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Enhanced Phase and Amplitude Synchronization Toward Focal Seizure Offset

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Abstract

Recent studies involving individual neurons in the seizure focal and surrounding areas have established heterogeneous firing patterns in single cells. However, the patterns become more homogeneous approaching the seizure offset. In this article, we show that similar observations are possible from intracranial recording if the right quantitative or engineering techniques are used. We have observed an increase in Hilbert transformation–based phase synchronization in the focal electrocorticoencehalogram (ECoG) in the gamma band (30-40 Hz) towards the end of the majority of focal epileptic seizures. An amplitude correlation measure shows an enhanced principal component (and hence enhanced correlation among the channels involved) approaching the offset of the large majority of seizures. Surprisingly, there are seizures which show the enhanced phase synchronization approaching offset but no enhanced amplitude correlation during the same period and vice versa. This study shows that suitable computational tools can sometimes compensate for more expensive and technologically demanding data acquisition systems. A possible neurophysiological explanation behind the observed phenomenon is also presented.

Keywords

amplitude correlation, electrocorticoencephalogram (ECoG), focal epilepsy, Hilbert transformation, gamma band phase synchronization

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Introduction

Recently single neuron studies have been undertaken in seizure focal and neighboring areas during ictal[1] and interictal[2] periods. It has been observed that even in areas remote from the seizure focus (up to 4 cm away) neuronal firing patterns alter minutes before seizure onset, are heterogeneous during seizures, and change homogeneously at seizure offset.[3] It has been observed that amplitude correlation in the focal ECoG increases toward the end of a partial generalized seizure.[4] We will show that the same is true for lower gamma frequency (30-40 Hz) phase synchronization, in the epileptic focal ECoG channel pairs (we have 3 focal channel data). All 3 pairs and their average have been considered for each of the 87 seizures in 21 patients. As the seizure progresses, more and more inhibitory neurons become active in the seizure generating network, which may be responsible for greater synchronization toward the end of the seizure rather than in the earlier onset and progression.

For the purpose of measuring phase synchronization, in this article we have used the classical Hilbert transformation–based method[5] which is computationally efficient. This indicates that a trade-off is possible between data acquisition and quantitative analytical algorithms to achieve the same results, at least in some cases. Since epilepsy is the second most prevalent neurological disorder, after stroke, and affects about 50 million of the world population,[6] it is worth exploring computational studies that have the potential to reduce the complications and expense of monitoring single neurons.

Synchronization is a fundamental mechanism by which different brain regions coordinate to build up sensory awareness of the environment[7] and maintain memory processes.[8,9] Abnormal synchronization is implicated in neurological disorders such as epilepsy[10,11] and Parkinson disease.[12] Unfortunately, there is no general agreement about synchronization in signal processing,[6] biology or even physics.[13] Different notions and techniques of synchronization have been in use in neural signal processing.[14,15] The notion of synchronization can be divided

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Table 1. Patient Details.

Patient	Gender	Age	Seizure Type	H/NC	Electrode[a]	Origin	# Seizures
1	F	15	SP, CP	NC	g, s	Frontal	4
2	M	38	SP, CP, GTC	H	d	Temporal	3
3	M	14	SP, CP	NC	g, s	Frontal	5
4	F	26	SP, CP, GTC	H	d, g, s	Temporal	5
5	F	16	SP, CP, GTC	NC	g, s	Frontal	5
6	F	31	CP, GTC	H	d, g, s	Temporo/occipital	3
7	F	42	SP, CP, GTC	H	d	Temporal	3
8	F	32	SP, CP	NC	g, s	Frontal	2
9	M	44	CP, GTC	NC	g, s	Temporo/occipital	5
10	M	47	SP, CP, GTC	H	d	Temporal	5
11	F	10	SP, CP, GTC	NC	g, s	Parietal	4
12	F	42	SP, CP, GTC	H	d, g, s	Temporal	4
13	F	22	SP, CP, GTC	H	d, s	Temporo/occipital	2
14	F	41	CP, GTC	H and NC	d, s	Fronto/temporal	4
15	M	31	SP, CP, GTC	H and NC	d, s	Temporal	4
16	F	50	SP, CP, GTC	H	d, s	Temporal	5
17	M	28	SP, CP, GTC	NC	S	Temporal	5
18	F	25	SP, CP	NC	S	Frontal	5
19	F	28	SP, CP, GTC	NC	S	Frontal	4
20	M	33	SP, CP, GTC	NC	d, g, s	Temporo/parietal	5
21	M	13	SP, CP	NC	g, s	Temporal	5

Abbreviations: SP, simple parietal; CP, complex parietal; GTC, generalized tonic-clonic; H, hippocampal; NC, neocortical.
[a] Electrode: grid (g), strip (s), depth (d). Seizure frequency varies between 0.1 and 6.8 per day (table 1 of ref[24]).

into two broad categories; *phase synchronization* or *phase coherence*[5] and *amplitude synchronization* or *amplitude correlation*.[4] Since phase synchronization is an important notion in neuroscience, it would be worthy to have an efficient method for its calculation. The most popular phase synchronization measuring methods in neuroscience are Hilbert transformation based[5] and wavelet transformation based.[16] They produce almost identical results.[17,18] Fast fourier transformation (FFT)-based phase synchronization measures have also been proposed.[19,20] The most efficient implementation of the Hilbert transformation–based measure takes $O(n\log n)$ time for an input size of n.

Amplitude correlation has been applied widely on electroencephalogram (EEG)/ECoG channel pairs. The definition and measure for amplitude correlation (cross-correlation or autocorrelation) are fairly uniform in the literature and provide much useful information about the evolving signals.[4,14] In the current study, we have implemented a multichannel zero time lag, amplitude cross-correlation measure[4] on our focal ECoG data, and compared our phase synchronization findings. This article includes a detailed list of seizures where phase and amplitude synchronization measure output did or did not match. A theoretical time complexity analysis of the phase and amplitude coherence methods has been undertaken.

Patient and Data

We have tested our hypothesis on the publicly available ECoG data from the Seizure Prediction Project of the Albert-Ludwig-Universitat Freiburg, Germany.[21] The ECoG data were acquired using Neurofile NT digital video EEG system (Itmed, Usingen, Germany) with 128 channels, 256 Hz sampling rate, and a 16-bit analog to digital converter. In all cases, ECoGs from all the three focal sites (channels 1, 2, and 3 are seizure focal channels for all patients, see[21] for detail) have been analyzed. See Table 1 for patient details. The patient population has been studied earlier[22-24] where further details are noted.

ECoG data are from 21 medically intractable focal epileptic patients.[21] For each patient there are 2 to 5 hours of data, during each hour exactly one seizure occurred lasting a few tens of seconds to minutes (Table 1).

Phase and Amplitude Synchronization

In this article, by *phase* of a time domain signal, we imply the instantaneous phase determined by Hilbert transform.[5] We call this measure *Hilbert phase synchronization*.

Hilbert Phase Synchronization

Hilbert phase synchronization between 2 ECoG channels has been calculated as phase synchronization between 2 chaotic oscillators.[25] Phase locking between 2 periodic oscillators is defined as[5,26]

$$|\phi_{n,m}(t)| < c, \phi_{n,m}(t) = n\phi_1(t) - m\phi_2(t), \quad (1)$$

where c is a constant, ϕ_1, ϕ_2 are phases of the ECoG from the first and the second channel, respectively. Equation (1)

describes $n : m$ phase locking between 2 signals. In the current work, we consider $n = m = 1$ case. Let $s(t)$ be any time domain signal. We define

$$\psi(t) = s(t) + j \cdot \hat{s}(t) = A(t) \cdot \exp(j \cdot \phi(t)) \quad (2)$$

where $\hat{s}(t)$ is the Hilbert transform of the signal $\hat{s}(t), j = \sqrt{-1}$, $A(t)$ is the *envelope* (*instantaneous amplitude*) of $\psi(t)$ and $\phi(t)$ is the (instantaneous) phase of $\psi(t)$. We define $\phi(t)$ and $A(t)$to be the *instantaneous phase* and *envelope* of $s(t)$, respectively.

$$\hat{s}(t) = \frac{1}{\pi} \int_{-\infty}^{\infty} \frac{\hat{s}(t)}{t - \tau} d\tau \quad (3)$$

In equation (3) only the Cauchy principle value is considered. For $A(t)$ and $\phi(t)$ to have a clear physical meaning, the signal $s(t)$ must be a narrow band.[27] In our study, we consider the lower gamma band (30-40 Hz) for the phase synchronization analysis, which is a sufficiently narrow band. Here the ratio of center-frequency-to-band width is $35/10 = 3.5$, which is much larger than in the case of the normal gamma range of 30 to 80 Hz. In the latter case, it is $55/50 = 1.1$. Hence, the phase synchronization study in the lower gamma range is more justified than a phase synchronization study in the normal gamma range.[5] The lower gamma range can be considered as representative of the normal gamma range from the physiological point of view[28,29]; 30 to 40 Hz is the range in which the amplitude of EEG goes up during auditory stimulation and after 40 Hz it comes down.[30] The representation in equation (2) allows removal of the influence of amplitude from the phase synchronization between 2 signals, thus allowing a direct measurement of phase locking between them.

It has been shown[26] that when 2 signals are in phase synchrony $\phi_{n,m}(t)$, cycles are through a set of "preferred" values. If there is no synchrony, then $\phi_{n,m}$ will exhibit a large number of values. The distribution of unique values of phase differences between 2 signals that are not in phase synchrony would thus resemble a uniform distribution.

Quantifying the deviation of the phase differences with respect to a uniform distribution would provide a measure of phase synchronization. Shannon entropy can be used to quantify such a deviation.[26] Since the value of phase differences can take on values uniquely in $[0, 2\pi]$, we divide the interval into N number of phase bins. We denote the Shannon entropy of the phase differences across all the bins by S. Then

$$S = -\sum_{i=1}^{N} p_i \ln(p_i) \quad (4)$$

where p_i is the probability of the phase difference being in the ith bin. By computing $S_{\max} = \ln(N)$, the entropy corresponding to a uniform distribution, we can compute a normalized measure of phase synchronization (γ)

$$\gamma = 1 - \frac{S}{S_{\max}}. \quad (5)$$

If $\gamma = 1$ signals are in perfect phase synchrony and if $\gamma = 0$ the signals are in perfect phase asynchrony.

Computation

The above method can be used to determine the phase synchronization between a pair of signals for any duration of time by using a sliding window. The signals are first band-pass filtered in order to get a narrow band for which the instantaneous Hilbert phase has to be determined. Consider a window of size T seconds starting at time $t = t_0$, that is the segments of the signal in the interval $[t_0,\ t_0 + T]$. We compute a value of γ corresponding to $t = t_0$. Next, we shift the window to time $t = t + \delta t$ and compute γ. This procedure is repeated until the synchronization has been computed over the requisite time interval of interest to obtain a time-varying synchronization profile.

Note that the integral in equation (3) is a convolution and therefore it can be computed in a time-efficient manner by using FFT.

$$\hat{s}(t) = \mathrm{IFFT}(-j\ \mathrm{sgn}(w)\mathrm{FFT}(s)) \quad (6)$$

where sgn() is the signum function. The phase of the signal is then extracted using equation (2) for all points in the interval $[t_0,\ t_0 + T]$. Then the interval $[0,\ 2\pi]$ is divided into N bins and the distribution of the phase differences is computed. Upon computing the entropy of this distribution using equation (4), γ can be evaluated by equation (5).

After computing γ, we test the null hypothesis of no synchronization, that is the synchronization we observe is not significant or $H_0 : \gamma = 0$. The decision rule we use to test this hypothesis is: Reject H_0 if $\gamma > \gamma_0$. For a given P value, γ_0 is chosen as the $100(1 - P)$ percentile of the distribution of γ values obtained by evaluating the phase synchronization between a large number of pairs (100 in our case) of independent shifted time surrogate signals. It has been shown that this method of obtaining γ_0 is equivalent to using white noise signals instead of shifted time surrogates.[16]

It should be noted that it is possible to use the wavelet transform to extract phase and amplitude information from the signals.[16] However, it has been shown that the results obtained by using wavelet transform are virtually indistinguishable from those obtained by the Hilbert transform.[17,18] Also the time complexity of the wavelet analysis is higher than the Hilbert method.

Multichannel Amplitude Correlation

If there are r channels, then $r \times r$ cross-correlation matrix has to be formed. The matrix is calculated for cross-correlation over a window with m time points. Then r eigen values of the matrix are calculated and sorted in descending order, and the window is slided and the process is repeated. Then the temporal plot of the highest eigen value is generated by the highest eigen values at all time points. Similarly, the plots for the second highest, third highest, . . ., lowest eigen value plots are generated. If the highest eigen value plot is increasing with respect to time, the

overall amplitude correlation is growing up. If it is decreasing, the overall correlation is also decreasing. For detail see ref.[4]

Computational Complexity

Time complexity of Hilbert transform by equation (6) is $O(n\log n)$, where n is the number of time points in the discrete signal. For study of phase synchronization between a pair of signals, two Hilbert transforms, one for each signal, are required. If an m time point long sliding window ($m < n$) is shifted one time point at a time (the so-called continuous shifting), it is possible to compute the phase difference distribution in each window in $O(1)$ time for all windows except the first. Thus, the time complexity in computing all the requisite phase difference distributions is $O(n - m + m\log N) = O(n)$, where $O(m\log N)$ is the complexity in obtaining the phase difference distribution in the first sliding window, N is the number of bins. Computation of γ itself is a single operation and each evaluation is $O(1)$, with $(n - m)$ evaluations. Thus, the complexity of the algorithm $O(n\log n)$.

In the multichannel amplitude correlation method, the time complexity for measuring the correlation coefficient between two signals in a window of length m time points is $O(m)$. Pairwise correlation coefficient measure for r channels will take $O\left(\frac{r(r-1)}{2}m\right) = O(r^2m)$ time. The eigen value computation requires $O(r^3)$ time. Even if the most efficient, the quick sort, is applied, it will take on an average $O(r\log r)$ time. So the total time taken will be $O(r^2m + r^3 + r\log r)$. The time taken for continuously sliding window of length m across $n(>>m)$ time points is $O((n - m)(r^2m + r^3 + r\log r)) \approx O(nmr^2)$.

Results

Data Conditioning

The data are band-pass filtered for gamma band (30-40 Hz) using an equiripple band-pass FIR filter with the following specification: first pass band at 30 Hz; second pass band at 40 Hz; a transition bandwidth of 1 Hz which determines both the stop bands at 29 Hz and 41 Hz; pass band attenuation of 0.1 dB; stop band attenuation of 40 dB.

To remove the time domain delay due to the filtering operation, each filter is applied twice. First, a filter is applied to the data in the forward temporal direction and then applied to this filtered data in the reverse temporal direction, thus the delay introduced due to filtering is negated irrespective of whether the delay is linear with frequency as in FIR band-pass filter or nonlinear as in the case with IIR filter. This technique of removing the delay is possible since the data are being processed off-line. These conditioned data are used in the analysis of all the methods described.

Hilbert Phase Synchronization

The conditioned data are used for evaluating the Hilbert phase synchronization method. The analysis window is of 10 seconds in duration. The analysis window is shifted by 1 sample (data point) at a time, that is continuous sliding. The pairwise response for all the 3, focal channels, that is all 3 possible different combinations, are evaluated. A multichannel trend among the 3 focal channels is evaluated as the average of all possible pairwise responses (Figure 1).

The criterion for identifying a given seizure displaying high-phase synchronization during seizure offset is enumerated here. The significance level is denoted as SL (In Figure 1 the SL is the horizontal [red] line in all the subplots). Here SL is equal to the maximum Hilbert phase synchronization value in 95% of the 100 pairs of shifted surrogate signals. Maximum synchronization during the first half of the seizure period is denoted as M1, and maximum synchronization during second half of the seizure duration is M2. If M1 is less than the SL then the threshold (T) is set to SL. If M1 is greater than SL then the T is set to M1. The criteria are—M2 should be greater than or equal to 1.25 times the T and minimum value of 0.1 (If M2 < 0.1, we ignore it altogether).

We generated a plot like Figure 1 for all the focal ECoG channels, for each of the 87 seizures recorded in 21 patients. We have applied the criterion of the previous paragraph on each of the four subplots associated with each of the 87 seizures, to determine whether or not the phase synchronization is increasing in the second half of the seizure compared to the first in each of the focal channel pairs and also in their ensemble average (the average of the seizure that occurred in the seventh hour of recording of patient 1 is shown in the bottom right plot of Figure 1). Since we have made our observations testing a publicly available ECoG database, we have furnished our findings with patient-specific channel details in Table 2 for future researchers to compare. In this article, we report our findings on all the 87 seizures of 21 patients irrespective of whether or not they support the trend that we want to observe. Then we have summarized the detailed observations of Table 2 in Table 3 in order to find the trends. The most important trends have been highlighted in boldface. In this subsection, we will discuss the average pairwise phase synchronization trends, and in the next subsection we will discuss the amplitude correlation trends.

The first three rows of Table 3 list the number of seizures that show enhanced gamma band Hilbert phase synchronization in the second half of the seizure compared to the first half in different focal channel pairs and also in their average.

The last 3 rows of Table 3 list the population trend of the "criterion" of enhancement of gamma band Hilbert phase synchronization in the second half of seizure duration compared to the first, according to the specification described in the second paragraph of this subsection. To simplify, we have expressed interpretation in percentage only. Since the recording is by more than 2 channels, in order to capture the multichannel phase synchronization trend, we have focused on the average of pairwise Hilbert phase synchronization across all the 3 focal channels (see the boldface entries in the fifth column of Table 3). Out of 21 patients, 18 (86%) exhibited enhanced

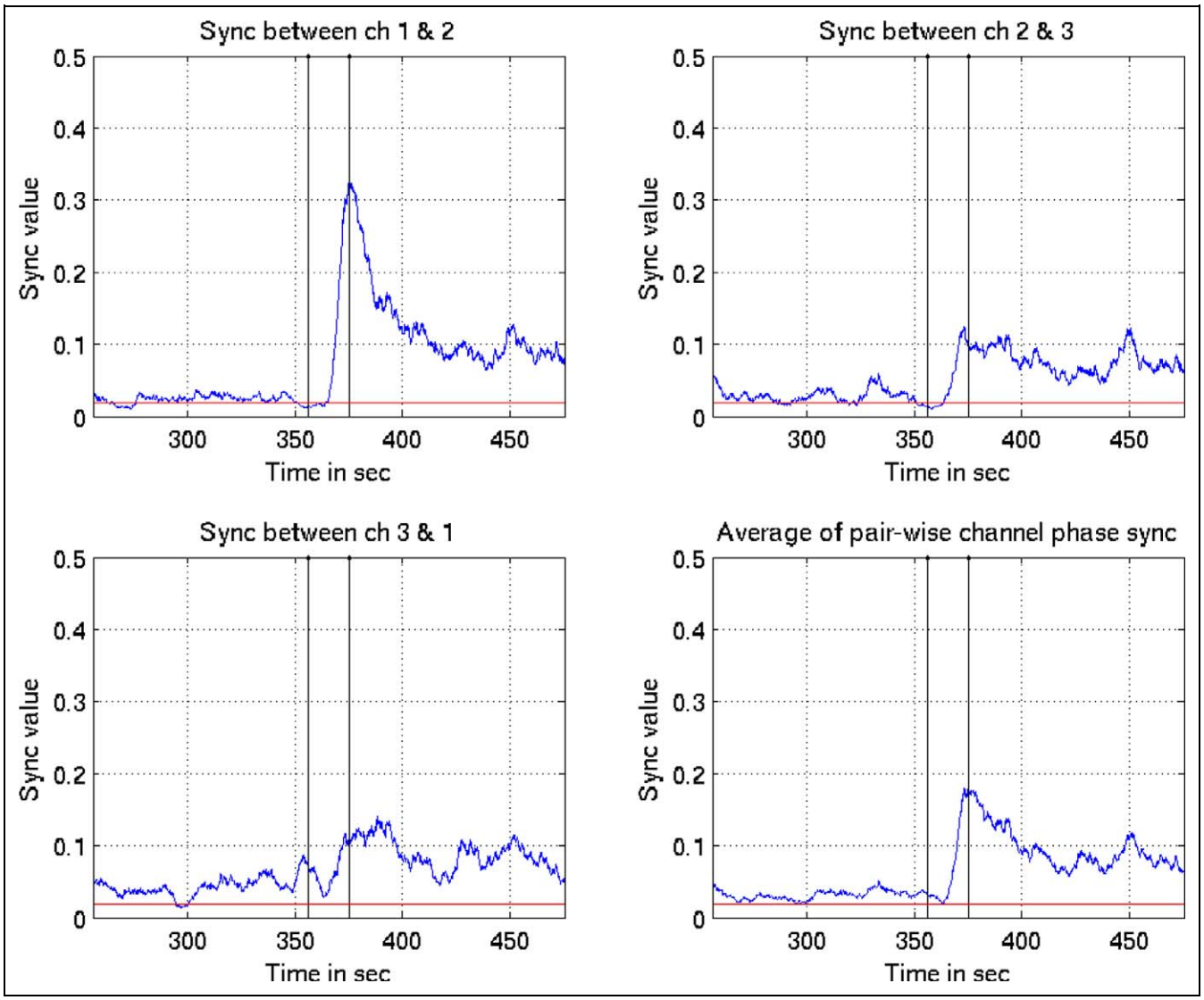

Figure 1. Hilbert transform–based phase synchronization between all 3 focal channels during seizure 1 (recorded at 7th hour) of patient 1 in the lower gamma frequency band (30-40 Hz). Level of synchronization is significant above the horizontal line (maximum synchronization value of 95% of 100 pairs of surrogate signals). The 2 vertical lines signify epileptologist-identified seizure onset and offset time.

gamma band phase synchronization in the second half of the seizure duration in at least 1 seizure (2-5 seizures have been recorded in each patient). Thirty-nine (52%) of seizures satisfied this criterion out of all the 75 seizures recorded from 18 patients who had shown the criterion at least once. These 39 seizures are 45% of 87 seizures recorded in all of the 21 patients. We will continue discussing trends in the next subsection as well as in the Conclusion.

Amplitude Correlation

The same conditioned data are again used for evaluating the amplitude correlation–based method. An analysis window of 2 seconds is used. The analysis window is shifted by 1 sample point at a time. The results are smoothed with a moving average filter of 1 second to enable us to clearly visualize the trend (Figure 2). The criterion for identifying a seizure as having high amplitude correlation during seizure offset is described. During the first half of the seizure, the maximum value that the highest eigen value reaches is denoted as M1 and during the second half of the seizure the maximum value is denoted as M2. M2 should be at least 1.1 times M1 while at most being a value of 3 for a 3-channel case (see ref[4]).

The patient-specific results for amplitude correlation are shown in the last column of the Table 2. The trends in Table 2 have been shown in Table 3, where the amplitude correlation trends in percentages have been presented in the last column (the boldface entries in the last 3 rows). Nineteen of 21 (90%) patients show enhanced amplitude correlation (here too the signals have been band-pass filtered between 30 and 40 Hz) in the second half of the seizure, compared to the first. Correlation among all 3 focal ECoG channels has been

Table 2. Details of Patient-Specific Results.[a]

Patient Number	Total Seizures Occurred	High-Phase Synch in Gamma Band Toward Seizure Offset				Amplitude Correlation: Enhanced Highest Eigen Value Toward Seizure Offset (also see ref[4])
		Pairwise ch 1 & 2	Pairwise ch 2 & 3	Pairwise ch 3 & 1	Avg. pairwise	
1	4	All 4	1,2	1,2,4	All 4	All 4
2	3	All 3	1,3	3	1,3	3
3	5	1-4	1-4	1-4	1-4	All 5
4	5	All 5	2-5	2-5	2-5	2-5
5	5	None	None	None	None	1, 3, 4
6	3	1	3	1	1	1
7	3	1,2	None	None	2	2
8	2	None	None	None	None	None
9	5	1,3,4,5	5	5	4,5	1, 3,4,5
10	5	2,4	2,4	2,4,5	2,4,5	2, 4
11	4	1	2, 3	2, 3	2, 3	1-3
12	4	All 4	All 4	2-4	All 4	All 4
13	2	None	1	1	1	1
14	4	3,4	4	4	4	4
15	4	2	2	2	2	2, 3
16	5	1,2,5	4	1,4	2,4	1,2,4
17	5	3,5	5	5	5	1, 5
18	5	1,2	1,2	1,2,3,4	1,2	1, 2, 5
19	4	All 4	All 4	1,3,4	1,3,4	2,3,4
20	5	5	5	3	5	1, 3, 4, 5
21	5	None	None	None	None	None

[a] Numerical values in the columns other than the first indicate either the total number of seizures recorded in a patient or the seizure number in the sense seizure 1, seizure 2, seizure 3, etc, from a single patient.

Table 3. Summary of Results.[a]

A total of 87 seizures recorded from the focal ECoG of a total of 21 focal epileptic patients has been tested	Ch 1 & 2	Ch 2 & 3	Ch 3 & 1	Average of pairwise	Amplitude correlation
Total number of seizures showing the criterion	45	34	36	39	51
Number of patients showing criterion at least once	17	17	17	18	19
Total number of seizures only from the patients showing the criterion at least once	73	72	72	75	80
Percentage of seizures satisfying the criterion from all the seizures only from the patients showing the criterion at least once	62%	47%	50%	**52%**	**64%**
Percentage of seizures out of the total number of seizures from all the 21 patients whose focal ECoG during seizures has been tested	52%	39%	41%	**45%**	**59%**
Percentage of patients showing the criterion at least once out of all the 21 patients whose focal ECoG during seizures has been tested	81%	81%	81%	**86%**	**91%**

Abbreviation: ECoG, electrocorticoencehalogram.
[a] Here the word criterion means the enhancement of phase or amplitude coherence during the second half of seizure compared to the first half. The most important trends have been highlighted in boldface.

determined by Principal Component Analysis (PCA). This is given by the highest eigen value of the cross-correlation matrix among the focal channels. If this eigen value is increasing we state the cross-correlation among the channels is increasing, and if the highest eigen value is decreasing, we state the cross-correlation is decreasing (see ref[4] for further details). Fifty-one out of 80 (64%) of all seizures from the 19 patients have shown enhanced amplitude correlation across the focal channels during the second half of the seizure compared to the first. This is in contrast to the 100% of the 100 seizures of 60 patients showing the same trend as reported in ref.[4] We have observed the trend only in 59% of all the 87 seizures in 21 patients.

Table 4 lists the differences in the observed results between phase synchronization and amplitude correlation. The second column records the recording hour of the seizure for each patient for which the phase synchronization method reported a higher value during the second half of seizure duration compared to the first (enhanced phase synchronization toward the seizure offset), while the amplitude correlation method did not show such a trend. The third column records the recording hour of the seizure for each patient for which the amplitude

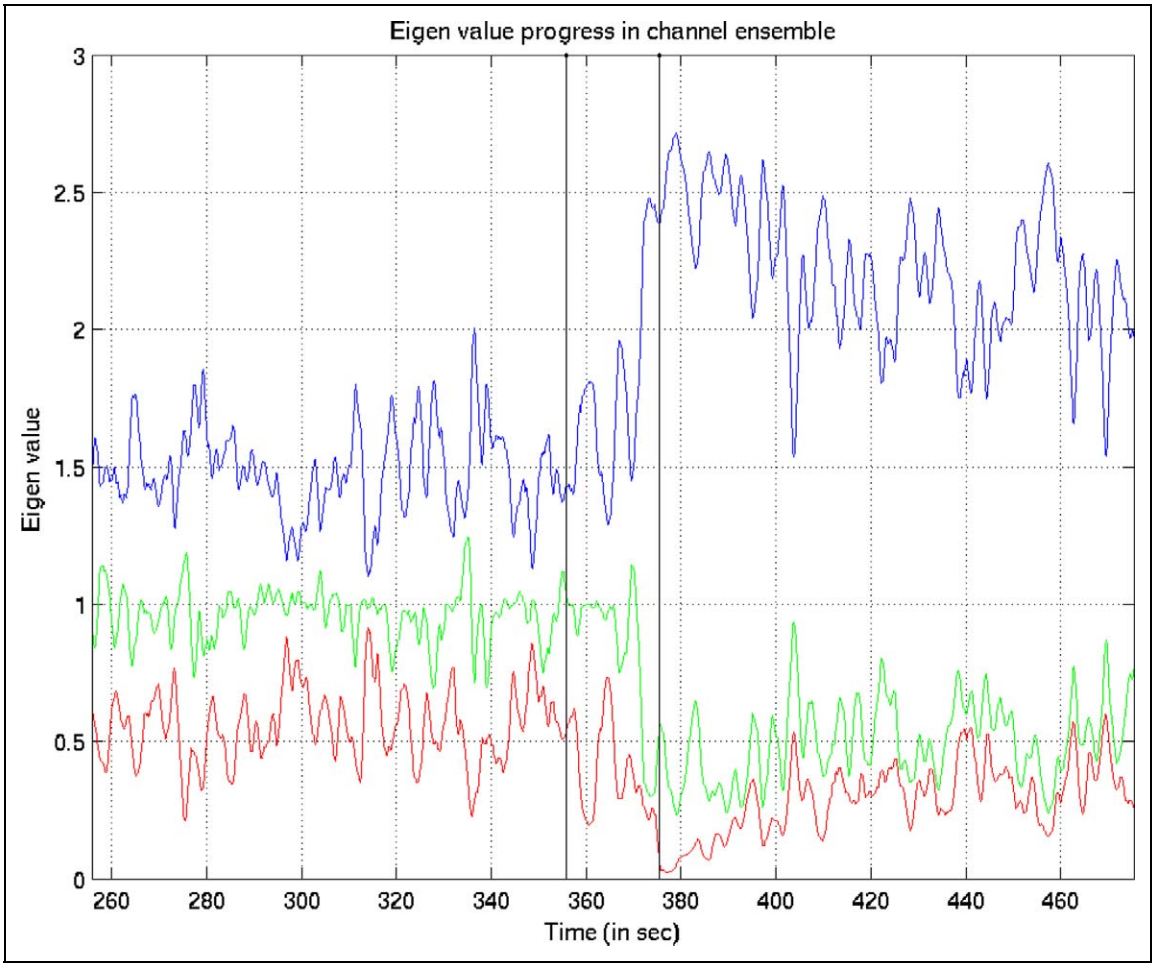

Figure 2. Amplitude correlation study among all the 3 focal channels during seizure 1 (recorded at seventh hour) of patient 1 in the lower gamma frequency band (30-40 Hz). The topmost graph represents the highest eigen value and the other graphs represent other eigen values in decreasing order respectively. The 2 vertical lines signify epileptologist-identified seizure onset and offset time. It is noted that an increase in synchronization as seen by an increase in the highest eigen value occurs during the end of the seizure offset.

correlation method reported a higher value during the second half of seizure duration compared to the first (enhanced amplitude correlation toward the seizure offset), while the phase synchronization method did not show any such trend. Each ''recording hour'' contains pre-ictal, ictal, and posti-ctal ECoG (the number of the patient has been shown in the first column of Table 4 and kept as it appeared in the Freiburg data set[21]) during a particular hour as mentioned in the second or third column of Table 4.

Table 4 shows that there are 3 seizures recorded in 3 patients which show enhanced phase synchronization toward seizure offset but does not show enhanced amplitude correlation during the same period. The same table also lists 15 seizures recorded in 10 patients which show enhanced amplitude correlation toward the seizure offset but not enhanced phase synchronization during the same period. Patient 19 has seizures of both types. Recent studies with single neuron recording in and around the seizure focus have highlighted that different cells start firing, differently some time ahead of a seizure onset. At the onset, and during the initial progress of an epileptic seizure, the firing patterns at the individual cell level remain quite heterogeneous. But the patterns usually become more homogeneous toward the end of the seizure.[1] However, we could not find any explanation why some the seizures have enhanced phase synchronization toward the end but no enhanced amplitude correlation, and some other seizures are reacting just the other way round even at times in the same patients.

Conclusion

Different types of coherence measures are the technological tools available for quantitative analyses of the binding problem (see ref[7]). Phase synchronization and amplitude correlation are the two most widely used coherence measurement tools. They are different from each other.[25] In this article, we have demonstrated that, in 18 patients, 3 (4%) of 75 seizures show enhanced phase synchronization toward seizure offset, but not enhanced amplitude correlation during the same period. Another 15 (19%) of 80 show enhanced amplitude correlation toward seizure offset, but not enhanced phase synchronization

Table 4. Phase Synchronization Versus Amplitude Correlation.

Patient Number	Seizure Hour in Which Gamma Band Phase Synchronization Increased Toward Seizure Offset	Seizure Hour for Enhanced Amplitude Correlation in Gamma Band Toward Seizure Offset
1	–	–
2	15th	–
3	–	176th
4	–	–
5	–	13th, 26th, 33rd
6	–	–
7	–	–
8	–	–
9	–	26th, 38th
10	200th	–
11	–	5th
12	–	–
13	–	–
14	–	–
15	–	41st
16	–	8th
17	–	99th
18	–	14th
19	15th	69th
20	–	13th, 55th, 82nd
21	–	–

[a] Seizure hour means 1 hour recording of pre-ictal, ictal, and post-ictal ECoGs during the specified numbered hour.

during the same period. The question is what kind of binding problems these 2 different coherence measures address and what are their biological significances? In view of recent single-neuron studies in and around the seizure focal points during ictal and interictal periods,[1-3] it would be useful to study phase and amplitude coherence simultaneously among such individual neurons.

It is interesting to note that a seizure can reduce brain pH from $\sim$7.35 to 6.8 through lactic acid production, CO_2 accumulation, and other mechanisms.[31] This enhanced acidity, due to a seizure, dampens excitatory neurons by reducing activities of the Na^+ and Ca^{++} ions. At the same time, it may excite inhibitory interneurons, because they have larger H^+-gated current, which is facilitated by extracellular acidity (for the detail see ref[31] and the references there in). From computational study, it is known that phase locking in a network is maintained by interconnected excitatory and inhibitory neurons in the network.[32] We hypothesize—as a seizure progresses the extracellular acidity increases leading to diminished firing of excitatory pyramidal neurons and enhanced firing of inhibitory interneurons. This induces greater synchronization in the seizure focal network toward the end of seizure. Study of covariance between extracellular acidity and synchronization across focal ECoG channels before, during, and after seizure will be interesting future research. This may help to understand some types of pharmacologically intractable epilepsies and their intervention methodologies.

Single-cell study by analyzing ECoG signals is relatively challenging, compared with local field potential study. By studying firing rate simultaneity among individual neurons in and around seizure focus, more homogeneous firing toward seizure offset than after the onset has been observed.[1] In our study, analyzing only 3 focal ECoGs (that is all we received from the Freiburg project[21]) channel data, we have observed higher signal coherence toward seizure offset than after onset in the majority of the seizures. Not surprisingly, this trend is widely variable across the patient population and even among seizures from the same patient. If this study can be extended to a larger number of ECoG channels, from seizure focal area up to a couple of centimeters beyond, more interesting and insightful patterns might be observed even in single individuals. One day this may even lead to some progress in seizure prediction. Our study underscores the fact that multiple signal processing techniques should be employed to have a deeper observation than is possible by a single technique alone.

One out of 21 patients had seizures, a fraction of which showed one type of coherence trend but not the other, and also another fraction showed the other coherence trend. This observation points toward an additional engineering challenge in the endeavor to develop automatic seizure monitoring techniques. Even in a single patient, multiple techniques might have to be employed simultaneously, in order to augment the success of automatic monitoring.

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Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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References

1. Truccolo W, Donoghue JA, Hochberg LR, et al. Single-neuron dynamics in human focal epilepsy. *Nat Neurosci*. 2011;14(5): 635-641.
2. Keller CJ, Truccolo W, Gale JT, et al. Heterogeneous neuronal firing patterns during interictal epileptiform discharges in the human cortex. *Brain*. 2010;133(pt 6):1668-1681.
3. Walker MC. Ups and downs of seizure activity. *Nat Neurosci*. 2011;14(5):535-536.
4. Schindler K, Leung H, Elger CE, Lehnertz K. Assessing seizure dynamics by analysing the correlation structure of multichanel intracranial EEG. *Brain*. 2007;130(pt 1):65-77.
5. Rosenblum M, Pikovsky A, Kurths J, Schafer C, Tass PA. Phase synchronization: From theory to data analysis. In: Moss F., Gielen

S., eds. *Neuro-Informatics and Neural Modeling*. Amsterdam, The Netherlands: Elsevier; 2001:279-321.
6. Iasemidis LD. Epileptic seizure prediction and control. *IEEE Trans Biomed Eng*. 2003;50(5):549-558.
7. Singer W, Gray CM. Visual feature integration and temporal correlation hypothesis. *Annu Rev Neurosci*. 1995;18:555-586.
8. Tallon-Baudry C, Bertrand O, Fischer C. Oscillatory synchrony between human extratriate areas during visual short-term memory maintenance. *J Neurosci*. 2001;21(20):RC177.
9. Fell J, Axmacher N. The role of phase synchronization in memory processes. *Nat Rev Neurosci*. 2011;12(2):105-118.
10. Chavez M, van Quyen ML, Navarro V, Baulac M, Martinerie J. Spatio-temporal dynamics prior to neocortical seizures: amplitude versus phase couplings. *IEEE Trans Biomed Eng*. 2003;50(5): 571-583.
11. Mormann F, Kreuz T, Andrzejak RG, David P, Lehnertz K, Elger CE. Epileptic seizures are preceded by a decrease in synchronization. *Epilepsy Res*. 2003;53(3):173-185.
12. Hammond C, Bergman H, Brown P. Pathological synchronization in Parkinson's disease: networks, models and treatments. *Trends Neurosci*. 2007;30(7):357-364.
13. Mormann F, Lehnertz K, David P, Elger CE. Mean phase coherence as a measure of phase synchronization and its application to the EEG of epilepsy patients. *Physica D*. 2000;53: 358-369.
14. Quian Quiroga R, Kraskov A, Kreuz T, Grassberger P. Performance of different synchronization measures in real data: a case study on electroencephalographic signals. *Phys Rev E Stat Nonlin Soft Matter Phys*. 2002;65(4 pt 1):041903.
15. Netoff TI, Schiff SJ. "Decreased neuronal synchronization during experimental seizures. *J Neurosci*. 2002;22(16):7297-7307.
16. Lachaux JP, Lutz A, Raudrauf D, et al. Estimating the time-course of coherence between single-trial brain signals: an introduction to wavelet coherence. *Neurophysiol Clin*. 2002;32(3): 157-174.
17. Van Quyen ML, Foucher J, Lachaux JP, et al. Comparison of Hilbert transform and wavelet methods for the analysis of neural synchrony. *J Neurosci Methods*. 2001;111(2):83-98.
18. Vishaka Datta S. Comparison of Hilbert, wavelet and Fourier transform for detecting phase synchronization, KVPY Project Report, Indian Statistical Institute, Bangalore; July 2010.
19. Uhlhaas PJ, Linden DEJ, Singer W, et al. Dysfunctional long-range coordination of neural activity during Gestalt perception in schizophrenia. *J Neurosci*. 2006;26(31):8168-8175.
20. Majumdar K. Constraining minimum norm inverse by phase synchronization and signal power of the scalp EEG channels. *IEEE Trans Biomed Eng*. 2009;56(4):1228-1235.
21. Freiburg Seizure Prediction Project, Freiburg, Germany; 2008. https://epilepsy.uni-freiburg.de/.
22. Aschenbrenner-Scheibe R, Maiwald T, Winterhalder M, Voss HU, Timmer J, Schulze-Bonhage A. How well can epileptic seizures be predicted? An evaluation of a nonlinear method. *Brain.* 2003;126(pt 12):2616-2626.
23. Maiwald T, Winterhalder M, Aschenbrenner-Scheibe R, Voss HU, Schulze-Bonhage A, Timmer J. Comparison of three nonlinear seizure prediction methods by means of the seizure prediction characteristics. *Physica D*. 2004;194:357-368.
24. Winterhalder M, Schelter J, Maiwald T, et al. Spatio-temporal patient-individual assessment of synchronization changes for epileptic seizure prediction. *Clin Neurophysiol*. 2006;117(11): 2399-2413.
25. Rosenblum MG, Pikovsky AS, Kurths J. Phase synchronization of chaotic oscillators. *Phys Rev Lett*. 1996;76(11):1804-1807.
26. Tass P, Rosenblum MG, Weule J, et al. Detection of n: m phase locking noisy data: application to magnetoencephalography. *Phys Rev Lett*. 1998;81(15):3291-3294.
27. Boashash B. Estimating and interpreting the instantaneous frequency of a signal. I. *Proc IEEE*. 1992;80:520-568.
28. Jefferys JGR, Traub RD, Whittington MA. Neuronal networks of induced '40 Hz' rhythms. *Trends Neruosci*. 1996;19(5):202-208.
29. Pfurtscheller G, Flotzinger D, Neuper C. Differentiation between finger, toe and tongue movement in man based on 40 Hz EEG. *Electroencephalogr Clin Neurophysiol*. 1994;90(6):456-460.
30. Pastor MA, Artieda J, Arbizu J, Marti-Climent JM, Penuelas I, Masdeu JC. Activation of human cerebral and cerebellar cortex by auditory stimulation at 40 Hz. *J Neurosci*. 2002;22(23):10501-10506.
31. Ziemann AE, Schnizler MK, Albert GW, et al. Seizure termination by acidosis depends on ASIC1a. *Nat Neurosci*. 2008;11(7): 816-822.
32. Lytton WW, Sejnowski TJ. Simulations of cortical pyramidal neurons synchronized by inhibitory neurons. *J Neurophysiol*. 1991;66(3):1059-1079.