Supplementary Material

Sensitivity Analysis
The pre-processing measures taken to prepare the data were investigated by performing a sensitivity analysis on select parameters.

Choice of Reference
Three references were investigated. The first was a common global reference, which was located either at the forehead or behind the ears and was thus at varying distances from each channel. The second was a local Laplacian reference, which is often used for scalp electrodes (Hjorth 1975). This approach uses the mean potential recorded from the surrounding electrodes as the reference for a center electrode – namely,

\[ J_i(t) \equiv V_i(t) - \frac{1}{M} \sum_{m=1}^{M} V_{im}(t), \]  

(S.1)

where \( V_{im}(t) \) is the potential at the \( m^{th} \) closest electrode to electrode \( i \). The surrounding potentials need to be taken in a symmetrical arrangement. The present study adapted the use of this reference to iEEG by using potentials from electrodes along the grid lines in the four cardinal directions from a center electrode (i.e., \( M = 4 \)). This symmetry was selected as opposed to using the four electrodes along the diagonals between the four cardinal directions because the distance between the grid line electrodes and the center electrode was smaller than the diagonal distance. The third reference used was the difference between adjacent electrodes (i.e., a differential montage). A sample of the complex wavelet coefficients computed from the time series obtained from each of these three references along with their respective MI values is illustrated in Figure S1. The Laplacian and differential references were found to have comparable MI values. However, the requirement of the Laplacian reference for symmetry around each channel resulted in the electrodes on the boundaries of the grid to be discarded. Thus the differential reference was used for the subsequent analysis.

Choice of FIR Filter Order
FIR filters were used for both lowpass and notch filtering purposes. Filter orders of 50, 500, 5000, and 10000 were compared. A filter order of 5000 was found to have a comparable -55 dB drop at the desired frequencies as the 10000-order filter. Moreover, the filter order was found to not have an effect on the resulting MI. As such, FIR filters with an order of 5000 were used for the subsequent analysis.

Choice of Downsampling Algorithm
Downsampling was performed after an anti-aliasing 750 Hz lowpass FIR filter was applied. Two MATLAB® algorithms were compared – namely, resample and decimate. The former interpolates between sample points if necessary, depending on the resampling ratio, while the latter discards sample points to produce a downsampled signal. MI was found to be unaffected by the choice of the downsampling algorithm. Resample was subsequently used for the remainder of the analysis.

Effect of Harmonics and Spiking Activity
To ensure that the HFO modulation being observed was not the result of harmonics, ensemble empirical mode decomposition (EEMD) was applied to a sample channel to extract the individual rhythms (Wu & Huang 2009; Huang et al. 1998). The resulting intrinsic mode functions (IMFs) are essentially monorhythmic and hence the application of the Hilbert transform to extract the amplitude envelope of the HFO and the instantaneous phase of the LFO was appropriate. The first and sixth IMFs were used for computing MI (Figure S2). The presence of MI after the extraction of a single HFO rhythm (i.e., IMF 1) suggests that the modulation was not due to harmonics. Additionally, to ensure that the observed modulation was not the result of artifactual or physiological spiking activity a recent study performing data simulations was examined. Ibrahim et al (2014) investigated the effect of spiking activity on MI in eight different scenarios. They observed significant CFC only when HFOs were synchronized to a slower
rhythm. Random spiking activity in the presence of HFOs and synchronized spiking activity in the absence of HFOs did not result in significant CFC.

**Choice of Mother Wavelet**

Four complex mother wavelets were investigated for this study – namely, complex Morlet, complex Gaussian, frequency b-spline, and complex Shannon. The complex wavelet coefficients of each were compared as well as the resulting MI when applied to a synthetic signal (Figure S3) and a physiological signal (Figure S4). The Morlet wavelet with a bandwidth of 5 Hz was found to be the appropriate choice when compared to other Morlet alternatives (Figures S3(b) and S4(b)) while the Gaussian wavelet with an order of 5 was found to be the appropriate choice in comparison to other Gaussian alternatives (Figures S3(c) and S4(c)). In both cases, the spread in the wavelet was minimized while maintaining the integrity of the MI. When comparing all four complex mother wavelets, the Morlet and frequency b-spline were comparable when applied to the synthetic signal (Figure S3(a)). However, when all four complex mother wavelets were applied to the physiological signal, the Morlet was the appropriate choice (Figure S4(a)) and was thus used for the subsequent analysis.

**Supplementary References**


**Video S1. The Spatiotemporal Progression of the MI Values for One of the Seizures from Patient D.** See attached video. Each box contains the MI values computed in the same 10 s window across all thirty-two channels of the grid and each frame is shifted by 1 s. Frames during the clinical seizure are indicated by a black background while those occurring during non-seizure activity are indicated by a white background. MI was computed between the phase of the frequencies 0.5 – 10 Hz along the x-axis and the amplitude of the frequencies 11 – 200 Hz along the y-axis. The scale for each channel was set as zero to 30% of the maximum MI value observed in that channel across all frames, which is analogous to the 3 dB point. MI is first observed in channels 2, 3, and 7, where the modulating LFO is the theta rhythm. This LFO shifts towards the delta rhythm as the seizure progresses, as seen in the mid-seizure frame. The shift towards delta-modulation is also the beginning of modulation in the upper region of the grid – specifically, channel 31. Once the seizure nears its termination, this delta modulation dominates the upper region of the grid, as seen in the seizure termination frame. This suggests that this patient has two ROIs: the first in the lower region of the grid when theta is the dominating LFO and the second in the upper region of the grid when the dominating LFO is the delta rhythm.

**Video S2. The Spatiotemporal Progression of the MI Values for One of the Seizures from Patient G.** See attached video. Each box contains the MI values computed in the same 10 s window across all twenty-four channels of the grid and each frame is shifted by 1 s. Frames during the clinical seizure are indicated by a black background while those occurring during non-seizure activity are indicated by a white background. MI was computed between the phase of the frequencies 0.5 – 10 Hz along the x-axis and the amplitude of the frequencies 11 – 200 Hz along the y-axis. The scale for each channel was set as zero to 30% of the maximum MI value observed in that channel across all frames, which is analogous to the 3 dB point. Note the smaller grid size (i.e., 24 channels) compared to the other six patients. MI is first observed in channels 5, 6, 10, 12, and 23, where the modulating LFO is the theta rhythm. This LFO shifts towards the delta rhythm as the seizure progresses. Moreover, the seizure spatially propagates towards the upper left region of the grid. Once the seizure nears its termination, this delta modulation becomes more dominant in the upper left region of the grid and is followed by no modulation after seizure termination.
Figure S1. **Effect of reference choice.** Three referencing schemes were compared using the same channel (channel 5 on the 32-channel array, which is electrode 10 on the 64-electrode grid, as illustrated in Figure 2) from the same seizure segment of Patient A. The global reference (top panel) made use of the reference electrodes placed on the forehead or behind the ears. The Laplacian (middle panel) and differential (bottom panel) references have removed the DC shift from the recording as well as artifact high amplitude spiking. Red horizontal bars over the local field potential (LFP) indicate the 10 s window for which MI was computed and illustrated on the right of each respective panel. The MI resulting from the Laplacian and differential references are comparable whereas the MI resulting from the global reference is significantly weaker and ultimately negligible. The Laplacian reference requires symmetry around each electrode and thus the electrodes on the edges of the grid must be discarded. However, differential references provide comparable MI values and allow for all electrodes to be included in the analysis. Thus, the differential montage was used for the subsequent analysis. Wavelet power was z-score normalized per frequency (in 1 Hz increments) using the mean and standard deviation of the wavelet power from a 30 s window more than 60 s before seizure onset. This allowed for all frequency activity to be visible on the same scale. MI was computed between the phase of the frequencies indicated on the x-axis and the amplitude of the frequencies indicated on the y-axis. All scales and axes labels are as indicated in the top panel.
Figure S2. Effect of harmonics on MI. The recording from channel 2 of Patient A (top panel) was used as a sample signal to determine if the observed MI was the result of a harmonic effect. Ensemble empirical mode decomposition (EEMD) was applied using a noise standard deviation of 0.1 and $N = 200$ ensembles. The Hilbert transform was applied to the first and sixth intrinsic mode functions (IMF 1 shown in the second panel and IMF 6 shown in the third panel, respectively) in order to extract the amplitude envelope of the higher rhythm and instantaneous phase of the lower rhythm. Frequency content of each IMF is shown in the fast Fourier transform on the right of each respective row. The frequency content of IMF 1 peaks around 80 Hz and includes frequencies $\leq 150$ Hz while IMF 6 peaks around 3 Hz and includes frequencies $\leq 5$ Hz. The resulting MI is shown in the bottom panel.
Figure S3. Effect of mother wavelet choice on a synthetic signal. Four complex mother wavelets were compared along with their corresponding MI values computed in a 10 s window of a synthetic signal generated such that the phase of a 4 Hz rhythm was modulating the amplitude of a 100 Hz rhythm. (a) The wavelet coefficients of each mother wavelet are shown in the top row. Their respective MI values are as indicated directly below. The complex Morlet had a bandwidth of $F_b = 5$ Hz while the complex Gaussian had an order of 5. (b) Three other bandwidths were compared for the complex Morlet and (c) two other orders for the complex Gaussian. The mother wavelets with the truest reflection of the modulation were the complex Morlet and frequency b-spline. For the complex Morlet, a bandwidth of $F_b = 5$ Hz was sufficient to minimize the spread of the modulation. The complex Gaussian and complex Shannon mother wavelets were not able to capture the modulation in the signal. MI was computed between the phase of the frequencies indicated on the x-axis and the amplitude of the frequencies indicated on the y-axis. All axes labels are as indicated on the leftmost panel of each sub-figure. Scales are as indicated by the colourbar beside the rightmost panel of each sub-figure.
Figure S4. Effect of mother wavelet choice on a physiological signal. Four complex mother wavelets were compared along with their corresponding MI values computed in the same 10 s window from a seizure of Patient A. As in Figure S3, (a) the wavelet coefficients of each mother wavelet are shown in the top row. Their respective MI values are as indicated directly below. The complex Morlet had a bandwidth of $F_b = 5$ Hz while the complex Gaussian had an order of 5. (b) Three other bandwidths were compared for the complex Morlet and (c) two other orders for the complex Gaussian. The versions selected for comparison with the other complex mother wavelets (as indicated in (a)) were found to minimize the spread without compromising the integrity of the MI. Similarly, the complex Morlet with a bandwidth of $F_b = 5$ Hz was found to be the appropriate choice in comparison to the other three complex mother wavelets and was thus used for the subsequent analysis. Although the complex Morlet and the frequency b-spline mother wavelets were comparable when applied to the synthetic signal in Figure S3, their application to a physiological signal that has multiple rhythms shows that the complex Morlet results in a narrower MI spread and less artifact when considering the higher frequencies. Wavelet power was z-score normalized per frequency (in 1 Hz increments) using the mean and standard deviation of the wavelet power from a 30 s window more than 60 s before seizure onset. This allowed for all frequency activity to be visible on the same scale. MI was computed between the phase of the frequencies indicated on the x-axis and the amplitude of the frequencies indicated on the y-axis. All axes labels are as indicated on the leftmost panel of each sub-figure. Scales are as indicated by the colourbar beside the rightmost panel of each sub-figure.
Figure S5. Spatial distribution of MI. The three frames selected at (a) seizure onset, (b) mid-seizure, and (c) seizure termination for Patient D are shown. Each box contains the MI values computed in the same 10 s window across all thirty-two channels of the reduced grid. MI was computed between the phase of the frequencies indicated on the x-axis (0.5 – 10 Hz) and the amplitude of the frequencies indicated on the y-axis (11 – 200 Hz), as indicated on the bottom left corner (channel 1) of each sub-figure. The scale for each channel was set as zero to the 30% of the maximum MI value observed in that channel across all frames, which is analogous to the 3 dB point. Surrogate analysis was performed on each of these frames and FDR was subsequently applied. White indicates MI values that were not found to be significant ($p > 0.05$). MI is first observed in channels 2, 3, and 7, where the modulating LFO was the theta rhythm. As the seizure progressed, this LFO shifted towards the delta rhythm, as seen in the mid-seizure frame. The shift towards delta-modulation was also the beginning of modulation in the upper region of the grid – specifically, channel 31. Once the seizure neared its termination, this delta-modulation dominated the upper region of the grid, as seen in the seizure termination frame. This suggests that this patient has two ROIs: the first in the lower region of the grid when theta is the dominating LFO and the second in the upper region of the grid when the dominating LFO is the delta rhythm. Note that the lower part of the grid also had a delta-dominated LFO, which would have extended the ROI estimated from the theta-dominated LFO – that is, channels 1 and 5 in addition to channels 2, 3, and 7.
Figure S6. Global coherence at each MI frame. Global coherence ($C_{\text{global}}$) was computed from the eigenvalues extracted from the matrices of mean MI values at seizure onset (top left panel), mid-seizure (top right panel), seizure termination (bottom left panel), and the overall cumulative summary of all three frames (bottom right panel). $C_{\text{global}}$ was found to be significantly lower when computed from the mean significant MI values in all patients across all frames as well as the overall summary. Mean delta-HFO modulation resulted in higher $C_{\text{global}}$ compared to mean theta-HFO modulation for Patients A, D, E, F, and G during seizure onset and for Patient C mid-seizure, seizure termination, and in the overall cumulative summary. For Patient B, delta-HFO and theta-HFO modulation resulted in comparable $C_{\text{global}}$ values. Horizontal lines indicate significant differences ($p < 0.1$).
Figure S7. ROIs identified for Patient A using all three MI frames. The channels defining the ROIs identified from all three MI frames for Patient A as well as the overall cumulative summary of these identified channels is illustrated. There was no significant difference in the identified channels over the three frames. This patient did not undergo resection surgery.
Figure S8. ROIs identified for Patient B using all three MI frames. The channels defining the ROIs identified from all three MI frames for Patient B as well as the overall cumulative summary of these identified channels is illustrated. There was no significant difference in the identified channels over the three frames for the significant MI and delta-HFO modulation schemes. The theta-HFO modulation identified additional channels mid-seizure and at seizure termination in the lower half of the grid. Resected tissue is shown as a black region on the grid. This patient was classified as Engel Class IV.
Figure S9. ROIs identified for Patient C using all three MI frames. The channels defining the ROIs identified from all three MI frames for Patient C as well as the overall cumulative summary of these identified channels is illustrated. The mid-seizure and seizure termination frames identified three additional channels in the lower half of the grid. Resected tissue is shown as a black region on the grid. This patient was classified as Engel Class II.
Figure S10. **ROIs identified for Patient E using all three MI frames.** The channels defining the ROIs identified from all three MI frames for Patient E as well as the overall cumulative summary of these identified channels is illustrated. There was no significant difference in the identified channels over the three frames. Resected tissue is shown as a black region on the grid. This patient was classified as Engel Class II.
Figure S11. ROIs identified for Patient F using all three MI frames. The channels defining the ROIs identified from all three MI frames for Patient F as well as the overall cumulative summary of these identified channels is illustrated. There was no significant difference in the identified channels over the three frames. Resected tissue is shown as a black region on the grid. This patient was classified as Engel Class I. Note the different numbering scheme for the channels compared to the other patients (i.e., channels 1 – 8 occupy the top two rows as opposed to the bottom two rows).
Figure S12. Receiver operating characteristic (ROC) curves for EVD-identified ROIs. ROC curves were generated using threshold values of the mean of the eigenvector components (associated with the largest eigenvalue) plus a multiple of the standard error of mean (SEM). Twelve SEM multiples were investigated – namely, $0 – 5.5$ in $0.5$ increments – for all three MI frames as well as the overall cumulative summary of all three frames. Delta-HFO modulation resulted in more stable ROC curves compared to theta-HFO modulation and achieved higher sensitivity values and lower FPRs compared to significant MI. The most appropriate sensitivity and FPR were found to be $75.4\%$ and $15.6\%$, respectively, with a threshold value of the mean plus three SEM using delta-HFO modulation of the overall cumulative summary of all three MI frames (indicated by the black arrow).