, complex spikes, and repetitive spikes) was obtained. The histograms and properties of the connectivity matrices are shown in Fig.2 and Table II. It can be observed that the connection mean value of single spikes is lower than the average values of the complex and repetitive spikes. The connection distribution for repetitive spikes represents a larger variance. All three distributions consist of powerful connections as a result of spike activity. Histograms of complex and repetitive spikes are negatively skewed,
indicating a higher number of strong connections in contrast to complex and repetitive spikes. The spike connection distribution is close to a mesokurtic (Kurtosis ≈ 3) distribution as compared to the complex and repetitive distributions.

The synchronization value was obtained from all EEG connectivity matrices by averaging the value of PS calculated for all pairwise electrodes in an EEG segment [15]. In Fig. 3, the synchronization values of the three spike categories are compared in a box plot, and higher synchronization in complex and repetitive spikes comparing to single spikes are observed.

To statistically evaluate the connectivity differences between three epileptic waveforms, the average matrices were tested by analysis of variance (ANOVA) with the null hypothesis of same means. The ANOVA test resulted in a rejection of the null hypothesis with 99% confidence (P-value = 2.05e-56). Analysis of the results with the multi-comparison test showed that single spikes are significantly different from the other two categories of spikes as shown in Fig. 4.

Several brain network topologies have been investigated in previous studies using the graph theory [6], [14], [23]. It is known that a healthy brain network shows the characteristics of small-world topology, which is an optimized tradeoff between integrated information processing and global communication [23]. Here, we have considered the connectivity matrices as a weighted undirected adjacency matrix of a graph in which nodes are electrodes, and edges represent connectivity strength links between the two related electrodes [23]. As each electrode represents the brain region underneath, the graph is showing the connectivity relation between brain modules. The average clustering coefficient (C) of all vertices that is a local connectivity feature was calculated [15]. The global communication attribute was presented by the average shortest path length (L) [15]. A network with small-world topology has a high clustering coefficient with a short average path length. The ratio of \( C / C_r \) and \( L / L_r \) is calculated to access these attributes in connectivity graphs. In which \( C_r \) and \( L_r \) are the clustering coefficient and the average path length of the randomized initial network. The small world index is calculated as (7) [15].

\[
S = \frac{C / C_r}{L / L_r}
\]  

(7)

Fig. 5 shows the clustering coefficient, average path length and the small world index of categorized EEG connectivity graphs. Based on Fig. 5, results indicate that the network topology of the three spike categories is close to a random network. These results show that the small-world characteristic is lost due to interictal abnormal activity. The same result has been obtained previously because of seizure activity in the EEG signal [15]. In this study, we used the MIT MATLAB network routine toolbox [24] for the calculation of \( L \) and \( C \). The small world index was coded using the MATLAB software.

To better visualize the calculated connections, the connectivity matrices are plotted concerning electrode placements on the head while the strength of links is coded by colors. The red color indicated strong relationship while blue indicates weaker bonding values. We applied a threshold set of [95% 90% 80%] to connectivity maps to make the comparison among the interictal epileptiform activities. A sample connectivity pattern of the spike, complex and repetitive is illustrated in Fig. 6.

By visual investigation of the head map plots in Fig. 6, it is noted that the connection patterns are different among various interictal epileptic discharges, reflecting the spread of spike activity in the brain. Since complex and repetitive spikes are globally synchronized events, the connections appeared in most of the brain regions. This global activation creates strong

<table>
<thead>
<tr>
<th>IDE Category</th>
<th>MEAN</th>
<th>STANDARD DEVIATION</th>
<th>SKEWNESS</th>
<th>KURTOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spike</td>
<td>0.7045</td>
<td>0.0580</td>
<td>0.1375</td>
<td>2.9772</td>
</tr>
<tr>
<td>Complex spike</td>
<td>0.8464</td>
<td>0.0587</td>
<td>-0.2635</td>
<td>2.1582</td>
</tr>
<tr>
<td>Repetitive spike</td>
<td>0.7876</td>
<td>0.0941</td>
<td>-0.0705</td>
<td>2.5193</td>
</tr>
</tbody>
</table>

Fig. 4. Multi-comparison test result shows that average connections of spikes are significantly different from complex and repetitive spikes.
relationships among the majority of electrodes in the connectivity maps. In contrast, the single spike activity, which was seen as sudden discharges in only some of the electrodes in EEG data, resulted in weaker and more localized connections in the connectivity maps.

Four main brain regions were considered to highlight the variety of connectivity maps quantitatively. The number of connections within and between regions is counted as an indication of activity. These four brain regions are:
- Anterior region (including electrodes: Fp1, Fp2, F7, F3, Fz, F4 and F8)
- Posterior region (comprised of O1, O2, T5, P3, Pz, P4, and T6)
- Left hemisphere (electrodes: Fp1, F3, C3, P3, O1, F7, T3 and T5)
- Right hemisphere (Fp2, F4, C4, P4, O2, F8, T4 and T6).

The border electrodes for the anterior/posterior are T3, C3, Cz, C4, and T4; and for the left and right hemisphere are Fz, Pz, and Cz. The within-region connections are located between two electrodes in the same region or one electrode in the area and the other one as a border electrode. Connections between border electrodes were ignored.

For each EEG segment, the counted links are compared with threshold levels of 95%, 90%, and 80%. Fig. 7 shows the comparison graph of the counted connections for the average connectivity map of various categories. In Fig. 7, it is observed that complex and repetitive spikes, which are more generalized activities, have a higher quantity of between-region connections in all threshold levels, while this same pattern is not seen in the single spike group. In fact, a significant amount of between-region connections is a sign of global synchronization activity that characterizes mostly the generalized epilepsy cases. Hence in focal epilepsy with local discharges, the focal patterns of abnormal activity as reflected in the connectivity maps shows a higher number of within-region connections and a lower number of between-region activities.

V. CONCLUSION

In this study, functional connectivity patterns of three primary interictal epileptic discharges were explored and characterized in direct relation to the patient’s seizure type. A set of 43 spikes, as recorded in the EEG signals from the four individuals, diagnosed with epilepsy, were collected and the phase synchronization among electrodes was calculated using the nonlinear recurrent-based method. The graph theory analysis of connectivity networks resulted in higher synchronization in addition to the abnormal regularized network topology during these epileptic activities. The connectivity maps were quantified by the number of connections within and between the four main brain regions mentioned earlier. The activities in these areas resulted in different connectivity patterns as a consequence of the various epileptic discharges. This difference was confirmed.
statistically by performing the ANOVA test among the average connectivity maps of the three types of spikes investigated. The null hypothesis of the connectivity means was rejected (P-value<0.001), indicating significant differences between connectivity maps related to focal epilepsy (spike group) and generalized epilepsy (complex and repetitive group). We conclude that the connectivity patterns (the connection strength and pattern of spread on brain regions) were related to the type of epilepsy. These results could be used to augment our understanding of seizures and to enhance the automatic diagnosis of the types of epilepsy by randomly selected EEG segments. A thorough scrutiny of these activity patterns in the connectivity maps could elicit new ways at determining a more accurate 3D source localization of seizure onset. This last assertion is part of the research we are currently conducting with a newly approved study with Baptist Hospital.

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