Penalized Functional Connectivity Maps for Patients With Focal Epilepsy

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ABSTRACT Objective: This study demonstrates how functional connectivity (FC) patterns are affected in direct relation to the lobe that is mostly affected by seizures. Methods: The novel idea of penalized FC (pFC) maps is compared against standard FC maps in the four fundamental EEG frequency sub-bands. The FC measure between any two specific electrodes is scaled depending on the probability of true FC between them, and their power content with respect to the two electrodes of maximum power within each frequency sub-band. The algorithm is automated and introduces adaptive power penalization based on the power distribution of the different sub-bands. Results: The pFC maps were found to be more effective at suppressing the local connectivity in the lobes that are less affected by the interictal epileptiform discharges (IEDs). More precisely, given the least amount of power penalization, pFC maps of the theta sub-band reveal statistical significance in terms of increased local connectivity margin of the affected region as compared to the standard FC maps. However, they cannot be solely relied upon as other sub-bands could alternatively show high local connectivity across different patients within the region of interest. Conclusion: penalized functional connectivity maps intrinsically provide more information regarding the whole brain network in context to regions of interest where the active lobe is determined by the neurologists to contain the focal source. Significance: Findings suggest that (1) the significant sub-band varies from patient to patient while remaining relatively consistent within the IED segments of a same patient, and (2) the pFC maps have an advanced capability in terms of pinpointing to a region of interest of the active lobe, and as such can play a critical role in providing insight as to a region of interest where the 3D source might be located when solving the ill-posed inverse problem.

INDEX TERMS Focal epilepsy, interictal epileptiform discharges (IEDs), penalized functional connectivity (pFC), penalized weighted phase lag index (pWPLI).

I. INTRODUCTION
Epilepsy is a chronic brain disorder characterized by seizures of different severity. Mainly due to abnormal neuronal activity, seizures could lead to loss of consciousness, convulsion, blurred vision, numbness, and other unforeseeable emotional and physical changes [1]. According to the Epilepsy Foundation, epilepsy affects 65 million people worldwide and 3.4 million in the US. Just over 30% of the people who have epilepsy suffer uncontrollable and recurring seizures with no available treatment, and not benefiting from any existing medication. According to the CDC, epilepsy accounts for about $15.5 billion in direct costs (medical) and indirect costs (lost or reduced earnings and productivity) each year.

These seizures are perceived as ictal activity categorized into two groups, namely focal and generalized seizures [2]. A generalized seizure ensues when the sources initiating the ictal activity are distributed among the two brain
hemispheres, while a focal seizure is characterized by having a single source located in one of the hemispheres. Focal seizures are the more dominant type as they occur in 60% of patients with epilepsy.

Although not all seizures are due to epilepsy, an initial diagnosis of epilepsy through scalp electroencephalography (EEG) in patients is made only with the advent of seizures or ictal activity. Scalp EEG is an efficacious recording modality due to its simplicity, cost-effectiveness as well as its non-invasive nature. Other invasive recording modalities such as intracranial electroencephalography (iEEG) or stereo-electroencephalography (SEEG) become useful for validating ultimately such initial findings prior to surgical planning with improved accuracy in localizing the 3D source [3–6]. Several studies were conducted to automate the detection of epileptic seizures [7], [8] that were further used to localize the seizure onset zone (SOZ) [9] using ictal high-density EEG (HDEEG). Both the SOZ as well as the irritative zone (IZ) were localized using electric source imaging (ESI) on intracranial EEG (iEEG) for children with focal cortical dysplasia (FCD) [10]. Recently, in [11], it was hypothesized that synchronously-acquired HDEEG along with magnetoencephalography (MEG) can capture the epileptogenic zone with greater accuracy. However, due to the severe randomness and unpredictable nature of ictal activity as well as its possible contamination by muscular artifacts [12], it is of utmost importance to examine the electrical patterns in between seizures in which interictal epileptiform discharges (IEDs) might occur. These IEDs, which are often seen as a precursor to seizures, can be extremely beneficial in establishing the epileptogenic network. Even the multiple spatially distinct spike populations that might co-exist in the same patient were investigated recently in [13] using iEEG and were found to localize the seizure onset.

In the Fourier domain, spectral characteristics of the standard EEG frequency sub-bands, namely delta (δ) (0.5–4 Hz), theta (θ) (4–8 Hz), alpha (α) (8–15 Hz) and beta (β) (13–30 Hz) have been extensively used as input features for the different interictal spike detection and classification algorithms such as Support Vector Machine (SVM) and Artificial Neural Network (ANN) [14]–[20]. We note that in this study as well as others [21], the gamma sub-band (30–48 Hz) was excluded due to the presence of evidence suggesting that the gamma frequency range in scalp EEG recordings may be strongly affected by muscle artifact [22]. In addition, [23] reported that the gamma sub-band yields low reliability graph metrics. However, it should be noted that high frequency oscillations (HFOs) (> 80 Hz) are good biomarkers of epilepsy that can be detected non-invasively [24], [25]. Some studies make use of the online-available EEG datasets [26] that include recordings for both healthy and epileptic subjects [27] in the context of classification and spike detection. The idea was further developed by [28] where the classifier was tested with varying sets of frequency sub-bands other than the four fundamental ones. Power spectral density analysis showed a significant power decrease in the θ-band for a group of patients with drug-resistant mesial temporal lobe epilepsy (MTLE group) as compared to patients with non-MTLE (NMTLE group) [29]. Although functional connectivity (FC) analysis has not yet been adopted in clinical settings, the results obtained are promising, especially in terms of visualizing the choreography in the FC patterns in context to the location of the 3D source [30]. Such revealing information is not visibly identifiable nor can it be ascertained from the raw EEG data. Thus, the dynamics of the epileptic brain can be assessed not only within locally defined regions, but by considering as well the potential coupling in between different regions. These FC patterns prove to be beneficial in different aspects. For instance, the distinction of healthy population from benign epilepsy with centrotemporal spikes (BECTS) was carried out utilizing FC maps [31]. Also, changes in the FC maps of MTLE patients were investigated using the non-linear correlation (h²) method [32], [33] suggesting that they could serve well as biomarkers. In [34], it was found that the epileptogenic zone as well as the propagation zone are characterized by an increased localized connectivity compared to the non-involved zone. Additionally, in [35], interictal iEEG networks were evaluated to identify targets for surgical treatment. It was found that greater overlap between electrodes falling within the resection zone and highly synchronous electrodes is associated with favorable post-surgical outcomes. Moreover, good-outcome patients have significantly higher connectivity localized within the resection zone compared to those with poorer postoperative seizure control. Hence, there is evidence suggesting the need to introduce a functional connectivity technique that offers high prospects for situating the 3D source within the active region of interest, defining as a consequence the main objective of this study.

In a previous study [36] by our research group, wide-band FC maps of IEDs were produced by applying a data-driven recurrence-based method to estimate the phase synchrony among EEG electrodes. This method can also be defined as the correlation between probabilities of recurrences (CPR). The results of that study were based on the 19 channels in scalp EEG signals of the 10-20 standard EEG system. Those electrodes were divided into six separate local regions, namely Left/Right Frontal (LF/RF), Left/Right Temporal (LT/RT) and Left/Right Parietal/Occipital (LP-LO/RP-RO). The local activity within each region was calculated in addition to the distant connections coupling one region to another. Intrigued by the findings of this initial study, while taking into consideration the spectral characteristics of the EEG in the four frequency sub-bands, the challenge was to determine what other potential characteristics and what other method could potentially be used to yield more effective FC analysis and thus a more enhanced deliberation process.

We summarize the contributions made through this new study as follows:  

1. We propose a novel method that incorporates the power content, functional connectivity, and the probability of this connectivity being true between any considered pair of electrodes in a single quantitative measure.
This finally leads to building what we termed as penalized FC (pFC) map of the brain. These pFC maps are more likely to yield higher margin of local connectivity within the electrodes attached to the active lobe as predetermined by the neurologists. The assumption here is that the connectivity between the considered pair is scaled by their power proportion with respect to the electrodes of maximum power within a specific frequency sub-band. We consider the weighted phase lag index (WPLI) method [37] as the basis for assessing the connectivity measure. Our choice for the WPLI is dictated by the facts that from empirical results, WPLI seems to be less sensitive to noise as well as its robustness to volume conduction effects. This idea can be extended to other measures such as phase lag index (PLI) [38], phase locking value (PLV) [39], mutual information [40], and Granger causality [41], among others. However, frequency-based methods are preferable as they provide more detailed information about the connectivity at different frequencies. ii) The introduced penalization technique is achieved through an algorithm that automates the generation of penalization factors for each IED segment and for each frequency sub-band independently rather than fixing a pre-defined factor. iii) Results of the proposed WPLI-based pFC maps, and WPLI-FC maps are presented in a comparative analysis to demonstrate the effectiveness of the pFC maps in revealing information that might be missed by the standard FC maps. To make the comparison completely fair, we use the same input segments in both methods. iv) We show that although there is a significant trend of decay in the average power across all electrodes as the frequency increases, the high-power δ-band can be misleading in terms of delineating the region of interest (ROI), while other less power-dominant higher frequency sub-bands achieve higher significance. v) Insights on distant connections coupling one lobe to another are also provided. Note: Throughout this article, we use the term “ROI” in reference to the active lobe determined by the neurologists to contain the focal source.

The rest of the paper is organized as follows: Section II presents the data-selection methodology as well as the preprocessing and segmentation procedures that were performed. Section III describes in detail the applied method. Results are shown in Section IV, and concluding remarks along with future research directions are provided in Section V.

II. DATA COLLECTION AND PREPROCESSING

In this study, the scalp EEG recordings of 20 patients were collected using the 10-20 standard EEG system. The 19 electrodes used for recording the EEG signals included Fp1, F7, T3, T5, O1, F3, C3, P3, Fz, Cz, Pz, Fp2, F8, T4, T6, O2, F4, C4 and P4. The different sampling frequencies used were 512, 256 and 200 Hz. All the signals were referenced with respect to channel Cz. Table 1 provides detailed information on the study population where the suspected lobes containing the epileptic foci were determined by neurologists at Baptist Hospital of Miami. For all the patients considered in this study, the origin of the condition is said to be idiopathic since their magnetic resonance imaging (MRI) scans appear normal. These are all adult patients ranging from 40 years to 80 years old. For this study, we consider only patients with focal epilepsy with the aim of highlighting the region of interest (active lobe) predetermined by the neurologists, a region that will ultimately be validated with higher spatial resolution in further analysis using either iEEG or SEEG.

The data was recorded at Baptist Hospital of Miami where subjects were told to be relaxed and avoid movement whenever possible during the EEG recording session. The Institutional Review Board of Florida International University (protocol number: IRB- 150247) approved the study process. The considered EEG data segments were those containing IEDs as marked by expert neurologists. IEDs are categorized by the International Federation of Societies for Electroencephalography and Clinical Neurophysiology (IFSECN) into four separate groups, namely sharp waves, spikes, spike-wave complexes and polyspike-wave complexes [42]. Sharp waves and spikes are generally associated with focal epilepsy. Since our study population consists solely of focal epileptic patients, we had mostly sharp waves and spikes reflected as the interictal epileptic activity, but there were specific instances where the spike was followed by a wave.

Data were 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. AC line noise was suppressed by a 60 Hz notch filter. The data sets are re-referenced to average montage. Artifact contamination involving eye blink, jaw and muscle movements are removed by applying principal component analysis (PCA) and independent component analysis (ICA) using EEGLAB software [43].

| TABLE 1. Patients’ information. |
|---------------------------------|
| Patient ID | Gender | Sampling Rate (Hz) | ROI | # IED Segments |
| P1         | F      | 512               | LT  | 6               |
| P2         | M      | 512               | RT  | 3               |
| P3         | M      | 512               | RT  | 5               |
| P4         | M      | 512               | RT  | 5               |
| P5         | F      | 512               | LT  | 5               |
| P6         | F      | 512               | RT  | 6               |
| P7         | F      | 512               | RT  | 4               |
| P8         | M      | 512               | LT  | 6               |
| P9         | M      | 512               | LT  | 5               |
| P10        | M      | 512               | LF  | 5               |
| P11        | F      | 256               | RF  | 5               |
| P12        | F      | 200               | LF  | 5               |
| P13        | M      | 200               | LF  | 3               |
| P14        | F      | 256               | RT  | 5               |
| P15        | M      | 200               | RF  | 4               |
| P16        | F      | 512               | LF  | 6               |
| P17        | F      | 200               | RF  | 8               |
| P18        | F      | 200               | RT  | 6               |
| P19        | F      | 200               | LF/LF | 6     |
| P20        | F      | 200               | LF/LF | 9     |

T: Temporal lobe, F: Frontal lobe, R: Right, L: Left
The filtered, artifact-free EEG data were divided into 3-second segments as suggested by the neurologist to be physiologically and computationally meaningful. Each segment was adjusted so that the spike peak is located in its middle, thus allocating the same amount of time before and after the occurrence of spike.

III. METHOD
A. MATHEMATICAL FOUNDATION
A wide range of available FC measures along with their varied application domains are well reviewed and presented in the literature [44]–[47]. FC methods between two time series, x and y, can be broadly categorized into time and frequency-based methods. The simplest time-based FC measure is the linear Pearson correlation coefficient. More sophisticated examples of time-based FC methods are the Granger causality, non-linear correlation coefficient, and the CPR method. These methods provide the FC measure as a scalar value ranging theoretically from 0 (no FC) to 1 (full FC).

A great advantage that frequency-based methods have over the time-based methods is that they provide the FC measure as a vector, \( C_{xy}(f) \), with each element representing the connectivity at a certain frequency, \( f \), that ranges from 0 to \( f_s/2 \) Hz where \( f_s \) is the sampling frequency. Thus, we can evaluate the connectivity within a specified frequency sub-band, \( B \), according to [48] as:

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

where \( f_L \) and \( f_U \) are the lower and upper frequency bounds of \( B \), respectively.

Among the proposed frequency-based FC measures is the WPLI that is given by [37]:

\[
\text{WPLI}_{xy}(f) = \frac{\left| \mathbb{E}\left[ \Re(X(f)Y^*(f)) \right] \right|}{\sqrt{\mathbb{E}\left[ |X(f)Y^*(f)|^2 \right]}}.
\]

where \( |.| \), \( \mathbb{E}[.] \), \( \Re\{\} \) and * represent the absolute, expectation, imaginary part, and the complex conjugate, respectively. \( X(f) \) and \( Y(f) \) are the frequency representation of signals \( x \) and \( y \), respectively. To compute the above formula empirically, the 3-second segments are divided into a sufficiently large number of overlapping windows, \( N \), with a constraint of having a minimum of 30 windows [37] to avoid large estimator bias [49]. 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 \( \mathbb{E}[.] \) would be replaced by \( \frac{1}{N} \sum_{n=1}^{N} \). In our implementation, we used \( N = 68, 54 \) and 50 and window length of 1000, 556 and 453 samples for \( f_s = 512, 256 \) and 200 Hz, respectively.

Our modification for the above formula has two substantial incentives:

\textbf{First Incentive:} a measure indicating the probability of having true FC between the signals has to be computed. This gives us a sense of whether the calculated FC value does indeed represent a true FC between the two signals or not, i.e., the computed FC value was not just achieved by mere chance. This can be done by generating multiple surrogates of the signals with \( \{x'_1, x'_2, \ldots, x'_M\} \) and \( \{y'_1, y'_2, \ldots, y'_M\} \) being the surrogates of \( x \) and \( y \), respectively. The WPLI among the surrogates \( \{\text{WPLI}_{x'y'}(f), \text{WPLI}_{x'y'}^B(f), \ldots, \text{WPLI}_{x'y'}^{M}(f)\} \) as well as the connectivity between the two original signals, \( \text{WPLI}_{xy}(f) \) are computed according to eq. (2). From those, we can then easily compute \( \{\text{WPLI}_{x'y'}^B, \text{WPLI}_{x'y'}^{x'M}, \ldots, \text{WPLI}_{x'y'}^{x'M}\} \) and \( \text{WPLI}_{xy}^B \) as given in eq. (1). The proportion of the \( M \) computed surrogate FC values that are above \( \text{WPLI}_{xy}^B \) is an approximate representation of the probability of true FC between \( x \) and \( y \), \( TC_{xy}^B \). That is, the complementary proportion represents the probability of having false positives [39]. The mathematical representation for the above explanation is given as follows:

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

where,

\[
I_i = \begin{cases} 1, & \text{if } \text{WPLI}_{x'y'}^B > \text{WPLI}_{x'y'}^B \text{ and } \text{WPLI}_{x'y'}^{x'M} \text{ and } \ldots \text{ and } \text{WPLI}_{x'y'}^{x'M} \text{ are all } \text{WPLI}_{xy}^B \\ 0, & \text{otherwise} \end{cases}
\]

The above expression holds true with equality as \( M \) tends to infinity offering higher confidence in evaluating this \( TC_{xy}^B \) measure. Surrogate signals should have the same spectral properties of the original signals. In fact, the more the surrogates resemble the original signal, the more accurate the results will be [50]. There are several methods for generating surrogates of a signal. A very simple way to generate a surrogate signal is by shuffling the phases in the frequency domain while maintaining the spectral shape of the original signal. \( M = 500 \) was used in our MATLAB implementation.

\textbf{Second Incentive:} it should be noted that the FC map is calculated by computing the FC of the signals coming from every two electrodes among the 19 electrodes on a pairwise basis. Thus, there is a need to differentiate between signals with high and low power since signals coming from electrodes affected by the IED the most tend to have high power when compared to other electrodes that include only background activity. For added intuition, assume having four electrodes with signals \( x, y, u \) and \( v \) where signals \( x \) and \( y \) are highly connected and contain IED-related activity. On the other hand, signals \( u \) and \( v \) are also highly connected but they both contain only weak background activity. If we consider only \( \text{WPLI}_{xy}^B \) and \( \text{WPLI}_{uv}^B \), their values might be nearly the same as FC is high in both. Hence, there is a need to penalize the high FC between \( u \) and \( v \) to make it less than that between \( x \) and \( y \). That is, taking into account the signals of the rest of the electrodes while computing FC between \( u \) and \( v \).

\textbf{Note:} FC measure between any two electrode recordings that is found high due to volume conduction where one source affects both recordings should not be reflected in a meaningful FC. Extensive research has been carried out to address this problem starting from using Imaginary Coherency (IC) [51] to using state-of-the-art WPLI method, which is used in
this study to overcome this problem. It is emphasized that the goal of this study is not to dwell on this challenging problem of volume conduction, which is well studied in the literature, but rather to introduce a new measure that helps in building more informative and reliable connectivity maps. This is why we choose to apply the proposed method on top of WPLI that already takes care of the volume conduction issue.

Summing these two points through a mathematical expression, our modified FC method that we call penalized WPLI (pWPLI), can thus be expressed as:

\[
p_{WPLI}^B_{xy} = (TC_B^{xy})^\epsilon \left( \frac{p^B_{xy} + p^B_{max1}}{p_{max1}^B + p_{max2}^B} \right)^\eta W_{xy}^{B}, \tag{4}
\]

where \(p^B_x, p^B_y, p^B_{max1}\) and \(p^B_{max2}\) are the powers of \(x, y\), the highest and the second highest electrodes within \(B\), respectively. These power terms are efficiently estimated with the well-known Welch method. Note that while evaluating the above expression for the two electrodes having the highest powers within \(B\), the second term in eq. (4) would be equal to one and hence there would be no power penalization. The exponents \(\epsilon\) and \(\eta\) are parameters that control how severely WPLI\(_B^{xy}\) will be penalized for having low true connection and low power, respectively. A fixed value that is slightly less than 1 (e.g., 0.9) is set for \(\epsilon\). The reason for not setting it to 1 is to limit the surrogate-penalization effect as the chosen \(M\) value (500) might not be large enough to exactly predict the probability of true connection. Note that the computational complexity increases significantly with the increase of \(M\).

The selection of a suitable \(\eta\) parameter is discussed in the next subsection. Thus, eq. (4) provides a quantitative measure that accounts for the functional connectivity, the reliability of that connectivity (represented by the \(TC_B^{xy}\) term) in addition to the power proportion present in the considered electrodes (\(x\) and \(y\)) with respect to the electrodes of the highest power.

**B. THE \(\eta\) PARAMETER SELECTION**

The selection of a suitable \(\eta\) value used in eq. (4) is crucial. If an arbitrary high value is chosen, i.e., high power penalization, the connections in the pFC map may become too concentrated around a specific electrode. This is due to its high relative power compared to the rest of the electrodes. This is what makes the second term in eq. (4) very low for any connection that does not include that specific electrode. To better visualize this issue, consider Fig. 1. Figures 1a, 1b and 1c represent different wide-band maps drawn for the same segment shown in Fig. 1d (belonging to P10) under different \(\eta\) values. Note how the FC map presented in Fig. 1a has all of its edges concentrated in the right hemisphere which is clearly misleading in such case as P10 is diagnosed with a focal source in the Left Frontal (LF) region (as described in Table 1). Fig. 1a is generated by the standard WPLI method given in equations (2) and (1) where no power penalization is applied (\(\eta = 0\)). On the other extreme side, for an arbitrarily large \(\eta\) value, the map in Fig. 1b has no relevant information to provide regarding the interaction between different regions. The only useful information that would be extracted from such a map is that electrode Fp1 has the largest power in the wide-band. Finally, Fig. 1c represents the case of a moderate \(\eta\) value where the density of connections has increased in the left hemisphere containing the focal source. At the same time, FC between the different regions are still represented providing information regarding the dynamics of the brain during the IED segment.

Fig. 1 represents a case study for one segment of a specific patient demonstrating the essential need to introduce a suitable \(\eta\) value that gives rise to the marginal local connectivity within the ROI while at the same time avoiding excessive power penalization that eventually leads to meaningless FC maps. Thus, the question that needs to be addressed now becomes: how to chose a minimal \(\eta\) value that leads to a statistical enhancement of the ROI delineation taking into account all the segments of all the patients included in the study?

Instead of fixing several \(\eta\) values for all segments and picking up the one satisfying our norm as discussed above, the authors choice was to specify a design criterion that automates the generation of \(\eta\) for every frequency sub-band and for every segment independently. The chosen criterion is as such: The calculation of the term \((p^B_x + p^B_y)(p^B_{max1} + p^B_{max2})\) for all possible electrodes combination yields a triangular \(19 \times 19\) matrix (with zeros across the diagonal) that would get mapped to another triangular \(19 \times 19\) matrix after raising each
element to the power of $\eta$. An $\eta$ value can then be chosen so that the new resulting matrix has 99% of its non-zero values above 0.65 which would result into a mild power penalization. The reason for specifying this criterion is discussed in the results section.

C. THRESHOLDING METHODOLOGY

Similar to the selection of the $\eta$ parameter, the selection of a threshold level would also depend on the distribution of the elements in the generated $pWPLI$ matrix. The threshold is chosen in a way such that it increases when too many values in the FC matrix have high values [36]. The reason for this is to eliminate as much as possible any background activity that in some instances might be unexpectedly high. Thus, by having an adaptive threshold, it is possible to get rid of the connections resulting from extraneous background activity while at the same time maintaining activity related to the IED, which is typically higher [52], especially when subjected to the proposed penalization procedure. At the same time, there should be a minimum value below which the threshold cannot go below. Theoretically, any $pWPLI^{\beta}_{\alpha}$ ranges from 0 to 1. It was found in the literature that values between 0.5 and 0.6 are a suitable range of values for establishing a link between two entities [53], albeit for a different method. In our method, the threshold is selected to consider almost one-fourth of all the available connections [36]. This is subject to the constraint of keeping those connections above the minimum selected threshold.

D. LOCAL CONNECTIONS FOR DIFFERENT SUB-BANDS

The 19 EEG electrodes were divided into six local regions defined as follows [36]:

1) Left Frontal (LF): Fp1, Fz, F3, F7
2) Right Frontal (RF): F2, Fz, F4, F8
3) Left Temporal (LT): T3, T5
4) Right Temporal (RT): F8, T4, T6
5) Left Parietal/Occipital (LP-LO): C3, Cz, P3, Pz, O1
6) Right Parietal/Occipital (RP-RO): C4, Cz, P4, Pz, O2

Local average FC of each of the above defined regions within sub-band $B$ is defined as the total sum of connectivity values within the region divided by the total number of possible connections within the same region.

IV. RESULTS

A. ILLUSTRATIVE EXAMPLES

Upon investigation of the power spectrum across the different segments, there was a tendency of a decrease in the power as the center frequency of the sub-band increases. However, the pFC maps resulting from the low-power sub-bands were deemed significant in terms of delineating the ROI for some of the patients. This can be clearly seen in Fig. 2A illustrating maps for the different sub-bands of the segment shown in Fig. 2e which belongs to P5. Fig. 2f indicates that the $\beta$-band has the least power among the rest of the sub-bands. At the same time, its pFC map (shown in Fig. 2d) is very focused around the active LT region (see Table 1). Note that the $\theta$-band which has higher power shows high connectivity around the RT region instead (Fig. 2b) which is misleading in this case.

To resolve this contentious issue, more IED segments for the same patient need to be inspected. It is believed that the patterns caused by the spike-related activity would show relative consistency across different IED segments compared to the background activity that is found to differ from one segment to another. Hence, a different segment for P5 is considered in Fig. 2B for added deliberation. Note how the RT connections have reduced in the $\theta$-band in Fig. 2h while the LT connections of the $\beta$-band are still high in Fig. 2j. Thus, it is of utmost importance not to rely on a single IED segment of a patient, but to instead consider the use of multiple IED segments in order to overcome the random nature of both the background activity and the IED itself. The use of multiple IEDs in concert elicits a better understanding of the epileptogenic network. It is worth mentioning that the spatial distributions of IEDs can fluctuate over time which again emphasizes the need to consider multiple IED segments when attempting to define a region of interest or localize the SOZ. In a recent iEEG study, it was shown that the electrode with the highest spike frequency can better localize the SOZ than predicted by chance [13]. Due to these temporal fluctuations, an adequate duration of at least 12 sequential hours capturing both sleep and wakefulness was recommended. It is also important to note the consistent existence of strong distant links between the left temporal and left frontal (LT-LF) lobes in both the $\alpha$-band and the $\beta$-band. In addition, strong LT-RT links are also exhibited in the $\beta$-band.

We now try to illustrate the fact that there is no fixed sub-band that can consistently attain the highest margin for all patients. On the contrary to what we have seen in Fig. 2 concerning the significance of the high frequency $\beta$-band, we consider here a segment for another patient (P1) shown in Fig. 3A where the low frequency $\theta$-band becomes the most significant in pointing at the LT ROI along with the $\delta$-band while the low-power $\beta$-band is more oriented to the right hemisphere. Moreover, the strong LT-LF distant connections are now more prominent in the $\theta$-band. However, the $\delta$-band for patient P14 was consistently misleading in all of her five studied segments. Shown in Fig. 3B is the analysis of one of those five segments. A physical explanation might be as such: the spike is generally characterized by high frequency contents that do not exist in the low frequency $\delta$-band. Therefore, the $\delta$-band pFC maps fail to grasp the spike-related activity. We also note the existence of strong coupling between the RT and LT lobes. Even by mere visual inspection of the IEDs of P5 presented in Fig. 2 and comparing them to that of P1 in Fig. 3A, the discharges of P5 are clearly much faster than that of P1. This explains why the high frequency beta band was significant for P5 while the low frequency theta band was more significant for P1 since its IED discharge is slower. To be more specific, consider channel F7 as it is the most strongly affected electrode by the IEDs in both patients.
Although the power of the $\theta$-band is higher than that of the $\beta$-band for channel F7 in both segments shown in Fig. 2k and Fig. 3e, the ratio between the $\beta$-band power and the $\theta$-band power is significantly higher for P5 (0.84 vs 0.11 for P1). Thus, the morphology of the IED clearly plays an important role in the determination of the most significant frequency sub-band.

B. SUMMARY OF RESULTS

To contrast this difference between pFC and FC methods, Fig. 4 shows the local average FC in each of the six regions for the whole wide-band calculated via pWPLI and WPLI as obtained using equations (4) and (2), respectively. Each sub-figure is dedicated to one group of patients where their local average FCs in every region are averaged together.
This is done after averaging all segments of each patient individually. To illustrate how the proposed method yields higher margin of the average local connectivity, observe Fig. 4c for the RT group for instance. Note how the solid black bar (for pFC) at the RT active region is higher than the closest solid bar at the RF region (by 0.24). On the other hand, the average local connectivity of the RT and LT areas are almost the same according to the standard WPLI maps.

It is also important to observe how the pFC maps suppress the average local connectivity in some regions such as the LP-LO and RP-RO in the pFC maps while other regions are protruded. For other groups, such as the LT group in Fig. 4a for instance, negative margins were achieved by the WPLI maps. More specifically, the average local connectivity in the LT area is lower than those in the Parietal/Occipital regions (LP-LO and RP-RO).
FIGURE 4. Local average FCs in different regions resulting from pFC & FC maps for the wide band. For the pFC method, $pWPLI_{Bxy}$ given in eq. (4) is used, while $WPLI_{Bxy}$ expression in eq. (2) is used for the FC method.
In terms of distant connections, we refer to Fig. 5. For patients with temporal lobe epilepsy, strong LT-RT links were found as well as links coupling the affected temporal lobe with its corresponding frontal lobe (Fig. 5a and Fig. 5b). The same finding was observed in subjects with frontal lobe epilepsy in addition to the existence of dominant LF-RF connections.

C. STATISTICAL COMPARISONS
To have a better understanding of the results achieved in Fig. 4 with a deeper emphasis on the individual sub-bands, statistical tests were performed to ensure that the proposed method outperforms the standard WPLI method. We formulate our hypotheses as follows:

\[
\begin{align*}
H_0 &: m_B^P \leq m_B^S, \quad \text{while} \\
H_a &: m_B^P > m_B^S.
\end{align*}
\]

where \(m_B^P\) and \(m_B^S\) are the mean of the margins in sub-band \(B\) for the proposed and standard WPLI, respectively. The margin for any FC map is defined as the difference between the local average FC of the active region and the maximum local average FC across the rest of the regions. For patients with two suspected regions, the difference between the maximum local average FC of those two regions and the maximum local average FC across the rest of the regions was taken as the margin. Thus, we end up with four dependent t-tests (one for each frequency sub-band comparing the proposed vs the standard methods) with a sample size of 20 patients. For each patient, the margin is calculated by averaging local average FCs of his/her different segments.

Different design criteria for choosing \(\eta\) parameter were investigated and the acquired results are shown in Table 2. Parameter \(x\) is the value above which 99% of the non-zero values of the \(19 \times 19\) triangular matrix \((p_B^P + p_B^S / p_{B \max 1}^S + p_{B \max 2}^S)^\eta\) lie. Therefore, in reference to Table 2, as \(x\) decreases, the power penalization increase. Each row in the table contains \(p\)-values resulting from comparing the standard WPLI with the proposed pWPLI (with criterion 99% > \(x\)) according to the statistical test presented in eq. (5). From this table, two important observations can be made:

1) The \(p\)-values decrease as the power penalization increases which agrees with the intuition provided in the explanation of Fig. 1 in section III B.
2) The \(\theta\)-band required the least amount of power penalization to yield significance in raising the margin. That is, when the design penalization criterion was fixed at 99% > 0.85, only the \(\theta\)-band margins of the pWPLI were higher than those of the WPLI significantly (\(p\)-value < 0.05).

For \(x \leq 0.65\), \(\theta\), \(\alpha\) and \(\beta\) sub-bands show statistical significance. This is the reason for choosing 0.65 to be our criterion since it results in the minimal penalization for yield-

### Table 2. Dependent t-test p-values.

| \(x\)  | \(\delta\)-band | \(\theta\)-band | \(\alpha\)-band | \(\beta\)-band |
|-------|-----------------|-----------------|-----------------|----------------|
| 0.95  | 0.98            | 0.3             | 0.63            | 0.16           |
| 0.9   | 0.95            | 0.11            | 0.4             | 0.1            |
| 0.85  | 0.88            | 0.03            | 0.23            | 0.06           |
| 0.8   | 0.77            | 0.01            | 0.13            | 0.04           |
| 0.75  | 0.64            | 0.007           | 0.08            | 0.03           |
| 0.7   | 0.53            | 0.005           | 0.05            | 0.03           |
| 0.65  | 0.43            | 0.001           | 0.03            | 0.02           |
| 0.6   | 0.35            | 0.001           | 0.02            | 0.02           |
| 0.55  | 0.28            | < 0.001         | 0.02            | 0.02           |
| 0.5   | 0.23            | < 0.001         | 0.01            | 0.02           |
| 0.45  | 0.18            | < 0.001         | 0.01            | 0.02           |
| 0.4   | 0.14            | < 0.001         | 0.01            | 0.02           |
| 0.35  | 0.1             | < 0.001         | 0.008           | 0.02           |
| 0.3   | 0.08            | < 0.001         | 0.007           | 0.02           |
| 0.25  | 0.06            | < 0.001         | 0.005           | 0.02           |
| 0.2   | 0.04            | < 0.001         | 0.004           | 0.02           |
Several studies indicated the importance of $\theta$-band regarding brain FC for epileptic patients [54]. It is suggested in [55] that IED spikes have a negative impact on theta rhythm and may thus play a role in theta-related cognition changes in patients with temporal lobe epilepsy (TLE). As already referred to in the introduction section, $\theta$-band showed a significant power decrease for patients with MTLE compared to the NMTLE group [29]. The results at hand also conform with the finding that the within-zone FC is higher in the epileptogenic zone compared to the non-involved zone [34].

V. CONCLUSION

In this study, an improved technique based on a novel idea of penalized functional connectivity (pFC) maps has been proposed for determining more effective and more informative EEG-based connectivity maps. Implementation of the proposed method combines three essential factors together, which are functional connectivity (FC) between two electrodes, the probability of existence of true synchronization between them, and their sum of powers with respect to the maximum sum of powers in each frequency sub-band. The proposed penalization scheme is introduced in an adaptive manner that differs for each segment and for each frequency sub-band.

EEG functional frequency perspectives have been incorporated to shed new light on the role played by the main frequencies of the human EEG waves and their resulting implications on the potential locations of the EEG interictal spikes. An evolution of the frequency rhythms and amplitudes over time is needed to distinguish an interictal spike from many other normal rhythmical events encountered in the epileptic EEG. The $\theta$-band is found to yield optimal statistical significance in determining the active region of interest when comparing the proposed pFC maps with the standard FC maps. However, $\alpha$ and $\beta$ sub-bands could also achieve significance but under more intense power penalization. Moreover, subjected to fixed penalization criterion, $\theta$-band could also achieve significant improvement in delineating the active area over the $\delta$-band. As per our findings, the significant sub-band varies from patient to patient while remaining relatively consistent within the IED segments of a same patient. In summary, theta neural rhythm might be able to mirror best epileptic activity processes, and hence pFC maps may serve as a biomarker to localize and lateralize brain dynamics in patients with focal epilepsy. Such maps would be beneficial in extracting more physiologically meaningful metrics as the graphs produced by the proposed method incorporate more information.

While this study relied solely on scalp EEG recordings to generate effective and informative connectivity maps, extensions to this method can be applied to invasive techniques such as iEEG and SEEG in order to observe the epileptogenic network at a higher spatial resolution and with a much-improved signal to noise ratio (SNR). We believe this would prove to be beneficial for eventually localizing more
accurately the 3D onset zone, especially in light of the promising results obtained in this study.

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