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Characterizing Focal and Generalized Epileptic Networks Using Interictal Functional Connectivity

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***Abstract* —Using electroencephalography (EEG) data from epileptic patients[1], we investigated and compared functional connectivity networks of three various types of epileptiform discharges (ED; single, complex & repetitive spikes) in 4 regions of the brain. Our results showed different connectivity patterns among three ED types within-and between-brain regions. The one-way ANOVA test indicated significant differences between the mean of the average connectivity matrices (ACMs) of the single spike, which characterize focal epilepsy, and the other two ED types (complex & repetitive) which characterize generalized epilepsy. The interictal EEG segments, through the connectivity patterns they yield, could be considered as one of the key indicators for the diagnosis of focal or generalized epilepsy.**

Keywords—focal and generalized epilepsy, interictal EEG, functional connectivity, normalized cross-correlation, graph theory analysis

I. INTRODUCTION

Epilepsy is a chronic noncommunicable disorder of the brain that causes seizures and affects people of all ages [1]. According to the World Health Organization (WHO), globally, about 50 million **p**eople are **l**iving **w**ith **e**pilepsy (PLWE), making it one of the most common neurological diseases [1]. In 2015 alone, around.4 million people had epilepsy across the United States (US); 470,000 children, and 3 million adults [2]. It is estimated that up to 70% of PLWE could live seizure-free if properly diagnosed and treated [1]. The everyday life of PLWE is affected dramatically by the unpredictable occurrence of seizures making it difficult for these patients to live with this uncertainty [3]. Therefore, it is crucial to investigate and predict seizures which can help to warn PLWE, and consequently improve their quality of life. Although the main feature of epilepsy is the occurrence of seizures (also termed as ictal discharges), between seizures the brain of PLWE generates pathological patterns of activity known as interictal epileptiform discharges (IEDs), which carry key traits of this health condition. IEDs are clearly distinguished from the activity observed during the seizure itself which makes it a yet-to-be fully investigated subject for researchers in this area [4].

The application of functional connectivity network analysis in epilepsy has provided important information not only on seizure onset, propagation, and termination but also on the interictal state of functional networks in epilepsy [5]. Therefore, these functional connectivity networks could provide valuable information concerning the brain's abnormal activities compared with their normal counterparts [6]. Over the past decades, the scalp electroencephalography (EEG) has been extensively employed as a cost-effective tool for non-invasive brain investigations in PLWE. This diagnostic tool has gained significant prominence for examining brain function in PLWE while simultaneously providing high temporal resolution data with negligible side-effects on PLWE.

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Interictal epileptic activities (i.e., spikes) that are observed at 1% of non-epileptic patients and around 60-90% of PLWE [7, 8] differ in two major types of disease; focal (or partial) and generalized epilepsy. Former (focal) indicates seizures that arise primarily within networks limited to one hemisphere of the brain. In the latter, however, it indicates seizures that occur when there is extensive seizure activity in the left and right regions of the brain. Investigating functional connectivity maps of interictal epileptic spikes is thus important to improve the diagnosis for both focal and generalized epilepsy based on EEG segments [9].

Therefore, in this case study, we applied the normalized cross-correlation procedure to estimate the temporal correlation between electrodes as a connectivity metric on data drawn from the EEG of two patients, one diagnosed with focal epilepsy the other with generalized epilepsy. Also, we aimed to obtain functional connectivity networks of three various types of epileptiform discharges (ED): i) single spike, ii) complex spike (spike and slow-wave), and iii) repetitive spike (i.e., poly spike-wave complexes).

II. MATERIALS AND METHODOLOGY

A. EEG data source and preparation

The EEG data were collected at Baptist Hospital in Miami, FL from a male patient diagnosed with generalized epilepsy and a female patient diagnosed with focal epilepsy having partial complex seizures. The Institutional Review Board of Florida International University (Protocol number: IRB-15- 0247) approved all study procedures and protocols and written informed consent was obtained from patients. We recorded multichannel scalp EEG signals using the standard10-20 montage with 200Hz sampling frequency. The EEG data were collected from the following 19 electrodes: Fp1, F7, T3, T5, O1, F3, C3, P3, Fz, Cz, Pz, Fp2, F8, T4, T6, O2, F4, C4, and P4. Although both ictal and interictal events were included in the EEG data, for the purpose of this study, only interictal segments were used.

We have selected 30 segments of one-second duration which include three various types of epileptiform discharges (ED): i) single spike, ii) complex spike (spike and slow-wave), and iii) repetitive spike (i.e., poly spike-wave complexes). We extracted 10 segments for each type of ED from the original data. Fig. 1 displays illustrative sample data segments for each type of ED.

The peak of the single spike was arranged to be placed at 0.5s, which was the center of the segment. For

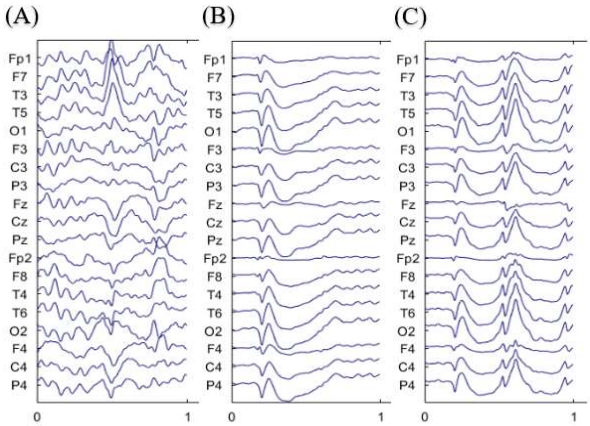

Fig. 1. Sample of 1-second EEG segment (A) Single spike, (B) Complex spike, (C) Repetitive spike

complex spikes and repetitive spikes, the peak of the first spike was placed at 0.2s of the one-second EEG segment due to their wider extent. The flowchart and main steps of the algorithm are shown in Fig. 2. For data analysis, the MATLAB software environment was used.

B. Preprocessing

According to the literature, EEG data can introduce unwanted effects from the ubiquitous presence of noise [10]. To deal with this issue, before segmentation, we processed the EEG signals to maximize brain-related activities and minimize the effects of noise. Hence, all EEG data were filtered by a 4th order band-pass Butterworth filter with a passing frequency range of [0.5, 70] Hz to remove the distortion effect of the filter on signals, and with the digital infinite impulse response (IIR) notch filter with 60 Hz notch frequency to suppress the AC power-line noise. For all EEG data, we removed signal baselines and re-referenced the data set to average montage in order to overcome the volume conduction problem [11]. To remove different artifact contaminations including eye blink, jaw, and muscle movements, we performed the Principle Component Analysis (PCA) and the Independent Component Analysis (ICA) using EEGLAB software [12].

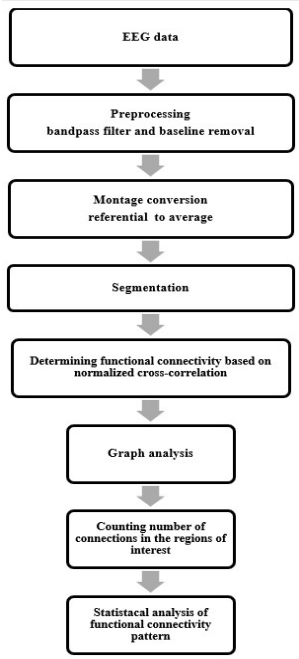

Fig. 2. Study flowchart

C. Functional Connectivity with Normalized Cross-Correlation

Cross-Correlation measures the similarity of two different series as a function of the displacement of one relative to the other in time lag [13]. As proposed by Lewis in 1995 [14], the normalized cross-correlation (NCC) is generally used to explore the similarity between two time series signals. In this study, by assuming that the signal is wide-sense stationary, we computed NCC between all pairwise montage of all nineteen EEG channels independently. As defined in the below equation, the NCC was computed for time sequence x_t and y_t of signals x and y, respectively:

$$R_{xy}(\tau) = \frac{\frac{1}{N}\sum_{t=1}^{N-\tau}\left[(x_t - \mu_x)(y_{(t+\tau)} - \mu_y)\right]}{\sigma_x \sigma_y}$$

where N denotes the length of signals x and y, τ is the time lag, μ_x is the time average of x_t with σ_x as its standard deviation (SD), and likewise, μ_y is the time average of y_t with σ_y as its SD. In order to maximize the absolute value of R_{xy} over lags and to select the maximum value in the range as the strength of functional connectivity of each pair, the strength of the connectivity C, between x_t and y_t was defined as expressed in [15]:

$$C\,(x, y) = A = \max_{\tau} |R_{xy}(\tau)|$$

where C is the absolute value between the range of zero and 1, which represents the maximal strength of correlation between two signals at time lags of $\pm$ 200 ms. The higher the value of C is, the higher the two signals fluctuate synchronously. Thus, we obtained a symmetric connectivity matrix for all electrodes of one EEG segment:

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

After calculating the connectivity strength matrices for 10 segments of each type of ED separately, we computed the average connectivity matrices (ACMs) for each type of ED by taking the average of all segments of each type of ED. For visual appreciation, thresholds of 75%, 80%, 90%, and 95% of the max NCC were applied to all connectivity matrices and ACMs.

D. Graph Analysis

Graph theory is a mathematical/computational technique used to model any complex system as a group of nodes (vertices) and links (edges) between pairs of nodes [16]. To visualize the results of connectivity matrices obtained from the NCC method, we constructed the head map plots (i.e., undirected graphs). In these plots, the electrodes are shown as the nodes of the plot that provide strength of connectivity through edges. We employed a color-coded line to represent the strength of the connection ranging from zero (blue for no connection) to one (red for highest connectivity strength).

E. Quantification of Brain Functional Connectivity

As shown in Fig. 3, in order to quantify the functional connectivity patterns and examine the similarities between the three types of ED, we use two specific cases to subdivide the cortex into various regions. In the first case, this subdivision was built on the left-right hemisphere (i.e., LR region). Each left and right hemisphere region is comprised of 8 electrodes; left hemisphere region: Fp1, F7, T3, T5, O1, F3, C3, P3, and right hemisphere region: Fp2, F8, T4, T6, O2, F4, C4, P4. The Fz, Cz, Pz electrodes were located in the central line of LR regions. The connection is characterized as "right intra-connection" if it occurred between two electrodes in either the right hemisphere region or in between the right central regions. Similarly, it is characterized as "left intra-connection" if the connection occurred between the left or between the right central regions. The connection is characterized as "LR interconnection" if it occurred between the left and right regions. In the second case, the subdivision was built on anterior-posterior regions (AP) with each region comprising of 7 electrodes. The electrodes in the anterior region include Fp1, Fp2, F7, F3, Fz, F4, F8, and those in the posterior region include T5, P3, Pz, P4, T6, O1, O2. The T3, C3, Cz, C4, T4 electrodes were located in the central line of AP regions. This concept was applied yielding labels defined as "anterior-intra-connection", "posterior intra-connection", and "AP interconnection" [17]. Since the connections in the central line are not quantified, therefore, the connections with both ends in this line were ignored. The mean of ACMs between three ED types was examined using one-way analysis of variance (ANOVA) in the MATLAB environment.

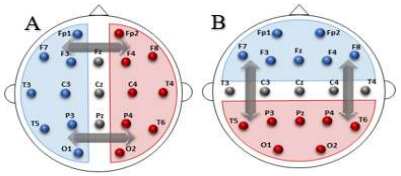

Fig. 3. Quantification of Brain Functional Connectivity. Panel A illustrates left-right hemisphere and panel B illustrates anterior-posterior hemisphere.

III. RESULTS AND DISCUSSION

Fig. 4 displays the head map connectivity plots of the ACMs for the three types of interictal ED (i.e., single, complex, and repetitive spikes) based on the selected thresholds. The connection patterns vary among these interictal ED, highlighting the distribution of spike activity in the subjects' brain. Weaker and more localized connections were observed in the single spike activity reflecting an abrupt discharge in only some of the EEG electrodes. Conversely, the presence of connections in most regions of the brain is more notable due to the globally synchronized characteristic of complex and repetitive spikes, which lead to strong relationships amongst most electrodes involved in the connectivity maps. In terms of connection patterns among the three types of ED, complex and repetitive spikes show patterns that are more symmetrical compared to the connectivity patterns observed for the single spike which were mostly asymmetrical. The higher number of connections is apparent in complex and repetitive spikes for all selected thresholds, in contrast to the single spike where the number of connections is reduced significantly with a higher threshold given their weaker strengths.

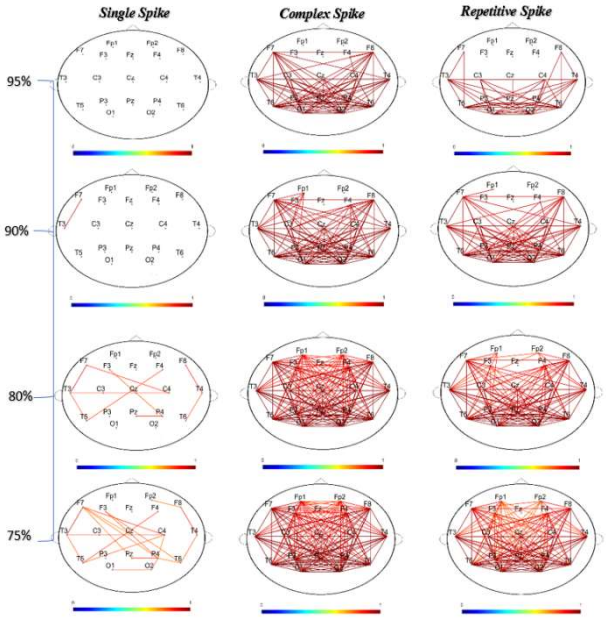

Fig. 4. Head map connectivity plots from average connectivity matrices (ACMs) of 3 type of epileptiform discharges (single, complex, and repetitive spikes) stratified by opted thresholds.

Fig. 5 summarizes and compares the number of connections for the ACMs of each ED type. Using the same chosen thresholds, compared to complex and repetitive spike, the single spike resulted in a lower number of connections with weaker connectivity strength in all regions. This finding affirms that single spike cases are more likely indicative of focal epilepsy, explaining the fact that the brain is connected locally in contrast to the complex and repetitive spikes for the generalized case where the connections are stronger (notable at all thresholds) and prevalent in all regions.

To test the mean of ACMs between three ED types (single, complex, & repetitive), we performed a one-way analysis of variance (ANOVA) test using the null hypothesis of the same mean between ED types. The results from the ANOVA test indicated that the null hypothesis is rejected ($p=2.76e^{-72}$), and the mean of ACMs between them (ED types) are not the same. Further, as shown in Fig. 6 (Panel A), multiple comparisons between these ED types showed a significant difference between the single spike connectivity matrix and the other two ED types.

The histogram diagram in Fig. 6 (panel B, C & D) displays the number and strength of the connections of ACMs for each ED type. Previously, our team, using the non-linear method, found a negatively skewed connection distribution for complex and repetitive spikes [18]. Similarly, our linear method yielded in negatively skewed connection distribution for the same types of ED; complex (skewness= -1.96; panel C) and repetitive= -1.16; panel D), reflecting a higher number of strong connections due to spike activity in the EEG segments for these two types of ED.

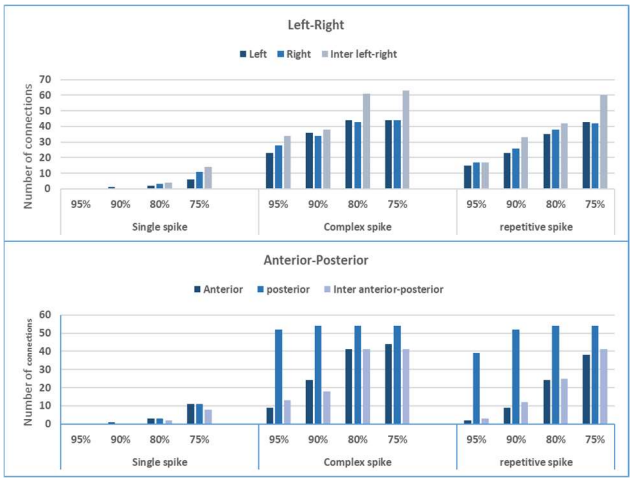

Fig 5. The quantification comparison of 3 types of ED for the main brain regions.

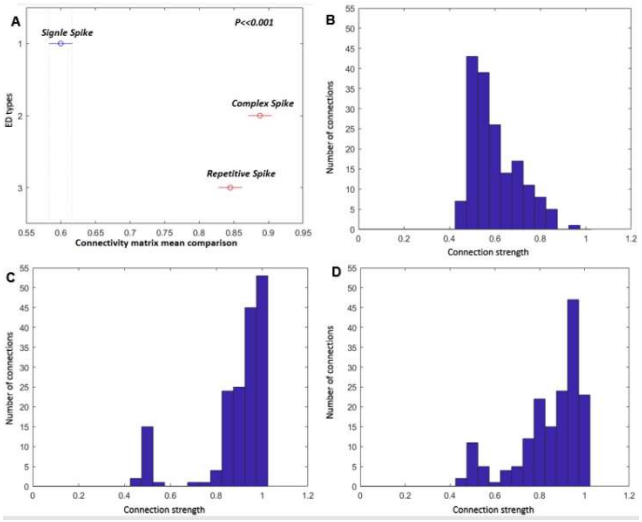

Fig. 6. Panel A indicates multiple comparison between 3 epileptiform discharge (ED) types. There is no overlap between single spike and complex or repetitive spikes. Panel B (single spike), C (complex spike), & D (repetitive spike) indicate histogram of average connectivity matrices (ACMs) for 3 ED types.

IV. CONCLUSION

Using functional connectivity patterns, this study used a new method to ascertain through interictal scalp EEG data only if the seizure is focal or generalized. The scalp EEG segments that were analyzed contained three different types of ED characterizing focal (single spike) and generalized epilepsy (complex & repetitive spikes). Connectivity patterns are extracted using a linear procedure to assess the maximum fluctuation of electrodes synchronously following the 10-20 system.

The number of connections in four major regions of the brain (i.e., Left & Right hemisphere, Anterior & Posterior sides) were used to assess the resulting connectivity maps. In line with our team's previous study using a non-linear procedure [19], we found significant differences between the single spike and the other two spikes (complex and repetitive), supporting the notion that higher global connections are observed in generalized epilepsy compared to the more local and weaker connections that were observed in focal epilepsy. These findings suggest that the different distributions of the connectivity patterns and the strength of the connections are associated with the types of epilepsy. Our findings revealed that interictal EEG segments could be considered as one of the key indicators for the diagnosis of focal and generalized epilepsy. With the asymmetry in patterns found in focal epilepsy, it would be interesting to investigate this further, to see if this asymmetry relates to the 3D source of the epileptogenic focus [20].

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