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Mapping the coherence of ictal high frequency oscillations in human extratemporal lobe epilepsy

*Marija Cotic, *Osbert C. Zalay, †Yotin Chinvarun, ‡Martin del Campo, §Peter L. Carlen, and *##Berj L. Bardakjian

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**Summary**

**Objective:** High frequency oscillations (HFOs) have recently been recorded in epilepsy patients and proposed as possible novel biomarkers of epileptogenicity. Investigation of additional HFO characteristics that correlate with the clinical manifestation of seizures may yield additional insights for delineating epileptogenic regions. To that end, this study examined the spatiotemporal coherence patterns of HFOs (80–400 Hz) so as to characterize the strength of HFO interactions in the epileptic brain. We hypothesized that regions of strong HFO coherence identified epileptogenic networks believed to possess a pathologic locking nature in relation to regular brain activity.

**Methods:** We applied wavelet phase coherence analysis to the intracranial EEG (iEEG)s of patients (n = 5) undergoing presurgical evaluation of drug-resistant extratemporal lobe epilepsy (ETLE). We have also computed HFO intensity (related to the square-root of the power), to study the relationship between HFO amplitude and coherence.

**Results:** Strong HFO (80–270 Hz) coherence was observed in a consistent and spatially focused channel cluster during seizures in four of five patients. Furthermore, cortical regions possessing strong ictal HFO coherence coincided with regions exhibiting high ictal HFO intensity, relative to all other channels.

**Significance:** Because HFOs have been shown to localize to the epileptogenic zone, and we have demonstrated a correlation between ictal HFO intensity and coherence, we propose that ictal HFO coherence can act as an epilepsy biomarker. Moreover, the seizures studied here showed strong spatial correlation of ictal HFO coherence and intensity in the 80–270 Hz frequency range, suggesting that this band may be targeted when defining seizure-related regions of interest for characterizing ETLE.

**KEY WORDS:** Epilepsy, High frequency oscillations, Coherence.

With the advent of new recording techniques, very fast activities have become a new research focus in the area of seizure genesis. Initially identified in animals, high frequency oscillations (HFOs) have since been successfully recorded in patients with epilepsy. HFOs were initially described in the hippocampus and entorhinal cortex of patients with temporal lobe epilepsy (TLE) using micro-electrodes, and have since been observed in patients with TLE and neocortical epilepsies using depth and grid clinical electrodes. HFO activity is commonly classified into two frequency categories: ripple activity, ranging from 80 to 250 Hz, and fast ripples (FRs), beginning at 250 Hz and extending to 600 Hz. Within these defined frequency bands, HFOs are thought to possess both broad-band and...
band-limited spectral features, which occur as transiently bursting or continuous events.\(^5\)

New studies have proposed high frequency activity as possible biomarkers of epileptogenicity.\(^5,7\) HFOs have been shown to occur reliably in brain tissue that generates seizures.\(^8,9\) In addition, studies have shown a focal increase of ictal HFOs in seizure-onset zones (SOZs).\(^6\) Of recent clinical interest are new studies demonstrating a correlation between the removal of areas with ictal and interictal HFO increases and a good postsurgical outcome.\(^10-14\) Despite these promising results, several challenges have also emerged when exploiting these fast activities as epilepsy markers. First, HFOs have been recorded in the normal brain, and it appears that spectral frequency alone cannot resolve physiologic from pathologic HFOs.\(^15\) Second, HFOs are not limited to SOZs, but can extend beyond them. Furthermore, studies have shown that HFO rates differ between anatomic locations in the brain and between patients, creating thresholding problems for standardizing the identification of epileptogenic regions.

Investigation of additional HFO characteristics that correlate with the clinical manifestation of seizures may yield additional insights for delineating SOZs and epileptogenic regions of the brain. Because the seizure state is associated with excessive neuronal entrainment,\(^16\) the objectives of this study were to investigate the spatiotemporal coherence properties of HFOs during interictal and ictal activity; that is, the span of relevant HFO frequency bands during extra-temporal lobe seizures and the manner in which the computed coherence profiles varied temporally and spatially, as well as across patients. We hypothesized that regions of strong HFO coherence identified epileptogenic networks, which are thought to possess a pathologic locking nature in relation to regular brain activity.

The coherence of neuronal activity, although not a new idea, has not yet been explored in relation to fast interactions in the human epileptic brain. As such, we also computed HFO intensity profiles (as related to the square-root of the wavelet power), with the aim of comparing our coherence results with those of HFO amplitude, as HFOs have been shown previously to localize to the epileptogenic zone.\(^17\)

**Methods**

**Patients and iEEG data acquisition**

We retrospectively analyzed the data of patients who underwent epilepsy surgery conducted by the Thailand Comprehensive Epilepsy Program, Phramongkutklao Hospital (Bangkok, Thailand). Intracranial EEG (iEEG) data were collected from five patients with extratemporal lobe epilepsy (ETLE), who were undergoing presurgical evaluation. Patient profiles are summarized in Table 1. All patients underwent surgery for the placement of intracranial grids, arranged in a 64 contact (8 × 8) grid pattern (PMT, Chanhassen, MN, U.S.A.) (Fig. 5). All recordings were

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**Table 1. Patient characteristics of iEEG data**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Gender</th>
<th>MRI findings</th>
<th>Seizure location</th>
<th>Electrode location</th>
<th>Electrode type</th>
<th>Type of surgery</th>
<th>Resected electrodes (N)</th>
<th>Max ictal WPC (N)°</th>
<th>Max interictal WPC (N)°</th>
<th>WPC with high intensity (N)°</th>
<th>Surgical outcome</th>
<th>Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>36</td>
<td>F</td>
<td>Abnormal perisylvian dysplasia</td>
<td>FT, frontotemporal</td>
<td>L F-T</td>
<td>Electrodes with high ictal WPC (N°)</td>
<td>1, 2, 9, 10, 17</td>
<td>1, 2, 9, 10, 17</td>
<td>9, 10, 17</td>
<td>0, 0, 0, 0, 0</td>
<td>0, 0, 0, 0, 0</td>
<td>0, 0, 0, 0, 0</td>
<td>Normal</td>
</tr>
<tr>
<td>2</td>
<td>16</td>
<td>M</td>
<td>Cortical atrophy</td>
<td>DF, dorsolateral frontal</td>
<td>R D-F</td>
<td>Electrodes with high interictal WPC (N°)</td>
<td>17, 18</td>
<td>17, 18</td>
<td>17, 18</td>
<td>17, 18</td>
<td>17, 18</td>
<td>17, 18</td>
<td>R F resection</td>
</tr>
<tr>
<td>3</td>
<td>28</td>
<td>M</td>
<td>Hippocampal sclerosis</td>
<td>F, frontal</td>
<td>L F-T</td>
<td>Electrodes with high ictal WPC (N°)</td>
<td>17, 18</td>
<td>17, 18</td>
<td>17, 18</td>
<td>17, 18</td>
<td>17, 18</td>
<td>17, 18</td>
<td>R F resection</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>M</td>
<td>No lesion</td>
<td>P, parietal</td>
<td>R P</td>
<td>Electrodes with high interictal WPC (N°)</td>
<td>17, 18</td>
<td>17, 18</td>
<td>17, 18</td>
<td>17, 18</td>
<td>17, 18</td>
<td>17, 18</td>
<td>R F resection</td>
</tr>
<tr>
<td>5</td>
<td>56</td>
<td>F</td>
<td>Normal</td>
<td>FT, frontotemporal</td>
<td>L F-T</td>
<td>Electrodes with high ictal WPC (N°)</td>
<td>17, 18</td>
<td>17, 18</td>
<td>17, 18</td>
<td>17, 18</td>
<td>17, 18</td>
<td>17, 18</td>
<td>R F resection</td>
</tr>
</tbody>
</table>

FT (frontotemporal); DF (dorsolateral frontal); NT, neocortical temporal; F, frontal; P, parietal.
sampled at 2,000 Hz (Stellate Systems, Montreal, QC, Canada). The recordings were referenced to an electrode located at the forehead and behind the ears, but subsequently reformatted offline in a bipolar arrangement to diminish artifacts. The bipolar reformatting consisted of taking the difference between pairs of neighboring electrodes, thereby reducing the number of channels for analysis to 32. Electrodes that possessed persistent artifacts were excluded from study. Electrical noise and harmonics were removed using finite impulse response (FIR) notch filtering. All analyses were performed using MATLAB (The MathWorks, Natick, MA, U.S.A.). The institutional review board of Phramongkutklao Hospital approved the study protocol, and all patients provided informed consent to the ethics committee of Phramongkutklao Hospital.

Classification of seizure-onset zones (SOZs) and surgical outcome

The recorded iEEG data were independently assessed offline by two neurologists (neurologists A and B; Fig. 5) to clinically delineate the SOZs for all five patients. Neurologist A, who was directly involved in patient care, was not blinded to the clinical history of the patients, whereas neurologist B, who was not involved in patient care, was blinded. SOZ identification (performed by both neurologists) was completed separately from the results of this HFO study. The SOZs identified by both neurologists were defined electrographically as the electrode(s) with the earliest seizure activity. The SOZs identified by neurologist B, herein referred to as blind SOZs (bSOZs), and those of neurologist A, were both compared to the HFO-defined regions of interest (ROIs) identified via the algorithms used in this study.

Four of the five patients underwent epilepsy surgery. If not limited by a proximity to functional cortex, brain tissue resection encompassed the areas in the electrographically defined SOZs (according to the SOZs defined by neurologist A; Fig. 5) and additionally marked contacts of the surrounding cortex. Patient 1 did not undergo surgery because of the proximity of the SOZ to eloquent cortex. Patient 4 underwent a limited resection because of the proximity of eloquent cortex (Table 1). Each patient’s surgical outcome was categorized according to Engel’s classification18: class I: free, class II: rare disabling seizures, class III: worthwhile improvement, and class IV: no worthwhile improvement.

Characterization of HFO interactions across brain sites via wavelet phase coherence

There is an interest in studying cohered brain oscillations by means of phase analyses. In contrast to classical coherence techniques, phase coherence allows for the isolation of phase components from amplitude for a given frequency or frequency range. Standard coherence techniques provide a measure of spectral covariance, but do not separate the effects of amplitude and phase when measuring the relations between two signals. As a result, the measured coherence values cannot be ascribed directly to changes in either amplitude or phase. The contribution of phase and amplitude to signal synchrony is an important issue when studying brain signals, as two signals recorded simultaneously in the brain can possess a high degree of phase locking, yet display a parallel disparity in amplitude. Furthermore, because fast brain activities are typically associated with low amplitudes, phase-based measures are effective tools for the study of spatiotemporal relationships spanning the frequency domain in general, and higher frequency activities in particular.

Phase coherence involves the estimation of the instantaneous phases of electrical brain signals followed by a statistical method for quantifying the degree of phase locking.19,20 The original real valued signals may be transformed into complex-valued signals by convolution with a complex wavelet.21 For an arbitrary complex-valued signal, \( s(t) = y(t) + i\tilde{y}(t) \), the instantaneous phase angle is computed over the range \( [-\pi, \pi] \) as, \( \phi(t) = \arctan\left(\frac{\tilde{y}(t)}{y(t)}\right) \) and the relative phase difference between two signals over the same range is expressed by the relationship:19,22

\[
\Delta \phi(t) = \arctan \left( \frac{\tilde{y}_1(t)y_2(t) - y_1(t)\tilde{y}_2(t)}{\tilde{y}_1(t)y_2(t) + y_1(t)\tilde{y}_2(t)} \right)
\]

Therefore, the relative phase difference between the complex wavelet coefficients of two signals, \( W_1(\sigma, \tau) \) and \( W_2(\sigma, \tau) \) for different scales, \( \sigma \), and time shifts, \( \tau \), can be written as follows for \( \sigma = \sigma_m \):

\[
\Delta \phi(\sigma_m, \tau) = \arctan \left( \frac{\tilde{w}_1(\sigma_m, \tau)w_2(\sigma_m, \tau) - w_1(\sigma_m, \tau)\tilde{w}_2(\sigma_m, \tau)}{\tilde{w}_1(\sigma_m, \tau)w_2(\sigma_m, \tau) + w_1(\sigma_m, \tau)\tilde{w}_2(\sigma_m, \tau)} \right)
\]

Next, the relative phase coherence between two signals for a given scale (frequency) and time segment centered at time \( t = t_k \), and for sampling period \( \Delta t \), is obtained as follows:

\[
\rho(\sigma_m, t_k) = \left| \frac{\langle \exp(i\Delta \phi(\sigma_m, t_k)) \rangle}{\sqrt{\frac{1}{(N+1)} \sum_{j=0}^{k+1} \sum_{j-k}^{N/2} \exp(i\Delta \phi(\sigma_m, j\Delta t))}} \right|
\]

The relative phase coherence varies between 0 (independent signals) and 1 (constant phase-lag between two signals).

For our analysis, iEEG segments from five patients were evaluated using the wavelet phase coherence (WPC)}
technique (Tables S1 and S2). Ictal segments comprised a seizure episode, as well as (on average) 1 min of iEEG leading up to and following the seizure to allow for the study of iEEG activity immediately preceding and following seizures. Interictal activity was recorded during periods when patients (1) did not experience clinical seizures and (2) they were at rest and/or undergoing minimal movement during the analyzed interictal iEEG activity. WPC was applied to every possible combination of channels from the implanted subdural grids. We calculated WPC, using the complex Morlet wavelet, for frequency scales $f_m$, where $f_m$ ranged from 1 to 400 Hz in steps of 1 Hz. A moving window of $(1/f_m)^{10}$ s duration was applied to each iEEG pairing, at each frequency scale $f_m$. This yielded a WPC matrix (for each pairing) with 400 rows, equal to the number of frequency scales, and N columns, equal to the number of time windows. The window size was a function of the given frequency scale $f_m$, and chosen large enough to contain several signal oscillations (i.e., 10), yet brief enough to reduce smoothing.

To obtain average WPC matrices (Fig. 1), the matrices described earlier, corresponding to every possible channel pairing, were averaged across time and frequency. To isolate HFO activity, the averaging was completed using defined HFO frequency bands for each patient. To characterize the relative frequency bandwidth of HFO WPC, we defined frequency bounds at $1/e$ or 37% of the maximal HFO coherence value, $WPC_{max}$, for each channel pairing. Although frequency bandwidths varied in space and time, and across seizures and patients, the defined HFO bandwidth for each patient was based on the widest frequency range of HFO activity identified across all channels in the

![Figure 1.](image)

Average wavelet phase coherence (WPC) matrices of HFO activity. (A) The iEEG activity recorded from channel 1 (patient 1) along with the bandpass filtered HFO activity (80–400 Hz) below. (B) Corresponding WPC distribution of seizure episode from A (channel pairing: E1 and E5). The maximum WPC ($WPC_{max}$) for pair E1–E5 was observed at 117.03 s and 113 Hz ($f_{max}$). The HFO bandwidth was bounded at frequency values equal to 0.37 $WPC_{max}$, yielding an HFO frequency band of 80–270 Hz for patient 1 (C1). The HFO ranges for patients 2–4 were similarly estimated and ranged from: 80–150 Hz (patient 2), 100–250 Hz (patient 3), and 100–250 Hz (patient 4). (C) WPC values were averaged across frequency, for the respective patient HFO bands, and over 1-s windows, yielding time plots of average WPC. Average WPC plots are shown for channel pairings E1–E5, E2–E5, E6–E5, E9–E5, and E10–E5. A comprehensive exploration of all channel pairings on the implanted subdural grids yielded average nonseizure and seizure matrices. For patient one, the strongest coherence was present in channels 5 and 9. Channel pairings with average WPC higher than the indicated threshold are shaded in green. Channel grids for patients 1–4 are shown at right for all analyzed seizures.
implanted grids, and across all recorded time intervals. A 10-s window was used to quantify averaged ictal and interictal HFO-WPC values for all patients except patient 2, where a shorter time window (i.e., 6 s) was chosen to accommodate the shorter seizure durations and corresponding briefer intervals of HFO coherence. This averaging (in time and frequency) generated an average WPC matrix, the elements of which consisted of mean WPC strength estimates for each channel pairing.

To obtain the maximum HFO coherence (Fig. 2) in time, WPC values were averaged across the patient-defined HFO frequency bands for all channel pairings on the grid, providing a single HFO coherence value for each pairing at each time interval. The maximal HFO coherence value, across all pairings, was identified for each time segment and the spatial location of the corresponding channels were obtained. To obtain a global average estimate of HFO coherence (Fig. 3), WPC values in the patient-defined HFO frequency band were averaged in space (across all possible channel pairs), and in time (within 1-s windows), yielding a global WPC mean value for each channel.

Characterization of HFOs via wavelet intensity

Time–frequency (TF) spectrograms were constructed from the magnitude of the coefficients of the complex Morlet wavelet transform (related to the square root of

![Figure 2.](image)

Maximum HFO WPC highlights ROIs. WPC values were averaged across (HFO) frequency, for all channel pairings on the grid, providing a single HFO coherence value for each pairing at each time interval. The max HFO coherence value across all pairings was identified for each time segment and the spatial location of the corresponding channels were plotted. Spatial location of max WPC pairs and the corresponding channels were plotted. Spatial location of max WPC pairs across time for patient 1 are shown in (A1). The three-dimensional (3D) plot illustrates the spatial distribution of the max pairs and corresponds to the grid at right. During ictal activity, the majority of max WPC pairs appeared in a limited area of the grid (corresponding to the bottom left corner of the grid). (A2) Channels identified in the maximally cohered HFO pairings for the indicated time windows. (B) The bandpass filtered HFO activity (80–270 Hz) for channel 5. (C1, C2, C3): The three grids illustrate the distribution of channels involved in the maximally cohered pairing across time at three separate time intervals of 20-s duration. The two interictal intervals illustrate the absence of any spatial selectivity for strongly cohered HFO activity during interictal activity, in contrast to the ictal grid in C2. (D) Grid distribution of channels (involved in the maximally cohered pairing across time) for patients 2–4 during interictal and ictal segments (time interval = 5 seconds). Note: all colorbars illustrate max-WPC channel counts (i.e. number of times each channel was identified in the max WPC pairing).
Due to the power spectrum scaling properties of iEEG activity, the wavelet coefficient magnitudes were standard normalized with respect to frequency, prior to further analysis:

\[ W_{\text{norm}}(f, t) = \frac{|W(f, t)| - \mu(f)|_{t_1}^{t_2}}{\sigma(f)|_{t_1}^{t_2}} \]

The variables \( \mu \) and \( \sigma \) represent the mean and standard deviation of a baseline segment of wavelet coefficient magnitudes for each corresponding frequency scale \( f \). Values for each scale were calculated from a 20-s period of baseline iEEG activity. The baseline was chosen before the seizure, ending at least 30 s prior to the observation of the earliest seizure activity. The 20-s baseline was selected to ensure a duration that minimized the effect of transient events and to obtain a representative mean value for electrical activity at various frequencies. Normalized wavelet TF distributions were then averaged across the indicated time windows and frequency bands to relate average iEEG intensity during ictal and interictal activity.

To characterize the relative frequency bandwidth of HFO intensity, we defined frequency bounds at \( 1/e \) or 37\% of the maximal HFO intensity value, \( W_{\text{max}} \), for each channel. The defined HFO bandwidth for each patient was based on the widest frequency range of HFO activity identified across all channels in the implanted grids and across all recorded time intervals (Fig. S1).

**Results**

**HFO coherence and seizures**

WPC profiles were calculated for all interictal and ictal iEEG segments, for all possible channel combinations. The WPC profiles of fast activities did not reveal any spatial selectivity during interictal activity, for all patients. HFO (>80 Hz) coherence was consistently transient and of weak to moderate strength during interictal activity, for all channel pairs across the entire grid. In contrast, high HFO WPC values were observed in select channel clusters, during ictal activity, in four of five patients.

Channel pairs possessing high ictal HFO coherence (i.e., channel pairings with mean HFO WPC values greater than the indicated thresholds in Figure 1) were further explored to elucidate the frequency spread of cohered HFO ictal activity. In Figure 1 (for patient 1, channel pairing 1 and 5), the maximum WPC was observed at 117.03 s for 113 Hz. The ictal HFO ranges for patients 2–4 were similarly bounded and yielded the following ranges: 80–150 Hz (patient 2), 100–250 Hz (patient 3), and 100–250 Hz (patient 4).

A comprehensive exploration of all channel pairings on the implanted subdural grids during ictal activity yielded spatial locations of strongly cohered channel clusters. Average WPC matrices (see Methods) during interictal and ictal activity were generated for patients 1–4. To isolate HFO...
activity, the averaging was completed using the patient-defined HFO frequency bands. Average interictal and ictal WPC matrices are shown in Figure 1 for patient 1. (Note, as each matrix is symmetric, only half of each matrix is displayed for clarity.) Channel pairings with mean ictal WPC values greater than the indicated threshold are highlighted. Thresholds were obtained from histograms of averaged ictal HFO-WPC values across all channel pairings, whereby the threshold chosen was greater than four standard deviations from the mean (Fig. 1D3). Channel grids for four patients are shown at right with respective suprathreshold channels marked. For all seizures and patients, a threshold of $\mu + 4\sigma$ highlighted clusters of channels with high HFO coherence.

**HFO features of WPC matrices**

Next, maximum and global HFO wavelet coherence was investigated. The max HFO coherence value, across all pairings, was identified for each time window, and the spatial location of the corresponding channels were plotted. In Figure 2A1, for patient 1, the band ranged from 80 to 270 Hz with a window size of $t = 0.033$ s. During ictal activity, the channels corresponding to the maximally cohered pairing belonged to a consistent channel cluster (Fig. 2A1,A2,C2). A similar trend was observed across all patients (Fig. 2D). In contrast, max HFO WPC was weaker and spatially distributed during interictal activity. It is of interest to note that high and spatially focused HFO coherence was consistently observed to occur only after seizure onset. For example, in Figure 2B, ictal onset occurred at 101 s, whereas the earliest signs of spatial selectivity appeared at 115 s (Fig. 2A2).

Global HFO WPC was computed to qualitatively characterize the spatiotemporal coherence patterns of HFO activity. Global WPC values for channels from patient 1 were computed over the range of 80–270 Hz (Fig. 3). Fifteen successive windows are shown for various segments of the plotted iEEG activity. It was observed that global HFO coherence increased and remained highest in a limited area of the grid during ictal activity. Because averaging was performed over all possible channel combinations, weaker or transient connections were smoothed out while stronger, consistent connections remained.

**HFO intensity profiles**

Normalized wavelet coefficient TF profiles were calculated for all interictal and ictal iEEG segments. The frequency spread of HFOs was more clearly observed in the normalized wavelet transform (Fig. 4C). These normalized profiles highlighted HFO events, in relation to mean HFO coefficient magnitude, by which each frequency scale was self-normalized according to equation (5). Figure 4 illustrates a normalized wavelet profile for patient 1, ranging from 1 to 400 Hz, over 170 s of iEEG data. A single seizure episode is indicated by a dashed box. Increases were evident in both low and high frequency bands during the ictal state. In general, during seizures, channels displayed the following patterns: increases in: (1) slow activity only, (2) fast activity only, and (3) both slow and fast activity. Channels possessing high-intensity HFOs during seizures (i.e., channels with statistically significant HFO wavelet magnitudes) were further explored to elucidate the frequency spread of fast iEEG ictal activities. In Figure 4 (for patient 1), the maximum wavelet magnitude, $W_{\text{max}}$, was observed at 125.89 s and 224 Hz ($f_{\text{max}}$). The HFO intensity bandwidth was bounded (see Methods) at 170–270 Hz. The HFO bands for patients 2–5 were similarly bounded and yielded the following frequency ranges during ictal activity: 80–170 Hz (patient 2), 100–250 Hz (patient 3), 90–170 Hz (patient 4), and 90–150 Hz (patient 5).

Wavelet coefficient magnitudes were averaged across frequency, for the respective patient-defined HFO bands, and over 1-s windows, yielding time series that were related to channel-specific HFO activity. Channel-specific averaged HFO activity plots are shown for channels 1–4 (patient 1, Fig. 4D), before, during, and following a seizure. Select channels indicated strong increases in intensity of HFO activity during seizures. A comprehensive exploration of all channels on the implanted grids yielded regions of high-intensity ictal HFO activity for all five patients (Fig. 4). However, the intensity of ictal HFO activity was observed to vary considerably across both channels and patients. The largest values were observed for patient 3, which ranged from 1.76 to 7.88 and the lowest for patient 5, with a range of 0.47–1.10.

**HFO intensity and HFO coherence mappings**

The spatial locations of channels exhibiting high ictal HFO coherence (i.e., $W_{\text{ij}} >$ threshold = $\mu + 4\sigma$; Fig. 1) and statistically significant high-frequency ictal activity (Fig. 4) were mapped as HFO-defined ROIs in Figure 5. Comparisons of mean HFO ictal intensity (between channels) were done using a one-way analysis of variance (ANOVA), followed by Tukey’s multiple comparison test ($\alpha = 0.01$). Also illustrated in Figure 5 are the SOZs identified by neurologists A and B, along with the electrodes resected during surgery. In general, regions exhibiting high ictal HFO coherence were in agreement with regions of high ictal intensity HFOs. Furthermore, although the small patient group limits the clinical significance of our results, it is of interest to note that a more positive surgical outcome was observed when the SOZ(s) (as identified by neurologist A) and resected electrodes were in proximity to intensity and/or coherence highlighted ictal HFO ROIs (Fig. 5, Table 2).

**Discussion**

In this study we applied WPC analysis and studied normalized wavelet TF profile changes to investigate whether certain channels demonstrated strong HFO coherence and/
or high-intensity HFOs, relative to all other channels on the implanted grids, during extratemporal lobe seizures. We hypothesized that regions of strong HFO coherence identified epileptogenic networks, which are thought to possess a pathologic locking nature in relation to regular brain activity. Although phase coherence analyses have been applied to slower rhythms, the phase-locking properties of HFOs in the epileptic brain have yet to be explored.

We observed clusters of channels possessing both high intensity HFOs and strongly cohered HFOs during seizures, relative to all other channels on the implanted grids. Several groups have identified increased HFO rates and spectral power changes during seizures, and we observed similar, yet not exact, topographical overlap of areas that possessed strongly cohered channels with simultaneous increases in HFO intensity. This suggests that strong ictal HFO coherence may also be used to distinguish epileptogenic regions. Although both HFO intensity and HFO coherence identified similar regions on the implanted grids, the coherence measure demonstrated less variability across patients in the choice of threshold, which was used to highlight channels displaying significant HFO activity.

It should be noted that HFO intensity changes were more readily visible after normalizing the iEEG time–frequency distributions. As a result, it was observed that even though both HFO coherence and intensity changes were broadly observed in the 80–270 Hz frequency band, the bandwidth of frequencies possessing the strongest WPC and intensity increases was selective to each patient. A more tailored (i.e., frequency specific) patient approach may prove beneficial for ETLEs, as in general, extratemporal seizures are associated with lower seizure-free outcomes after surgery compared to temporal lobe resections. ETLEs are harder to localize, when compared to TLEs, because extratemporal seizures can originate in any of the other three lobes of the brain, which cover a large area of the cortex. In a recent study by Haegelen et al., the authors concluded that while the removal of HFO-generating regions appeared to lead to improved surgical outcomes in TLE, less-consistent findings emerged for ETLE. Normalizing the time–frequency profiles of patients may allow investigators to more accurately isolate HFO bands on a patient-by-patient basis to more accurately identify seizure-related ROIs.

Figure 4.
HFO intensity increased during seizures in select channels. (A) The iEEG activity recorded from channel 1 (patient 1) along with the bandpass filtered HFO activity (80–400 Hz) below. Corresponding wavelet (B; no normalization) and normalized (C) wavelet distributions of seizure episode from A. The maximum wavelet magnitude, $W_{\text{max}}$, for channel 1, was observed at 125.89 s and 224 Hz ($f_{\text{max}}$). The HFO bandwidth was bounded at frequency values equal to 0.37 $W_{\text{max}}$ yielding an HFO frequency band of 170–270 Hz for patient 1 (D1). The HFO ranges for patients 2–5 were similarly estimated and ranged from 80–170 Hz (patient 2), 100–250 Hz (patient 3), 90–170 Hz (patient 4), and 90–150 Hz (patient 5). Wavelet coefficients were averaged across frequency for the respective patient HFO bands, and over 1-s windows, yielding time plots of average HFO intensity (D). Average HFO plots are shown for channels 1–4. A comprehensive exploration of all channels on the implanted subdural grids yielded regions of high-intensity ictal HFOs for all five patients (see rectangle at right). Units of normalized wavelets and average intensity are in standard deviations (SD) from the mean.

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Although it is important to note that the number of patients included in this study was small (and therefore the clinical significance of our results is limited in this regard), and no patients achieved a seizure-free status postsurgery, we propose the idea that the proximity of HFO-defined ROIs to excised tissue possibly predicts a positive postsurgical outcome. Similarly, we speculate that the removal of all areas identified by coherence and/or intensity measures might have resulted in better outcomes, as several studies have demonstrated good seizure-free postsurgical outcomes resulting from HFO-guided resections.10–13 This idea is supported by the spatial overlap observed here between strongly cohered channels during seizures, with simultaneous increases in ictal HFO intensity, as ictal HFO intensity (as related to power) has already been shown as an effective biomarker of SOZs in the literature.17 It has also been observed that the removal of tissue-generating HFOs was apparently predictive of a better surgical outcome, when compared to the excision of tissue based solely on SOZs.12

It has been suggested that faster activities are generated by the hippocampus, whereas neocortical structures tend to generate HFOs in the ripple range.9 The seizures studied here were recorded from patients with ETLEs, and minimal coherence and intensity increases were observed in activity >270 Hz. Therefore, when defining seizure-related ROIs for ETLE, targeting ripple activity may be more relevant. Furthermore, HFO features such as the global average and maximum coherence, which retain spatial and temporal information, may enhance the detection and delineation of seizure-related ROIs.

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**Disclosure**

The authors do not have any conflicts of interest to disclose. We confirm that the work described here is consistent with the Journal’s guidelines for ethical publication.

**References**


**Supporting Information**

Additional Supporting Information may be found in the online version of this article:

- **Table S1.** Intracranial seizure analysis.
- **Table S2.** Intracranial interictal analysis.
- **Table S3.** SOZs and HFO ictal intensity and coherence.
- **Figure S1.** The normalized wavelet magnitude distributions for electrodes 1, 5, 6, 26, and 32 from seizure 1 for patient 1.
- **Figure S2.** Histograms of mean seizure HFO-WPC values for all electrode pairings from one seizure for patients 1–4.
- **Figure S3.** Evaluation of HFO coherence with surrogate test estimation.