Dynamics of Electrical Activity in Epileptic Brain and Induced Changes Due to Interictal Epileptiform Discharges

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ABSTRACT Background: Understanding functional connectivity (FC) patterns of epileptic brain networks as they relate to the presence or absence of interictal epileptiform discharges (IEDs) can enhance machine learning (ML) algorithms identifying them. Methods: Changes in brain dynamics induced by the presence of IEDs are demonstrated by constructing FC maps from scalp electroencephalography (EEG) data. The intent is to demonstrate how unique IED characteristics present in the FC maps could be useful in training ML algorithms to yield an effective IED detection process. Results: a) The active frontal-temporal (FT) region as predetermined by the neurologists during an IED segment is found to be characterized by a statistically significant increase in the average local FC over the other FT region and over FT regions with the highest average local FC when using non-IED (NIED) segments of the same patient. This statistical significance is found for the theta, alpha, and beta sub-bands. b) Distant connections coupling one region to another also show a statistically significant difference between IED and NIED segments. Depending on the IED morphology, the significant sub-band matching those findings differs from patient to patient. Hence, while the theta sub-band results in the highest area under receiver operating characteristic curve (ROC-AUC) among the rest, it is still important to include features of other sub-bands since together they yield even higher ROC-AUC. Conclusions: FC maps intrinsically reflect the significant changes occurring in the dynamics of the epileptic brain. The obtained results provide added confidence in utilizing FC maps as biomarkers for detecting IEDs.

INDEX TERMS Scalp EEG, functional connectivity, weighted phase lag index (wPLI), interictal epileptiform discharge (IED).

I. INTRODUCTION

Epilepsy is one of the major brain disorders affecting more than 64 million people worldwide out of which 3.4 million reside in the US. Of this population, it is reported that 30% to 40% do not benefit from any available treatment and continue to suffer recurring seizures which can cause serious consequences that are not limited to physiological dysfunction and neuronal death [1]. According to the Centers for Disease Control and Prevention (CDC), seizures are grouped into two broad categories, namely generalized seizures that affect both brain hemispheres and focal seizures that are located in just one area of the brain. Scalp electroencephalography (EEG) remains to be the most prevalent recording modality utilized for the diagnosis of epilepsy. This is due to its cost-effectiveness, simplicity as well as its non-invasive...
nature. Stereo-EEG (SEEG) and intracranial EEG (iEEG) are more invasive recording modalities that offer higher spatial resolution. In general, due to its high temporal resolution, EEG comes with the advantage of exploring the evolution of brain electrical dynamics over the course of time. This led to using EEG as a biomarker in classifying several brain disorders such as schizophrenia for instance [2]–[4].

A wide variety of functional connectivity (FC) methods introduced in the literature provide quantitative estimates of the inter-areal synchronization of neuronal oscillations. Although FC analysis has not yet been clinically adopted, the information revealed by FC maps are in some instances not visibly identifiable from raw EEG data. Due to the challenging state of randomness of seizure activity within an epileptic brain, FC maps produced by interictal epileptiform discharges (IEDs) can prove to be beneficial in bringing our attention to a specific region of interest. Such maps can play a critical role in defining an epileptogenic network that could augment the prospects for localizing the 3-D source more accurately. Frequency-based FC methods provide more information regarding the synchronization within specific frequency sub-bands, information that augments time-based FC methods. In this study, we analyze scalp EEG FC maps for focal epileptic patients within the four standard frequency sub-bands, namely delta (δ) (0.5–4 Hz), theta (θ) (4–8 Hz), alpha (α) (8–13 Hz), and beta (β) (13–30 Hz). Although some studies have relied on high frequency oscillations (HFOs) (>80 Hz) as biomarkers of epilepsy that can be detected non-invasively [5], [6], there are empirical evidences suggesting that the gamma frequency range (30–48 Hz) is prone to strong muscular artifact for scalp EEG [7] in addition to its low reliability graph metrics [8]. Hence, the gamma sub-band is excluded in this study.

In a previous study by our research group [9], IED FC maps of 20 epileptic patients were analyzed using a wide-band data-driven recurrence-based method. This method is defined as the correlation between probabilities of recurrences (CPR). The brain was divided into six regions, namely Left/Right Frontal (LF/RF), Left/Right Temporal (LT/RT), and Left/Right Parietal/Occipital (LP-LO/RP-RO). The 19 scalp electrodes were also grouped based on the region they are connected to. Both the average local FC within each region as well as the distant connections coupling one region to another were investigated. In this study, we follow a similar approach with the following set of distinctions: i) For the IED segments, we investigate the statistical significance of the hypothesis suggesting an increased local connectivity within the active region that is predetermined by the neurologists. Significant results were achieved in each of the θ, α, and β bands. ii) To build on the findings reported in i, non-IED (NIED) segments with artifacts were extracted from the same patients. In those segments, the active region was defined as the region with the highest local connectivity. The average local FC of the active region for the IED segments were found to be significantly higher. iii) The density of distant connections coupling the active region to the neighboring regions is also found to be statistically higher for the IED group compared to the NIED group. iv) Based on the findings in i, ii, and iii, such FC-maps-extracted features are used to train artificial neural networks (ANNs) for the detection of IEDs. The performance of the proposed architecture outperformed the one in [10] in terms of the area under receiver operating characteristic curve (ROC-AUC) metric. Several spike and seizure detection algorithms have been reviewed in the literature [11]–[19]. In the early phase of developing such algorithms, several morphological features (such as rising/falling edges) along with EEG-segment statistics (such as mean of peak values) were used in rule-based algorithms for the detection of spikes. To cite a few, context-based detection was used in [20], Walsh transform in [21], wavelet transform in [22], and mathematical morphology in [23]. More recently, several multi-step machine learning (ML) spike detection algorithms were used, among them random forest [24], support vector machine [25], and clustering algorithms [26]–[28]. Convolutional neural networks (CNNs) and long short-term memory (LSTM) neural networks were deployed in [29] and [30] for detecting spikes in a supervised learning manner, respectively. However, the role played by FC maps in the detection of spikes has not been widely explored as reflected by the nature of the proposed study. v) We finally make some important conclusions from those findings and discuss the limitations as well as future research directions that we think are worth investigating given the results as currently obtained.

The rest of the paper is organized as follows: Section II presents the data collection and the required data preprocessing steps undertaken. Section III describes the methods implemented in relation to the weighted phase lag index (wPLI), true connectivity definition, thresholding, and in terms of what defines local and distant connections. The results are provided in Section IV. Finally, concluding remarks, limitations and suggested future research directions are given in Section V.

II. DATA PREPROCESSING

Scalp EEG recordings of 21 patients with focal epilepsy were collected from Baptist Hospital of Miami. Patients were told to be relaxed and avoid movement whenever possible during the recording session. The Institutional Review Board of Florida International University (protocol number: IRB-150247) approved the study process. Table I contains detailed information of the study population. Subjects are all adults ranging from 40 years to 80 years old. The ROI denotes the region of interest that is predetermined by the neurologists (the region mostly affected by the IED). All patients considered in this study present idiopathic condition due to their magnetic resonance imaging (MRI) scans appearing to be normal.

The 19-electrode recordings were based on the 10–20 international placement montage with different sampling frequencies of 512, 256, and 200 samples per second. Channel Cz was used as the reference throughout the recording process. Two
TABLE 1. Patients' information.

| Patient ID | Gender | Sampling Rate (Hz) | ROI | # IED Segments / # NIED segments |
|------------|--------|--------------------|-----|----------------------------------|
| P1         | M      | 512                | RPT | 5 / 5                            |
| P2         | F      | 512                | LPT | 6 / 6                            |
| P3         | F      | 200                | LPT | 6 / 6                            |
| P4         | M      | 512                | LPT | 5 / 7                            |
| P5         | F      | 200                | RPT | 9 / 9                            |
| P6         | M      | 512                | L/R FT | 10 / 10                         |
| P7         | F      | 256                | RPT | 5 / 7                            |
| P8         | F      | 200                | RPT | 8 / 8                            |
| P9         | M      | 512                | RPT | 5 / 5                            |
| P10        | F      | 200                | LPT | 3 / 3                            |
| P11        | M      | 200                | LPT | 3 / 3                            |
| P12        | F      | 512                | RPT | 6 / 6                            |
| P13        | M      | 512                | LPT | 6 / 6                            |
| P14        | F      | 256                | RPT | 5 / 7                            |
| P15        | M      | 200                | RPT | 4 / 0                            |
| P16        | F      | 512                | LF  | 5 / 4                            |
| P17        | F      | 512                | LPT | 5 / 0                            |
| P18        | F      | 512                | LPT | 6 / 6                            |
| P19        | M      | 512                | RPT | 3 / 1                            |
| P20        | F      | 256                | L/R FT | 4 / 4                           |
| P21        | F      | 200                | RPT | 6 / 6                            |

types of segments were extracted for most of the patients: IED segments and NIED segments. The International Federation of Societies for Electroencephalography and Clinical Neurophysiology (IFSECN) categorizes IEDs into four groups, namely sharp waves, spikes, spike-wave complexes, and polyspike-wave complexes [31]. Since the study population consists solely of focal epileptic patients, we had mostly sharp waves and spikes reflected as the interictal epileptic activity in the IED segments. However, there were instances where spikes were followed by waves.

Data was preprocessed before segmentation to minimize the effects of unwanted noise. A 4th order Butterworth band-pass filter with 0.5-70 Hz passing frequency range was applied. The 60 Hz AC line noise was suppressed by a notch filter. The EEG datasets were re-referenced to average montage. Principal component analysis (PCA) and independent component analysis (ICA) were used for removing artifact contamination involving eye blink and jaw and muscle movements using EEGLAB software [32] for IED segments. The filtered EEG data were divided into 3-second segments as suggested by the neurologists for these segments to remain meaningful. IED segments were adjusted so that the IED peak is located in its middle, thus allocating the same range of time before and after the occurrence of the discharge.

III. METHODS

A. FUNCTIONAL CONNECTIVITY

A wide variety of FC measures along with their different applications are well reviewed in the literature [33]–[36]. FC methods between two time series, x and y, are broadly categorized into time-based and frequency-based methods. Time-based FC methods vary from the simple Pearson correlation coefficient to more sophisticated methods such as Granger causality, non-linear correlation coefficient, and the CPR method. These methods provide a scalar value that ranges from 0 (no FC) to 1 (full FC). On the other hand, frequency-based methods result into a vector, \( C_{xy}(f) \), of FC measures at frequency, \( f \), that ranges from 0 to \( f_s/2 \) Hz where \( f_s \) is the sampling rate. This makes it possible to evaluate the connectivity within each frequency sub-band, \( B \), as in [37]:

\[
C_{xy}^B = \frac{\int_{f_L}^{f_U} C_{xy}(f)df}{f_U - f_L},
\]

where \( f_L \) and \( f_U \) are the lower and upper frequency bounds of \( B \), respectively. wPLI is one of the most widely used frequency-based FC measures due to its reduced susceptibility to volume conduction and for its robustness to noise. The wPLI measure between signals \( x \) and \( y \) at \( f \) is obtained using the following equation [38]:

\[
wPLI_{xy}(f) = \frac{E\left|\mathcal{N}(X(f)Y^*(f))\right|}{E\left|\mathcal{N}(X(f)Y(f))\right|},
\]

where \( \mathcal{N} \), \( E[.] \), \( \mathcal{N}[.] \), and \( * \) represent the absolute, expectation, imaginary part, and the complex conjugation, respectively. \( X(f) \) and \( Y(f) \) are frequency representations of \( x \) and \( y \), respectively. To empirically evaluate the above formula, the 3-second segments are divided into a sufficiently large number of overlapping windows, \( N \), each of length \( l \), with the constraint of having a minimum of 30 windows [38] to avoid large estimator bias [39]. Hence, \( X(f) \) in eq. (2) is replaced by \( X_n(f) \) which is the Fast Fourier Transform (FFT) of the \( n^{th} \) window of \( x \). Similarly, \( Y(f) \) is replaced by \( Y_n(f) \), while \( E[.] \) would be replaced by \( \frac{1}{N} \sum_{n=1}^{N} \).

For our MATLAB implementation, \( N = 68, 54, \) and 50, and \( l = 1000, 556, \) and 453 samples were used for \( f_s = 512, 256, \) and 200 Hz, respectively. Once \( wPLI_{xy}(f) \) can then be computed through eq. (1). This is done for each pair of electrodes separately.

B. THRESHOLDING TECHNIQUE

A 3-step thresholding technique is proposed as such:

1) In [40], it was mentioned that connectivity values between 0.5 and 0.6 indicate the start of a link establishment between two entities. Thus, a minimum threshold level is set. In our setting, we fix the minimum threshold to be 0.75.

2) If thresholding relies solely on the minimum level set in the previous point, there would be instances with a huge portion of FC values surpassing this minimum level. Hence, an adaptive threshold needs to be introduced in order to eliminate the existence of such peculiar high background activity. A threshold is set to consider almost one-forth of the existing connectivities given
that this threshold is already above the minimum specified level.

3) To get a sense of whether the calculated FC represents actual coupling between x and y, we estimate the probability of true FC between them. This estimation is carried out first by generating multiple surrogates with \{x_1', x_2', ..., x_M\} and \{y_1', y_2', ..., y_M\} being the surrogates of x and y, respectively. wPLI values among the surrogates ((wPLI_{x_i'y_i'}'(f), wPLI_{x_i'y_i'}'(f), ..., wPLI_{x_i'y_i'}'(f))) are computed according to eq. (2). From those, we compute \{wPLI_{x_i'y_i'}^B, wPLI_{x_i'y_i'}^B, ..., wPLI_{x_i'y_i'}^B\} as given by eq. (1). The proportion of the M computed surrogate FC values below wPLI_{xy}^B approximates the probability of true FC between x and y, \(TC_{xy}^B\). That is, the complementary proportion represents the probability of having false positives [41]. The mathematical representation for the above explanation is given as follows:

\[
TC_{xy}^B \approx \frac{\sum_{i=1}^{M} I_i}{M}, \quad \text{where,}
\]

\[
I_i = \begin{cases} 
1, & \text{if } wPLI_{xy}^B > wPLI_{x_i'y_i'}^B \\
0, & \text{otherwise} 
\end{cases}
\] (3)

As M gets larger, the estimate of the true \(TC_{xy}^B\) measure becomes more accurate. For optimal results, surrogate signals should have the same spectral properties as those of the original signals [42]. One of the simplest ways to generate a surrogate signal is to shuffle the phases in the frequency domain while maintaining the spectral shape of the original signal. In our implementation, M is set to 500. Only connectivities with corresponding \(TC_{xy}^B\) above a certain level (0.95) are considered.

**C. LOCAL & DISTANT CONNECTIONS**

In this study, we follow an approach similar to the one introduced in [9] where the electrodes are divided into groups according to the brain lobe they are connected to. The ROIs referred to in Table 1 are divided as shown in Fig. 1. After applying the thresholding methodology described in the previous subsection, the average local FC within each of the four defined regions as well as the distant connectivity coupling one region to another is calculated. The average local FC within a specific region is defined as the number of available connections divided by the total number of possible connections. Distant connectivity is computed similarly.

**IV. RESULTS**

**A. ILLUSTRATIVE EXAMPLES**

For the IED segments, we define the active frontal temporal (AFT) region to be either the RFT or LFT matching the ROI referred to in Table 1. The active central parietal occipital (ACPO) corresponds to the set of electrodes attached to the central/parietal/occipital region of the same hemisphere as the AFT. Inactive frontal temporal (IFT) and inactive central parietal occipital (ICPO) correspond to the set of electrodes attached to the other hemisphere. For example, if the ROI in an IED segment happens to be the RFT, then the correspondence goes as follows: AFT \(\rightarrow\) RFT, IFT \(\rightarrow\) LFT, ACPO \(\rightarrow\) RCPO, and ICPO \(\rightarrow\) LCPO. In Fig. 2, the FC maps shown on the left side are generated according to the proposed methodology from the IED segment of patient P10 shown in Fig. 2i for the different frequency sub-bands. Circled in blue are the electrodes attached to the LFT region that happens to be the ROI as determined by the neurologists; i.e. AFT. In Fig. 2g for instance, it is quite obvious that the average local FC within the AFT is higher than that within the IFT of the same segment. It also happens to be higher than that within the AFT region in Fig. 2h. We consider the RFT in Fig. 2h to be the AFT since its average local FC is higher than that of the LFT. However, this is considered to be a misnomer due to the fact that no region can be affected by missing IEDs in NIED segments. Hence, no blue markings are added to the maps on the right side that correspond to the NIED segment of the same patient shown in Fig. 2j. Moreover, stronger coupling between the left and right hemispheres is observed in Fig. 2e as compared to Fig. 2f.

Similarly, presented in Fig. 3 are also different FC maps for patient P8. While we observed how the \(\beta\)-band FC map in Fig. 2g resulted in high average local FC within the AFT (LFT for patient P10), the \(\theta\)-band FC map in Fig. 3c better emphasizes the AFT (RFT for patient P8) compared to the \(\beta\)-band shown in Fig. 3g. Thus, we can conclude that the significant frequency sub-band differs from patient to patient. In other words, the significant sub-band is inconsistent. It is believed that the morphology of the IED plays an essential role in the determination of the significant sub-band. For instance,
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FIGURE 2. FC maps for IED and NIED segments for patient P10.

channels Fp2 and F4 in the segment shown in Fig. 3i are not connected in the high frequency $\beta$-band (Fig. 3g) but rather in the high power $\theta$-band. While the summation of the $\theta$-band power in channels F7 and T3 is also higher than that of the $\beta$-band in the segment shown in Fig. 2i, their $\beta$-band power ratio is higher compared to that of channels Fp2 and F4 in Fig. 3i ($0.0124$ vs. $0.0096$). This might provide an explanation for the $\beta$-band FC map becoming more significant for patient P10 as compared to P8.

Finally, in Fig. 4, three segments are shown for patient P6 with bilateral epilepsy. The FC maps on the left column are generated for the segment shown in Fig. 4m where the left source is active. On the other side, Fig. 4o shows another segment for the same patient where the right focus is active. The middle column FC maps correspond to an NIED segment of the same patient shown in Fig. 4n. The same set of observations made in Fig. 2 discussion are also applicable here. For example, it can be clearly observed how the blue marked electrodes (representing the AFT) in Fig. 4j and Fig. 4i are characterized by an increased average local connectivity compared to the IFT. Moreover, the density of connections within those AFTs is higher than the density of connections within the left and right hemispheres in Fig. 4k and Fig. 4h. Finally, the stronger coupling between the left and right hemispheres during the IED segments (with left or right source active) compared to NIED segments is evident from the presented FC maps. All these individual observations are validated through statistical tests shown in the following subsection.

B. STATISTICAL ANALYSIS

Several studies were found in the literature suggesting the increase in the average local FC in the region most affected by the IED compared to other regions. This is in agreement with one of our findings in the previous subsection. To examine the generality of these findings, we ran statistical independent t-tests on the available data. First, we test the hypothesis that for a specific IED segment, the average local FC within the AFT is higher than that within the IFT. Each of the theta, alpha, and beta sub-bands yield significant results with p-values of $0.00249$, $< 0.001$, and $0.0037$, respectively. Only the delta range did not yield statistical significance (p-value $= 0.245$).

We also examined the existence of disparity between the average local FC within the AFT of an IED segment as compared to an NIED segment which might also serve as potential biomarker for spike detection. Hence, in our Second hypothesis test, it is found that the average local FC of the AFT of IED segments is significantly higher than those of NIED segments belonging to the same patients. The acquired p-values for the delta, theta, alpha, and beta sub-bands are $0.1066$, $0.001483$, $< 0.001$, and $0.01128$, respectively and therefore, as in our First test, only the delta band does not yield a p-value less than 0.05.

To emphasise more on the disproportions in the graph structure resulting from the FC analysis between IED vs. NIED segments of a certain patient, we test our Third hypothesis regarding the discrepancy among distant connections. We first investigated the distant connections involving the AFT region; i.e., AFT-IFT, AFT-ACPO, and AFT-ICPO.
It is found that for the theta, alpha, and beta sub-bands (sub-bands yielding statistically significant results in the First test), distant connections in the IED segments were significantly higher than those in the NIED segments with p-values < 0.007. This also corresponds with the finding in the previous subsection and with the established fact that IEDs propagate in a network fashion emerging from the active region to the neighboring ones. Other distant connections not including the AFT region were also found to be significantly higher in IED segments with p-values < 0.011.

C. ARTIFICIAL NEURAL NETWORKS (ANNs)

In the previous subsection, it was statistically shown that the graphs created by the FC analysis are highly affected by the presence of epileptogenic activity. Hence, we train ANNs using the ten FC-maps-extracted features (AFT, IFT, ACPO, ICPO, AFT-IFT, AFT-ACPO, AFT-ICPO, IFT-ICPO, ACPO-ICPO) to detect IED segments using the data shown in Table 1 in an inter-patient fashion. Due to lack in abundance of data, the training was done in a 5-fold cross validation manner where the 21 patients were randomly distributed among five groups as such:

1. P7, P10, P12, P15, P21 → g1 [24 IEDs + 20 NIEDs]
2. P3, P9, P13, P16 → g2 [22 IEDs + 21 NIEDs]
3. P4, P8, P17, P18 → g3 [24 IEDs + 19 NIEDs]
4. P2, P5, P14, P19 → g4 [23 IEDs + 21 NIEDs]
5. P1, P6, P11, P20 → g5 [22 IEDs + 22 NIEDs]

Training was done using Pytorch Lightning [43], a deep learning framework that organizes Pytorch code such that the research and engineering codes are decoupled. Leaky rectified linear unit is used as the activation function for all layers except for the output neuron where sigmoid activation function is used instead. Adam optimizer was used with a learning rate of 0.0001 [44]. The highest ROC-AUC is reported for the different neural network (NN) architectures shown in Table 2 using early stopping.

To better understand the role played by the different frequency sub-bands in the detection process, a separate multilayer perceptron (MLP) is trained using the ten features of each frequency sub-band independently. The following MLP architecture was used when training using a single frequency sub-band: 5 layers with sizes 10 (input layer), 8, 4, 2, and 1 (output layer). The \( \theta \)-band resulted in the highest average validation ROC-AUC (0.8516) as shown in Table 2. However, as discussed in subsection A, the significant frequency sub-band varies from patient to patient. Hence, it is expected that feeding the MLP with extra features extracted from other frequency sub-bands would enhance the performance. Therefore, another MLP (FC-NN\textsubscript{Dense} in Table 2) is trained with 40 inputs (4 frequency sub-bands \( \times \) 10 features/sub-band). The problem with such an architecture is its susceptibility to overfitting due to the existence of a relatively large number of weights in the first hidden layer, especially when training using a relatively small dataset like the one at hand. This is due to the high-dimensionality of the input layer. Table 2 shows that the associated average validation ROC-AUC is 0.8376 which is worse than that of the MLP fed by the \( \theta \)-band features only (0.8516).
FIGURE 4. FC maps for IED and NIED segments for patient P6. (2-Column).
TABLE 2. Validation ROC-AUC scores for the 5 groups of patients.

| Group | FC-NN_{δ} | FC-NN_{θ} | FC-NN_{α} | FC-NN_{β} | FC-NN_{Dense} | FC-NN_{Pruned} | ML-NN_{Dense} | ML-NN_{Drop} |
|-------|-----------|-----------|-----------|-----------|---------------|----------------|---------------|--------------|
| g1    | 0.7521    | 0.8385    | 0.7042    | 0.851     | 0.8323        | 0.8479         | 0.6854        | 0.7812       |
| g2    | 0.7716    | 0.8485    | 0.7352    | 0.8485    | 0.8323        | 0.8918         | 0.7619        | 0.8745       |
| g3    | 0.7686    | 0.8059    | 0.8432    | 0.7939    | 0.8377        | 0.8871         | 0.5417        | 0.6687       |
| g4    | 0.7143    | 0.8685    | 0.7681    | 0.6056    | 0.8075        | 0.8768         | 0.7055        | 0.7688       |
| g5    | 0.8058    | 0.8967    | 0.7862    | 0.8833    | 0.8781        | 0.8998         | 0.9618        | 0.9091       |
| Avg.  | 0.7625    | 0.8516    | 0.7711    | 0.7969    | 0.8376        | 0.8807         | 0.7313        | 0.8005       |
| Std. Dev. | 0.0333 | 0.0339 | 0.0506 | 0.1118 | 0.0255 | 0.0201 | 0.1523 | 0.0949 |

FC-NN: FC-based NN, ML-NN: Multi-level NN

To resolve the overfitting predicament, a structured pruning technique is introduced that substantially reduces the number of weights in the first hidden layer. Rather than dealing with the first hidden layer as a dense layer, it is divided into sub-layers of two kinds: Sub-band encoder sub-layers and features encoder sub-layers. Each frequency sub-band ($\delta$, $\theta$, $\alpha$, and $\beta$) has its own encoding taking into account only the features of that specific frequency sub-band FC map as depicted in Fig. 5. Moreover, each feature is encoded by combining the values of that feature from the different frequency sub-bands through the feature encoding sub-layer. The output from all sub-layers is concatenated together to form the first hidden layer which is then forwarded through the rest of the MLP. In our setting, each sub-layer is represented as a single neuron. This pruning technique results in a significant decrease in the number of trainable parameters...
in the whole neural network (167 vs 377). Dropout layers were also added since they resulted in an observed increase in the average validation ROC-AUC. The resulting regularized neural network showed a significant increase in its average validation ROC-AUC (0.8807).

1) COMPUTATIONAL COMPLEXITY
Since the method relies on frequency-based FC analysis, the complexity of the algorithm is dominated by the FFT which is a rather fast operation. Since \((M + 1) \times N\) FFT operations of length \(l\) are performed, the computational complexity is \(O(MNl \log l)\). However, for a fixed EEG segment length (3 sec), \(M\) would be the only variable parameter dominating the computational process. Note that no hyperparameter tuning was carried out for the whole FC analysis process, e.g., the thresholding technique described in Section III, which could possibly yield better results than the reported (0.8807).

Finally, we compare the performance of the proposed FC-based NN with that of an existing approach described in [10] which we call Multi-level NN (ML-NN). This is one of the early approaches to detect epileptogenic spikes. In brief, the algorithm consists of two NN modules (hence the name Multi-level) detecting spikes in a sliding window of 100 msec. The first module (NN1) generates the encoding of each EEG channel separately from the given 100 msec samples of that channel. Note that the same module is used to generate the encoding for all channels. The second module (NN2) is then used to integrate those encodings together to finally detect the existence of a spike in the processed window. Sampling rates for all patients are brought down to 200 samples/sec as described in the study. This reduction in the number of unnecessary features helps in regularizing the model. As that study consisted of EEG of only 16 channels, we started with the suggested setting and then finely tuned the model to report the highest achieved validation ROC-AUC. During validation, spike peaks are centered in the middle of the window and the whole 3-second IED segment is set as True Positive (TP) or False Negative (FN) depending on the output of the ML-NN. An NIED segment is set as True Negative (TN) only if ML-NN fails to detect any IED in all of its windows. Otherwise, it is set as False Positive (FP). ML-NN\textsubscript{Dense} in Table 2 shows the results of the described setting with NN1 consisting of 21 input, 7 hidden, and 1 output neuron. NN2
consists of 19 input (number of channels), 7 hidden, and 1 output neuron. This setting resulted in a higher validation ROC-AUC than with 8 hidden neurons as described in [10]. Tuning the model further, input normalization, Dropout layer in NN1, and batch normalization [45] in NN2 were found to yield higher validation ROC-AUC as shown in Table 2 (ML-NN\textsuperscript{Drop}). Fig. 6 shows the described architecture. However, as can be observed FC-NN\textsubscript{Pruned} yielded a higher average validation ROC-AUC (0.8807 vs 0.8005) with less variance on the same dataset.

2) CLINICAL IMPLICATIONS
The goal of building a robust IED detector is to decrease the methodical selection biases that have limited the applicability of manual spike detection protocols to clinical practice. Also, this enhanced detector can assist physicians to investigate the spatial-temporal propagation patterns of interictal spikes since they constitute the main biomarker of epilepsy, yet their precise location and propagation within the epileptic cortex are poorly understood. Even in cases where these networks seem to be localized to one particular area, resection of the predicted irritative zone may not result in seizure freedom. Mapping these EEG events prior to epilepsy surgery is critical for detecting the epileptogenic zone in order to achieve post-surgical seizure control.

Moreover, this approach may allow clinicians to incorporate the location, extension and propagation of the epileptic network into the pre-surgical evaluation. Also, another clinical benefit of our research is that it is based on the interpretation of interictal spikes and not seizures that are characterized by their severe randomness and unpredictability. Improved understanding of spike propagation networks can lead to an optimal prediction of the epileptogenic zone.

V. CONCLUSION
In this study, we proposed a technique to investigate FC network analysis for scalp EEG of patients with temporal lobe epilepsy (TLE). Both IED and NIED segments are extracted and the following observations are made based on the results of the performed statistical tests: First, the most active region with the highest density of connections within an IED segment tend to be the one affected by the IED for the theta, alpha, and beta frequency sub-bands. Second, and more importantly, a disproportion exists between the FC graph frameworks of the IED vs NIED segments. These findings conform with the revised literature suggesting the existence of the so-called epilepsy-specific brain networks [46], [47] that are essential for understanding the mechanisms underlying the electrical activity within focal epileptic brains. For instance, it was found that the epileptogenic zone (EZ) as well as the propagation zone are characterized by higher within-zone FC as compared to the non-involved zone [48]. Strong interictal coupling was also observed between the epileptogenic zone and propagation zone using SEEG. Finally, it was found that patients with high local connectivity within the non-involved zone generally have poorer post-surgical outcomes. It was also found in [49] that greater overlap between electrodes falling within the resection zone and highly synchronous electrodes is associated with favorable post-surgical outcomes. Good-outcome patients have significantly higher connectivity localized within the resection zone compared to those with poorer postoperative seizure control. Finally, the MLP trained by the features of the $\theta$-band FC maps showed the highest validation ROC-AUC. The importance of the theta rhythm as an epileptic biomarker has been hinted at in previous studies [50]–[53]. However, including features corresponding to other sub-bands increases the attained validation ROC-AUC. This is believed to be due to the inconsistency of the significant sub-band among different patients depending on the IED morphology. To the best of our knowledge, the usage of FC analysis in training any ML algorithm for the purpose of detecting interictal spikes was not reported in the literature.

A. LIMITATION
In a typical setting, IED detection is performed using two steps: First, a rule-based detector is placed to collect IEDs. Morphological features of discharges such as the rising and falling edges, among others are typically used in that rule-based detector. This detector should have high sensitivity to collect all IEDs, and hence many false positives are also detected, i.e., highly unbalanced dataset. Second, the discharges detected by the rule-based detector triggers a machine learning algorithm whose job is to distinguish actual IEDs from the false positives and other artifacts. While the available data was sufficient to successfully perform the statistical tests mentioned above to provide insights on patterns of FC maps, it is however considered to be limited to build, train, and deploy a reliable IED-identification system as in a typical clinical setting. Nevertheless, we decided to train small neural networks to give further insight regarding the use of FC maps to detect IEDs with the available hand-picked segments. The main reason for choosing to compare our method with that described in [10] specifically was that it followed a similar training approach on selected discharges of IEDs and artifacts. This explains why the available dataset does not suffer the high unbalance issue. The comparison results however, conform with the results of the statistical analysis in shedding light on the potential benefit FC maps can provide. Hence, further investigation in this direction should be carried out.

B. FUTURE WORK
The findings of this study suggest that Graph Neural Networks (GNNs), as a potential deep learning architecture, can be successful in the task of IED detection due to their ability to exploit this inherent characteristic of disproportionality in the graph structures of IED and NIED segments. GNN-based architectures are recently gaining great attention due to their ability to deal with the complex graph data structures. What makes GNNs very adept at handling graph structures is the fact that they are order invariant, where only the features of the nodes are taken into consideration without any attention.
Another application of concern for the purpose of IED detection is graph classification where the input to the GNN is the FC graph along with possibly some node features and the output would be the label of the graph. An example of node features might be the power present in each of the frequency sub-bands. A recent study [54] followed a similar approach where the gender of an individual was identified by utilizing graph isomorphism network (GIN) [55] applied on resting-state functional MRI (rs-fMRI). Such GNN-based architectures could potentially be deployed in future studies on raw EEG data without any hand-crafted features, but the reliability of the results is strengthened only if a relatively large amount of available data is used in the training phase.

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