Complex phase synchronization in epileptic seizures: Evidence for a devil's staircase

J. L. Perez Velazquez,[1,*] L. Garcia Dominguez,[1] and R. Wennberg[2]
[1]*Brain and Behaviour Programme, Department of Paediatrics, University of Toronto and Hospital for Sick Children, Toronto M5G1X8, Canada*
[2]*Krembil Neuroscience Centre, Toronto Western Hospital, Toronto M5T2S8, Canada*
(Received 6 September 2006; published 22 January 2007)

We describe multifrequency phase synchronization in epileptic seizures. Using magnetoencephalographic recordings from three patients suffering generalized seizures, the evidence is presented that, in addition to the commonly studied 1:1 frequency locking, there exists complex multifrequency coordination that, in some cases, follows a classical "devil's staircase." Within the limitations of observing this phenomenon in a clinical experimental setting, these observations reveal that in pathological brain activity, complex frequency locking can be found similar to that identified in certain pathological cardiac re-entrant arrhythmias. This may suggest the existence of similar re-entrant mechanisms active in cerebral neocortex during epileptic seizures.

DOI: 10.1103/PhysRevE.75.011922 PACS number(s): 87.19.La, 05.45.Xt

While it is known that complex rhythms are present in living organisms, the synchronization of these oscillations tends to occur in simple frequency locking ratios. In general, for most biological systems studied, synchronization at low-order frequency ratios (1:1, 1:2) is commonly found. Instances of more complex (larger integers) frequency locking in biology have been observed in male-female bird signing [1], in some specific cases of sensorimotor coordination in humans [2], in muscle-brain synchronization during Parkinsonian tremor [3], and in periodically driven action potentials in neuronal axons [4], and in cardiac cells [5]. But it is in the study of cardiac activity and in cardiorespiratory synchronization where multifrequency locking has been most abundantly reported [6–10]. Current approaches in neuroscience use synchronization as a tool to determine coordinated activity in brain areas, or, in other words, to determine how specific brain regions interact in order to give rise to behavioral responses or sensory perceptions. Methods for estimating synchronization are also used to assess pathological interactions between brain areas, and, in particular, synchrony studies have been applied, to a very large extent, to the characterization of epileptiform activity [11–14].

Spatial and temporal patterns of phase synchronization during epileptiform activity have been recently studied [12–15], concentrating on the typical 1:1 frequency locking. In the present study, we report evidence that there exist more complex frequency locking ratios during seizures, and in some cases, a typical "devil's staircase" can be observed. We concentrate on spontaneous brain activity recorded from the neocortex during epileptiform events, obtained from magnetoencephalographic (MEG) recordings in three patients suffering from generalized seizures, who gave informed consent to have the MEG recording performed as part of their clinical investigations for diagnosis and pre-surgical assessment. The recordings were obtained at a sampling rate of 625 Hz, using a CTF Omega 151 channel whole head system (CTF Systems Inc., Port Coquitlam, Canada). The data consisted of 45 episodes (15 per patient) of 2 min each, simultaneously recorded by 146 MEG sensors. During the recording time, seven seizures occurred in one patient with symptomatic generalized epilepsy (patient 1), two seizures in a second patient with frontal lobe epilepsy (patient 2), and one seizure in the third patient, with absence epilepsy (patient 3). Seizures had durations between 8 and 18 sec. We use the analytic signal approach, employing the Hilbert transform to estimate instantaneous phases [16,17] and calculate phase locking between two MEG recording channels (sensors). With noisy data, phase synchronization is defined in a statistical sense: two signals are phase synchronized if the difference between their phases is nearly constant over a selected time window, that is, it clusters around a single value; a measure of this is the circular variance R [13], of the phase differences $\Delta\theta(t)$:

$$R_{jk} = |\langle \exp(i\Delta\theta_{jk}(t)) \rangle|.$$

Here $|\cdot|$ denotes the norm and $\langle\cdot\rangle$ the mean value. $\Delta\theta_{jk}(t) = \theta_j(t) - \theta_k(t)$ are the series of phase differences between the analytic signals of series indexed by j and k over a given time window T. The value of R varies from 0 to 1, the higher the value the tighter the clustering of the phase differences $\Delta\theta$ about a single mean value; that is, the closer the R value to 1 the more synchronized the signals. There are alternative measures such as those based on Shannon entropy that will offer similar results. This issue has been thoroughly treated in some excellent works, such as Refs. [16,18–21]. Thus, phase synchrony analysis was performed on band-passed signals, using a constrained least square finite impulse response filter (FIRCLS), with a specified central frequency "f" and cutoffs $f \pm 2$ Hz; we studied synchrony in the range 5–35 Hz. Synchrony values (R) were calculated, using 1-sec time windows, following the procedure described in Ref. [13] (see also [14] for details of phase locking estimation in this specific setting).

We follow Tass *et al.* [3] to detect $m:n$ phase locking from noisy data. The condition for $m:n$ synchronization

*Mailing address: The Hospital for Sick Children, Division of Neurology, Room 6535 Hill Wing, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada. E-mail address: jose-luis.perez-velazquez@sickkids.ca

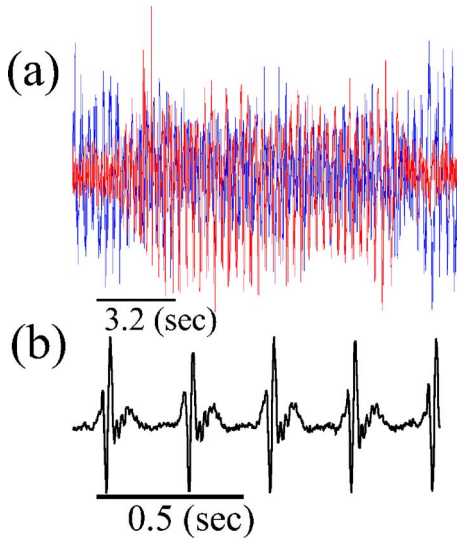

FIG. 1. (Color online) (a) Original MEG trace corresponding to an absence seizure (red in color appears as light gray in grayscale) and one surrogate obtained as described in the text (blue in color appears as dark gray in grayscale). (b) Detail of the absence seizure recorded at one MEG sensor. Note the 3–4 Hz spike-and-wave and the higher frequency components embedded in the main oscillation.

reads $|\varphi_{m,n}(t)| < \text{const}$, where $\varphi_{m,n}(t) = n\theta_1(t) - m\theta_2(t)$. Here n and m are integers, $\theta_{1,2}$ are the phases of the two oscillators, and $\varphi_{m,n}$ is the generalized phase difference. When this is used for higher order frequency ratios, it is important to consider that the cutoffs are wider than ±2 Hz: for instance, if 1:2 (signal #1:signal #2) is assessed, then the cutoff would be $f \pm 2$ Hz for signal #1, and $2f \pm 4$ Hz for signal #2. Thus, whenever $m:n$ was the ratio to be analyzed, signals were band passed according to the following formulas: Signal 1: $F \pm 2$ Hz; Signal 2: $(F \pm 2 \text{ Hz}) \times n/m$ with $n > m$. These procedures are also clearly explained in detail in Ref. [22].

To avoid spurious detection of phase locking, we derive significance levels by comparing with surrogate data sets. In this particular study, we compared the phase locking between two original signals (from two MEG sensors) and that obtained from 20 surrogates (details in the text below). Surrogates, in our study, were obtained from the original seizure events, by randomizing their phases, in that the original signals were initially Fourier transformed and the phases of the coefficients were randomized. Then, the resulting coefficients were transformed back (inverse Fourier transform) to the signal.

Figure 1 depicts one original MEG recording of an absence seizure and one surrogate, for comparison. In Fig. 1(b), a detail of the epileptiform activity is shown, to demonstrate that, while the main frequency in human absence seizures is the so called spike-and-wave oscillation seen here at around 4 Hz, there are many higher frequency components, thus creating the possibility of multifrequency locking. The signals from several MEG sensors were selected, of which some were neighboring (adjacent) channels detecting cortical signals in nearby areas. In total, 30 pairs were (arbitrarily) selected for patient 1, 4 pairs for patient 2, and 20 pairs for patient 3. Of these, 1:1 phase locking was first analyzed (examples in Figs. 2 and 3). Only those pairs for which 1:1 locking was found during the seizure [which was the case in most (>90%) of the pairs], were further processed for the possibility of multifrequency locking ratios. Instances of phase locking at multifrequency ratios were detected most clearly in patients 2 and 3, while for patient 1, only 1:2 and 1:3 phase locking was detected in the synchronization analysis of only two pairs of MEG sensors. However, for patients 2 and 3, the presence of phase locking at very different frequency ratios was commonly detected: 75% of the sensor pairs for patient 2, and 70% for patient 3. Of these, it was most common to observe instances of multifrequency locking between neighboring MEG sensors (75%). Examples of 3:4 phase locking are presented in Figs. 2 (patient 3) and 3 (patient 2). Multifrequency phase synchronization was not observed at all frequency ranges studied: for patient 2, multifrequency locking was evident at frequencies between 10–20 Hz, and for patient 3 at frequencies between 5–8 Hz. This could be expected, at least for patient 3, because the main signal in her seizure is the 3–4 Hz spike and wave, typical of absence epilepsy (Fig. 1). The main signals recorded during the seizures in patients 1 and 2 were of lower amplitude and less uniform in frequency, ranging between 10–30 Hz. Figures 2 and 3 depict how we estimated synchronization, by defining a threshold during the time when the seizure occurs. The upper panels of the figures show the phase difference, where phase locking is represented by hori-

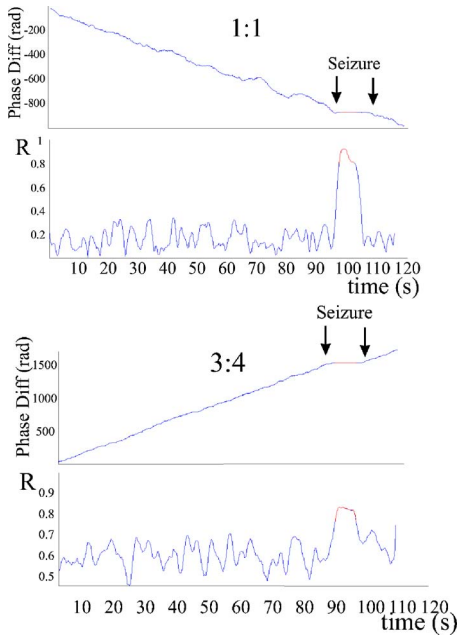

FIG. 2. (Color online) Phase difference and synchrony indices (R) between two cortical areas, corresponding to MEG sensors RC32 (located over the right central neocortex) and RF11 (right frontal) for the upper plots, and LC14 (left central) and LC15 (left central, adjacent to the previous LC14) for the lower plots. The time of the seizure (which lasted approximately 12 seconds, detail shown in Fig. 1) is marked by arrows. Upper plots show the phase synchrony for 1:1 frequency locking, and the lower plots correspond to a 3:4 locking. Central frequency was 5 Hz. In the phase difference plots, phase locked modes are visualized as horizontal lines.

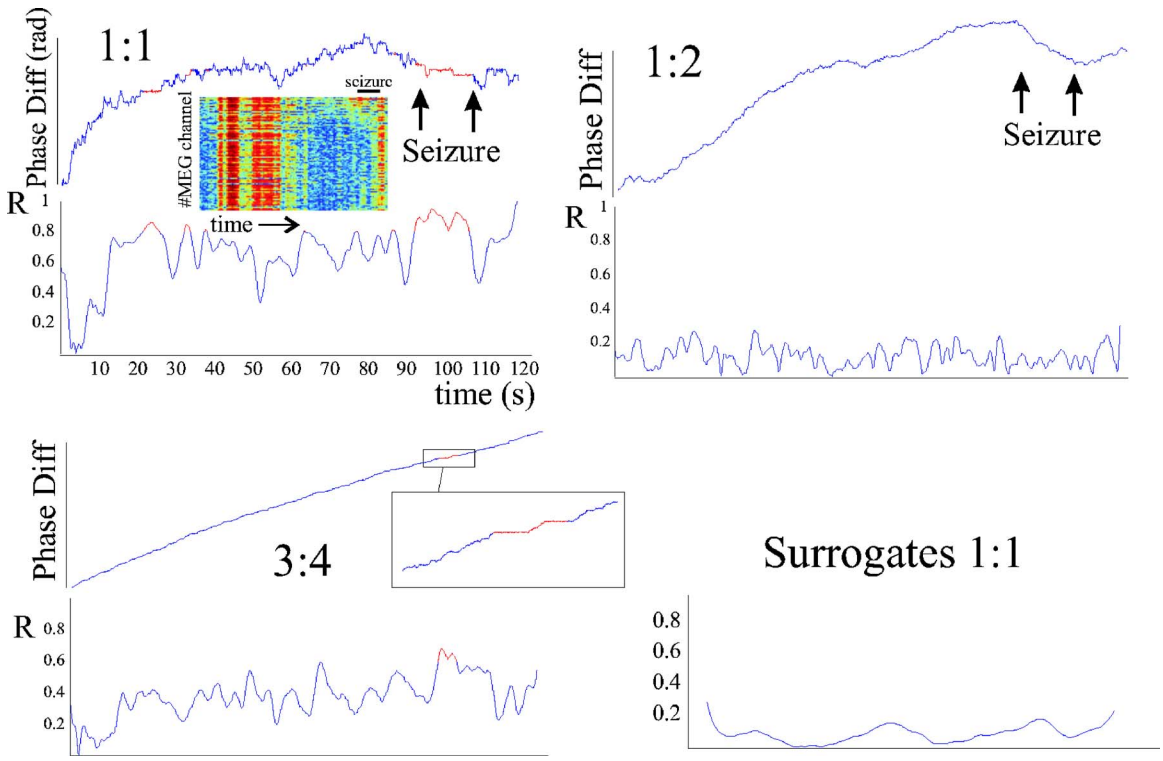

FIG. 3. (Color online) Similar representations as in Fig. 2, showing 1:1 and 3:4 locking for another recording in a different patient. The seizure, in this case, occurs between the 94th and 108th second (marked by arrows). No 1:2 phase locking was detected in this case. Also shown are the R values for the synchronization between two surrogates ("surrogates 1:1") corresponding to the original signals in the other plots. Note how low the R values are, compared with the original 1:1 graph. The inset on the first panel shows the color-coded 1:1 synchronization for this 2-min recording (red in color appears as light gray in grayscale is maximum, blue in color appears as dark gray in grayscale is minimum), to show that, about 1.5 min before the seizure, there is a period of time with high synchrony. This inset represents the average of all MEG channels (on the y axis); the high synchrony in this time period before the seizure can also be seen in the 1:1 plot for the two specific channels shown in the figure, by the red line segments at ~20–40 sec, both on the phase difference time series (flat red segments) and the R values (red peaks).

zontal segments; the lower panels are the synchrony indices (R) derived from the phase differences. Note that the R values are higher during the time of the seizure than during the rest of the recording (as aforementioned, each segment was of 2-min duration). Hence, a threshold was defined (red segments in the figures), to compare the R values thus obtained with those from surrogate series. Surrogates were obtained from the same signals that revealed multifrequency locking, and the presence of phase locking was searched for between surrogate series. Twenty surrogates were generated from the original time series per each frequency ratio that was found in the phase synchrony between the original series; thus, a total of 320 surrogates were generated for patient 2, and 500 for patient 3. To estimate when the surrogate series were synchronized, the same thresholds for R as defined for each case of the original series were used (red segments in Figs. 2 and 3). One plot in Fig. 3 shows the typical R values for two surrogate series. The probability of finding multifrequency locking in the surrogate population was 0.3% for the surrogates of patient 2, and 10% for patient 3. This indicates that the high probability of finding multifrequency locking in our recordings is not due to stochasticity of the time series.

High synchrony values, approaching as high as those observed during some seizures, were found as well in some other, nonseizure, parts of the recordings (which are called, in clinical terms, the interictal activity, or activity between seizures). However, only 1:1 phase locking was found in these cases, and never any higher order. We hypothesize that one possibility is that multifrequency locking is revealed during seizures because the 1:1 synchrony is stable for a relatively long period of time, almost the entire time of the seizure (in our cases seizures lasted between 8 and 18 s). During normal brain activity, finding long periods of phase locking is uncommon, and so it is almost impossible to assess the aforementioned hypothesis. However, the case of patient 2 gave us an extraordinary opportunity to address that line of reasoning, because this patient had two segments of high and sustained 1:1 phase locking during interictal periods, both of which were between 10 and 12 seconds in duration, very similar to the duration of her seizures (~14 seconds). These periods of high synchronization, which occurred ~1 min before the seizure event in Fig. 3, can in fact be clearly identified in the 1:1 synchrony color-coded plot in the figure (inset). The seizure here occurred between the 94th and 108th second. The high synchrony in these two interictal time periods (between ~20–40 seconds in the plot time axis) was not related to any observable seizure activity (or to any recording artifact), upon inspection of

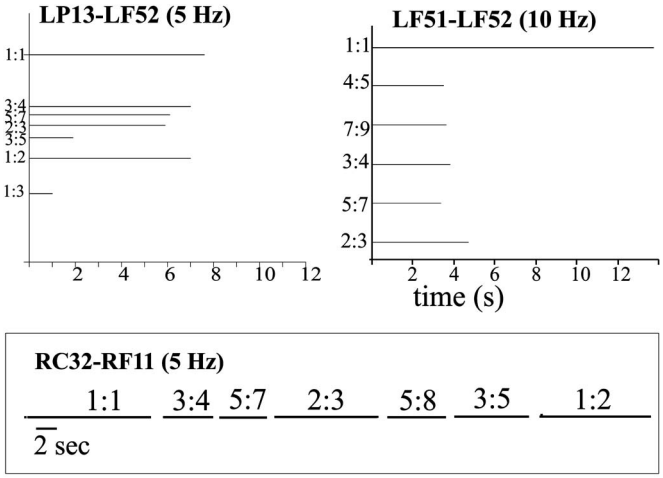

FIG. 4. Higher-order synchronization plateaus found during a seizure in patient 3 (left-hand side plot), and patient 2 (right-hand side), the MEG sensors and central frequencies are indicated at the top of the graphs. Sensor LP13 records activity in left central neocortex, and LF51 and LF52 in left frontal lobe. The x axis is the duration (in seconds) of the phase locking region derived from plots like those shown in Figs. 2 and 3. Notice that low-order ratios tend to be of longer duration than more complex ones. If, instead of time, a control parameter could be identified and used for the x axis, these plateaus would form a devil's staircase structure. Lower graph shows the time duration of several phase locking ratios, for two MEG sensors during the absence seizure in patient 3. Sensors RC32 and RF11 record activity in right central and right frontal cortex, respectively. Note here the Arnold tonguelike structure, and again, how the low-order ratios last longer than higher-order ones.

the MEG recordings. However, no clear higher-order phase locking ratios were detected in these two segments of sustained 1:1 locking, indicating that the observation of multifrequency locking may not be simply related to the relative duration of the 1:1 synchrony, but may be associated with an abnormal synchronization mechanism operating in seizures, as discussed below.

Interestingly, the organization of some of the frequency ratios in which phase locking was found, for specific signals, followed the typical trend of a so-called devil's staircase (Fig. 4). This point deserves comment. In essence, the mathematical representation of synchronization is a torus [21–23], with winding number $m:n$ (frequency ratio between the two oscillators), which has been described by the circle map [16,21,24]. A property found in the analysis of the circle map is self-similarity: if there are two regions of synchronization with winding numbers $m:n$ and $r:s$, then there exists one in between, with number $m+r:n+s$. This dependence of the winding number with a detuning parameter (for circle maps), leads to a complex picture of phase locking regions that has been termed the "devil's staircase" [25] : in essence, the variation of the winding number as a function of a control parameter (the forcing period, or, alternatively, the frequency detuning between oscillators, are two commonly used) [21,26,27] . The phase locking graph is eventually densely covered with frequency-locking intervals, but most of these infinite steps have an infinitesimal width, so the ones observed are the simpler ratios between small integers, such as 1:1 and 2:3. Obviously, in our studies, because we use spontaneous brain signals, we neither have access to a control parameter (which means we do not have an appropriate x axis to construct our plot), nor do we really know what possible parameters may be influencing the synchronization regime during seizures (which are probably many, this is currently an active area of research). Nevertheless, the synchronization plateaus shown in Fig. 4 are strongly reminiscent of the structure of a devil's staircase. In Fig. 4, we plot the duration (in seconds) of the phase locking segments within the seizure found in the analysis. Note how the low winding numbers (1:1, 1:2) tend to last longer than higher numbers. The lower plot in Fig. 4, an example of the synchronization plateaus found between the two MEG sensors specified in the figure legend, depicts a classical Arnold tongue structure. Arnold tongues represent phase locking regions in parameter space [16]. The observation of a more complete Arnold tongue plot, as well as a clear devil's staircase that incorporates a control parameter, is precluded in the case of studies like ours that use spontaneous events. For example, in principle, the devil's staircase has infinite steps, as the winding number is considered a continuous function of a control parameter, which cannot be observed in clinical experimental situations like the one here described. Similarly, the Arnold tongue structure is formed by many synchronization plateaus for different values of, say, a control parameter or frequency detuning, so that real "tongues" are formed. In our case, we are probably looking at what occurs for just one value of one (or many) control parameter(s) operating during seizures.

In general, frequency locking is a structurally stable phenomenon [27], thus it may be no surprise that it is observed in the case of seizures, which persist for a relatively long time. The common presence of low-order synchrony ratios in natural phenomena has been proposed to be due to the structural stability of rational frequency ratios (for a detailed discussion, please consult Ref. [27], pp. 298–300). The phase synchrony we detect in these types of studies, however, may not correspond exactly to the classical, physical definition of synchrony: adjustment of frequencies between two coupled oscillators [16]. First, we are not sure that the brain areas from which recordings are made are truly (functionally) coupled; and second, it is possible that the synchrony we detect may be imposed by a remote, deep brain area connected to the two neocortical areas from which the recordings are obtained. With all these limitations in mind (this is not the place to address them in detail), synchrony studies still provide important information to understand the coordinated activity of brain circuits. Thus, we propose that, rather than true "synchrony," studies like ours might be more accurately described to measure, in a more general sense, coordinated brain activity. In this regard, we take the position of others that transient phase locking is necessary for dynamic correlations in nervous tissue [2,28], but that whether or not such phase locking represents pure, classical synchronization processes may not be crucial for the purpose of unravelling brain dynamics. For a general, wider discussion on these topics, we recommend Ref. [29].

The presence of complex phase locking indicates that epileptiform activity could be captured using circle map models,

so that the synchronization regime can in principle occur in an invariant manifold (torus). Indeed, some studies have addressed the general question of whether the synchronization manifold is normally hyperbolic [30], and thus persistent [31,32]; perhaps this is the case in epileptiform activity. The findings here reported are also related to specific dynamical regimes found in epilepsy, particularly intermittency and period doubling [33,34]. Intermittency and multifrequency synchronization are intimately related [2]. Theoretical studies on circle maps applied to cardiac activity have suggested that 1:1 phase locking arises from a tangent bifurcation and loses stability via period doubling [24]. In general, the phenomenon here described fits with current thoughts in neuroscience, especially the concepts of metastable states in neuronal activity [2,29,35–39] and multifrequency sensorimotor coordination [2].

We can only speculate as to the physiology underlying higher order phase locking in brain activity, by comparing with the more frequently observed multifrequency locking in pathological cardiac re-entrant arrhythmias, specifically atrial flutter [7,8]. In the heart, re-entrant arrhythmias are dependent on the presence of asymmetrical conduction within cellular networks [40]. The cytoarchitecture of the cerebral neocortex is unquestionably much more complex than the heart. Nevertheless, cardiac arrythmias and epileptic seizures share certain characteristics as dynamical disorders of human physiology, and the common finding of complex phase synchronization in both at least raises the possibility of common re-entrant mechanisms. Simulation studies using neuronal networks have addressed these concepts [38,39,41]. A recent theoretical study using Kuramoto-type oscillators [42] has demonstrated that the re-entrance of the synchronization transition is a function of the coupling between oscillators, at least for intermediate values of coupling. In general, it has been proposed that re-entrant connections establish and maintain cooperation among neural network regions [41], thus this process could be intimately involved in the continuous formation and dissolution of neuronal assemblies in brain function [2,28,29,37–39]. Hence, for a fluctuating parameter such as coupling between brain cells, which changes significantly during epileptiform activity (for instance, inhibitory synaptic potentials become excitatory during seizures [43]), we could expect to see this phenomenon of re-entrant synchronization, and thereby encounter the relatively uncommon phenomenon of multifrequency phase locking during seizures.

ACKNOWLEDGMENTS

Our work is supported by a Discovery grant from the National Science and Engineering Research Council of Canada (NSERC).

[1] R. Laje and G. B. Mindlin, Phys. Rev. Lett. **91**, 258104 (2003).
[2] J. A. S. Kelso, *Dynamic Patterns* (MIT Press, Cambridge, 1995).
[3] P. Tass, M. G. Rosenblum, J. Weule, J. Kurths, A. Pikovsky, J. Volkmann, A. Schnitzler, and H-J. Freund, Phys. Rev. Lett. **81**, 3291 (1998).
[4] G. Matsumoto, K. Aihara, Y. Hanyu, N. Takahashi, S. Yoshizawa, and J. Nagumo, Phys. Lett. A **123**, 162 (1987).
[5] J. Hescheler and R. Speicher, Eur. Biophys. J. **17**, 273 (1989).
[6] A. Garfinkel *et al.*, J. Clin. Invest. **99**, 305 (1997).
[7] A. Castellanos, F. Moleiro, N. Saoudi, A. de la Hera, and R. J. Myerburg, Am. J. Cardiol. **75**, 947 (1995).
[8] A. Castellanos, F. Moleiro, N. Saoudi, A. Interian, and R. J. Myerburg, Am. J. Cardiol. **76**, 523 (1995).
[9] C. Schäffer, M. G. Rosemblum, J. Kurths, and H-H. Abel, Nature (London) **392**, 239 (1998).
[10] M-C. Wu and C-K. Hu, Phys. Rev. E **73**, 051917 (2006).
[11] R. Cohn and H. S. Leader, Electroencephalogr. Clin. Neurophysiol. **22**, 421 (1967).
[12] M. Chavez, C. Adam, V. Navarro, S. Boccaletti, and J. Martinerie, Chaos **15**, 023904 (2005).
[13] F. Mormann, K. Lehnertz, P. David, and C. E. Elger, Physica D **144**, 358 (2000).
[14] L. Garcia Dominguez, R. Wennberg, W. Gaetz, D. Cheyne, O. C. Snead, and J. L. Perez Velazquez, J. Neurosci. **25**, 8077 (2005).
[15] M. Le Van Quyen, J. Martinerie, V. Navarro, M. Baulac, and F. J. Varela, J. Clin. Neurophysiol. **18**, 191 (2001).
[16] A. Pikovsky, M. G. Rosemblum, and J. Kurths, *Synchronization: A Universal Concept in Nonlinear Sciences* (Cambridge University Press, Cambridge, 2001).
[17] F. J. Varela, J-P. Lachaux, E. Rodriguez, and J. Martinerie, Nat. Rev. Neurosci. **2**, 229 (2001).
[18] V. S. Afraimovich, N. N. Verichev, and M. I. Rabinovich, Radiophys. Quantum Electron. **29**, 795 (1986).
[19] L. M. Pecora, T. L. Carroll, G. A. Johnson, D. J. Mar, and J. F. Heagy, Chaos **7**, 520 (1997).
[20] M. Rosenblum, P. Tass, J. Kurths, J. Volkmann, A. Schnitzler, and H. J. Freund, in *Chaos in Brain?* edited by K. Lehnertz, J. Arnhold, P. Grassberger, and C. E. Elger (World Scientific, Singapore, 2000).
[21] V. S. Anishchenko, V. V. Astakhov, A. B. Neiman, T. E. Vadivasova, and L. Schimansky-Geier, *Nonlinear Dynamics of Chaotic and Stochastic Systems* (Springer, Berlin, 2002).
[22] M. G. Rosenblum, P. Tass, J. Kurths, J. Volkmann, A. Schnitzler, and H-J. Freund, in *Chaos in Brain?* edited by K. Lehnertz *et al.* (World Scientific, Singapore, 2000).
[23] G. B. Ermentrout and N. Kopell, J. Math. Biol. **29**, 195 (1991).
[24] L. Glass, M. R. Guevara, A. Shrier, and R. Perez, Physica D **89**, 7 (1983).
[25] B. Mandelbrot, *Fractals: Form, Chance and Dimension*. (Freeman, San Francisco, 1977).
[26] S. J. Shenker, Physica D **5**, 405 (1982).
[27] P. Berge, Y. Pomeau, and C. Vidal, *Order within Chaos* (John Wiley & Sons, New York, 1984).
[28] K. J. Friston, K. M. Stephan, and R. S. J. Frackowiak, Hum.

Brain Mapp **5**, 48 (1997).
[29] I. Tsuda, Behav. Brain Sci. **24**, 793 (2001).
[30] S. Wiggins, *Normally Hyperbolic Invariant Manifolds in Dynamical Systems* (Springer, Berlin, 1994).
[31] K. Josic, Phys. Rev. Lett. **80**, 3053 (1998).
[32] L. Kocarev, U. Parlitz, and R. Brown, Phys. Rev. E **61**, 3716 (2000).
[33] J. L. Perez Velazquez, H. Khosravani, A. Lozano, P. L. Carlen, B. L. Bardakjian, and R. Wennberg, Eur. J. Neurosci. **11**, 2571 (1999).
[34] J. L. Perez Velazquez, M. A. Cortez, O. C. Snead, and R. Wennberg, Physica D **186**, 205 (2003).
[35] V. I. Kryukov, G. N. Borisyuk, R. M. Borisyuk, A. B. Kirillov, Y. I. Kovalenko, in *Stochastic Cellular Systems: Ergodicity, Memory, Morphogenesis* (Manchester University Press, United Kingdom, 1990).
[36] A. A. Fingelkurts and A. A. Fingelkurts, Int. J. Neurosci. **114**, 843 (2004).
[37] J. L. Perez Velazquez and R. Wennberg, in *Recent Research Developments in Biophysics* (Transworld Research Network, Kerala, 2004) Vol. 3.
[38] I. Tsuda, H. Fuji, S. Tadokoro, T. Yasuoka, and Y. Yamaguti, J. Integr. Neurosci. **3**, 159 (2004).
[39] K. Kaneko and I. Tsuda, Chaos **13**, 926 (2003).
[40] M. S. Spach and M. E. Josephson, J. Cardiovasc. Electrophysiol. **5**, 182 (1994).
[41] E. M. Izhikevich, J. A. Gally, and G. M. Edelman, Cereb. Cortex **14**, 933 (2004).
[42] F. Radicchi and H. Meyer-Ortmanns, Phys. Rev. E **74**, 026203 (2006).
[43] J. L. Perez Velazquez and P. L. Carlen, Eur. J. Neurosci. **11**, 4110 (1999).