Epilepsia, **44**(Suppl. 12):30–43, 2003
Blackwell Publishing, Inc.

Toward a Neurodynamical Understanding of Ictogenesis

*Michel Le Van Quyen, *†Vincent Navarro, *Jacques Martinerie, *†Michel Baulac, and *Francisco J. Varela

**LENA (Laboratoire de Neurosciences Cognitives et Imagerie Cérébrale), and †Unité d'Epileptologie,CNRS UPR 640, Hôpital de la Pitié-Salpêtrière, Paris, France*

Summary: Although considerable information on cellular and network mechanisms of epilepsy exists, it is still not understood why, how, and when the transition from interictal to ictal state takes place. The authors review their work on nonlinear EEG analysis and provide consistent evidences that dynamical changes in the neural activity allows the characterization of a preictal state several minutes before seizure onset. This new neurodynamical approach of ictogenesis opens new perspectives for studying the basic mechanisms in epilepsy as well as for possible therapeutic interventions. **Key Words:** Seizure anticipation—Ictogenesis—Nonlinear analysis—EEG—Synchronization.

In Memoriam
Francisco J. Varela (1946–2001)

On May 28, 2001, Franscico J. Varela passed away. With his passing, the science of brain dynamics and consciousness has lost one of its most brilliant, original, creative, and compassionate thinkers. During the latter years of his career, he was the head of the Neurodynamics Group at the Laboratory of Cognitive Neurosciences and Brain Imaging (CNRS UPR 640), at the Pitié-Salpêtrière Hospital in Paris. He gave a considerable impulsion to the group working in different fields: experimental studies using multiple electrode recordings of epilepsy patients and mathematical analysis of large-scale neuronal integration during cognitive processes; philosophical and empirical studies of the "neurophenomenology" of human consciousness; and mathematical studies on the nonlinear dynamical analysis of brain activity (seizure anticipation), by sharing his exceptional skills and considerable knowledge in neurobiology, neural dynamics, cognitive neuroscience, and philosophy. The spirit of his unique and exemplary style of research has never been stronger and will continue to inspire many of us for years to come (to see more details: Francisco's obituary: http://psyche.csse.monash.edu.au/v7/psyche-7-12-thompson.html).

One of the most disabling aspects of epilepsy is that seizures appear to be unpredictable. For patients with intractable epilepsy, this unpredictability of seizure is responsible for enhanced risk for morbidity (1) and represents a major factor of worse quality of life (2). Anticipation of seizure onset, even of short term, would provide time for the application of preventive measures to minimize seizure risk and, ultimately, to improve quality of life. Moreover, successful completion of this goal will provide some light for the characterization of basic pathophysiologic mechanisms responsible for individual seizures, the so-called "ictogenesis," and for the development of an epileptic condition (3).

After a few negative findings (4,5), the search in EEG signals for hidden information, predictive of an impending seizure, has been a focus of much recent interest (6,7). This resurgence of interest has been motivated mainly by new advances in mathematical methods to analyze complex systems. In particular, the techniques of nonlinear dynamics have been subject of recent developments in theoretical or experimental neurobiology (8). According to this new approach called *Neurodynamics* (9), EEG signals can no longer be regarded as a purely stochastic phenomenon but reflect the behavior of hidden dynamical patterns that are not detected by traditional linear signal analysis. Because of its high versatility, nonlinear time-series analysis was successfully applied in a variety of disciplines, including cardiology (10), psychiatry (11,12), and neurology (13,14). One of the most challenging arenas for the application of the nonlinear analysis is the problem of seizure anticipation.

In recent years, several studies based on nonlinear analyses of EEG recordings have provided strong evidence that the interictal–ictal state transition is not always an abrupt phenomenon (15–23). These findings indicate that it is possible to detect a *preseizure* state of several minutes, anticipating the electroclinical onset of a seizure.

Address correspondence and reprint requests to Dr. M. Le Van Quyen at LENA (Laboratoire de Neurosciences Cognitives et Imagerie Cérébrale), CNRS UPR 640, Hôpital de la Pitié-Salpêtrière, 47 Blvd. de l'Hôpital, 75651 Paris cedex 13, France.

This possibility of seizure anticipation has generated both excitement and concerns. Most of the concerns result from overstatements and misunderstanding that have polarized parts of the scientific community. We review here some of the ongoing work of our group concerning seizure anticipation. We also present the limitations of this approach and the many open questions. We do not believe that nonlinear analysis will answer all of the questions about seizure anticipation, and this review should be thought as a report of work in progress. However, we suspect that this approach may help us to reframe this old question in a new, effective way and contribute to a better understanding of why, how, and when the transition from interictal to ictal state takes place.

CLINICAL CONSIDERATIONS

As stated earlier, a fundamental feature of epilepsy is the spontaneous occurrence of seizures, often without warning and for no apparent reason. For only ~3% of all patients with epilepsy (the so-called reflex epilepsies), the seizures are explicitly evoked by an external stimulus. For the other patients, no clear events determine when a seizure will occur. Nevertheless, a number of clinical observations indicate that an epileptic seizure is not an abrupt phenomenon that occurs like a bolt from the blue:

Changes in internal milieu (stress, startle, sleep or lack of it, biorhythms, menses) and external environment (intermittent photic stimulation) are known to be favorable to facilitate seizures (3). The term *seizure threshold* is used to explain this tendency to have seizures determined by predisposing and facilitating factors (i.e., they do not necessarily evoke seizures, but may increase the likelihood of attacks by sensitizing the brain to some stimulus for the period in which they operate). Lennox (24) first proposed some of these factors in his Reservoir Theory. In brief, this theory implies that the input of various metabolic, emotional, and other factors fill a reservoir until it overflows (i.e., seizure threshold is reached) and a seizure ensues.

Some *warning symptoms*, also called prodomi, also have been reported sometimes to precede epileptic seizures from several minutes to hours. These symptoms include depressive disorder, irritability, sleep disorders, nausea, and headache. A multicenter study of 562 patients recently investigated the frequency of the occurrence of warning symptoms (25). Unexpectedly, ~50% of the patients experienced warning symptoms before a smaller or greater part of their seizures. Usually a long interval >5 minutes (in 42% of the cases) elapsed between the warning symptom and the onset of the seizure. This interval may allow a distinction between the warning symptoms and the "aura" considered as the early part of the seizure.

Autonomic changes were reported before temporal lobe seizures (26). The dynamics of autonomic functions were derived from oscillations in heart R-R interval by using a time–frequency mapping during preictal, ictal, and postictal periods. The results showed that subclinical autonomic changes hallmark clinical seizure onsets for several minutes.

Penfield (27) was the first to note that the *cerebral blood flow* (CBF) changes before an epileptic seizure. He hypothesized that electrical and clinical seizure onsets appear to be only epiphenomena that are preceded by significant changes in CBF. More recently, this hypothesis was further supported by invasive techniques measuring regional CBF in a continuous fashion (28) or fortuitous noninvasive SPECT (single-photon emission computed tomography) observations (29). The studies demonstrated that preictal modifications occur in CBF ~10 min before temporal lobe seizures. Significant alterations have been reported in both epileptogenic and contralateral nonepileptogenic neocortex, consistent with a widespread alteration of brain perfusion before seizure onset.

PROBLEM DEFINITION: SEIZURE DETECTION VERSUS SEIZURE ANTICIPATION

The EEG correlate of the seizure in partial epilepsy is characterized by the sudden appearance of an ictal discharge out of the ongoing background activity (3). These ictal patterns are identified by the expert's visual inspection of EEG recordings—still the "gold standard" for seizure identification. The term *seizure detection* refers to the identification of these *visible and known* electrographic patterns. Gotman (30) is one of the pioneers in this area of automatic seizure-event detection in human EEG. A recent article addressing seizure-onset detection describes a system that extracts six features from the time and frequency domain, feeds them into a modified nearest-neighbor classifier, and yields a 100% detection rate with an average of 0.2 false positives per hour. The warning was given on average 9.6 s after the electrographic seizure onset. More recently, another promising approach was followed by Osorio et al. (31), applying a wavelet filter to intracranial recordings for classification between seizure and no-seizure states.

Conversely, the term *seizure anticipation* is used to refer to the process of identifying a state from the EEG that precedes a clinical seizure that is known to have occurred. Rather than referring to a declaration in advance, anticipation refers to the time between the earliest identification of a preseizure state and either the onset of the clinical seizure or the time at which a well-trained clinician can pick up evidence by visual inspection of the EEG (16,20,21,32,33). In contrast to seizure detection, no known electrographic clues predict the occurrence of a seizure (5). A few studies have hypothesized that changes

in interictal epileptiform activity can anticipate the pathophysiologic recruitments that give rise to a seizure. Nevertheless, conflicting findings were reported: Wieser (34) reported a decrease in spiking before seizure. Lange et al. (35,36) observed that the spatial organization of spike patterns appears to change several minutes before temporal lobe seizures, whereas others (37,38) found no change in spiking before seizures. Gotman et al. (39) used prolonged telemetry recordings (11–16 days) in six patients whose medication levels were stable. Spike rates were sometimes found to increase seconds before seizures, but the main finding was that repeated seizures caused a build-up in spike rate. It is apparent from these findings that merely quantifying spike rate is unlikely to yield information to heralding seizure onset. Therefore, in contrast to seizure detection, anticipation involves the *detection of nonvisible electrographic patterns*, at least until the epileptogenesis issue is clearly resolved.

NEURODYNAMICS: HOW NONLINEAR ANALYSIS MEETS NEUROSCIENCES

Research in physiology often involves the analysis of irregular signals. In particular, the brain recordings at all levels represent complex signals that follow various dynamical transitions, and of which the statistical properties depend on both time and space. Bursting behavior, intermittent phenomena, and amplitude-dependent frequency behavior are among typical patterns that have proven difficult to understand with current statistical techniques. Furthermore, these standard methods do not offer an adequate characterization of phenomena referred to as "bifurcation" between different behaviors or "rapid state changes" in brain activity. In this respect, the sudden unpredictable start of an epileptic seizure is paradigmatic.

In the last decade, new answers were proposed to this problem (40). It was suggested that one difficulty of analyzing complex signals was the result of examining the time series in terms of static rather dynamic behavior. Traditional signal-processing procedures *decompose*, for example, through Fourier analysis, the frequency components of the signal and thus reflect a limited amount of information (one-dimensional). In contrast, the dynamical view suggests that a time series may reflect an unambiguous relation between present and future states and take into account all other variables participating in the dynamics of the system (multidimensional). This approach has drastically modified the manner in which physiologic processes are viewed and described (see ref. 41 for a review). For example, some neuronal processes formerly perceived as random are now viewed in terms of lawful nonlinear patterns (42).

Given that a complex dynamic system (such as the human nervous system) can involve an enormous number of interrelated dependent variables that are impossible to measure directly, the main problem is how to analyze a multidimensional dynamics knowing only a few variables that can be measured. It can be mathematically established (43) that, if we can measure any single variable with sufficient accuracy, for a long period, then it is possible to make quantitatively meaningful inferences about the underlying dynamical structure of the *entire* system from the behavior of this single variable. The geometric properties of the trajectories evolving in the phase-space can be then expressed quantitatively by using nonlinear measures (Fig. 1). An important measure is the dimensionality of the dynamics, referred to as the "correlation dimension" or D_2, which defines the minimal number of variables that allow the full description of the system. Considerable discussions concern parameters such as what would constitute sufficient accuracy, how often the signal should be sampled, as well as how long data segments should be (44). Of course, the mathematical rigor is not always easy to translate to the biologic domain. Nevertheless, the nonlinear approach provides a practical toolkit for the analysis of complex behaviors at different levels of organization of the nervous systems from single neurons to neuronal ensembles (8).

BRAIN STATE CHANGES: SHORT AND LONG TIME SCALES

The brain dynamics exhibit many different time scales and can be viewed as a succession of transient spatiotemporal patterns of activity that mediate perceptual synthesis and sensorimotor integration. This formulation embodies one fundamental point: any proper description of brain dynamics should have an explicit temporal dimension. In other words, measures of brain activity are meaningful only when specified over extended periods. Very crudely, some variations may occur on a *short time scale* on the order of tenths of a second. This time scale is particularly important for fast dynamics interactions among neuronal populations that are characterized by transient synchrony in the high-frequency ranges (45). Thus, variations on time scales shorter than 1 min are thought of as variations within a single dynamic state. Conversely, other qualitatively different variations may occur on a *long time scale* of minutes or hours. Many variations typically occur within 1 h of the state of human consciousness: alert wakefulness or drowsiness, open or closed eyes, and different sleep states, including rapid eye movement (REM). These variations over time scales much longer than 1 min mark transitions among heterogeneous dynamic states. When looking for preictal signs, we are looking for changes among dynamic states on long time scale. If one method is ultimately successful in predicting seizures, it will be important to be sensitive to preictal changes in the brain, but also to be able to distinguish clearly between benign changes in behavioral state and

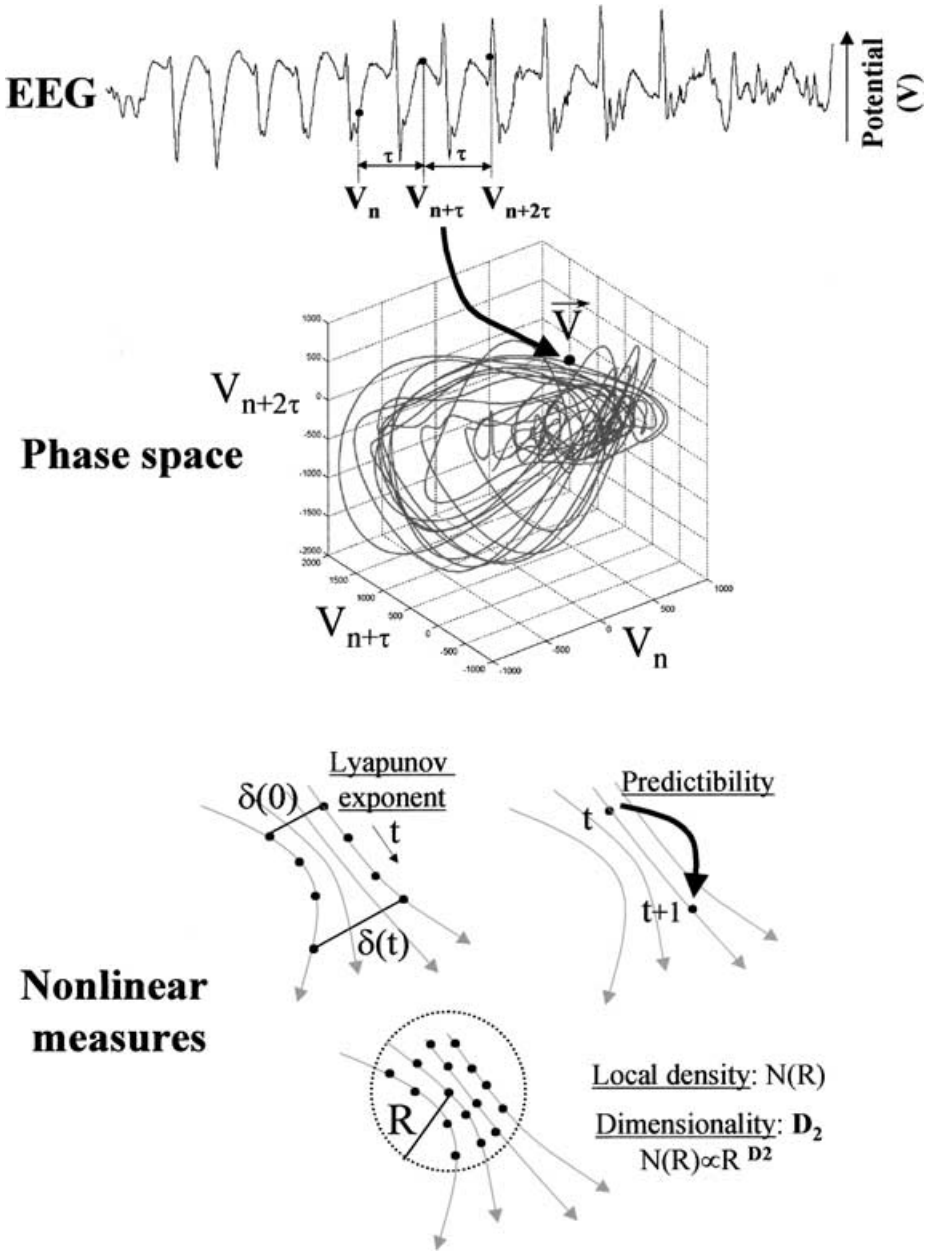

FIG. 1. Dynamical analysis of EEG signals. The method of delays is one way of representing the EEG dynamics in a phase space. In this representation, the state at each point in time is represented by a vector generated by taking successive amplitudes separated by a time lag τ. This reconstruction of the underlying dynamics is the first step of all techniques of nonlinear analysis. The geometric properties of the phase space can then be expressed quantitatively by using nonlinear measures**.** The *Lyapunov exponent* (measuring the average rate of expansion in time), the *predictability* (measuring the uncertainty about the future state of the system), the *density* at some tolerance R, and the *dimensionality* D_2 (measuring the minimal number of variables that must be considered in the description of the system) are commonly used to characterize dynamical structures.

changes that portend the onset of a seizure. Moreover, it is well known that normal brain states can have a facilitating effect on seizures (see preceding section). For example, sleep and circadian variations in arousal have a marked influence on the expression of epilepsies (46), and sleep deprivation has a dramatic impact on epilepsy. This interaction also is reciprocal, because epilepsy also can alter sleep/wake cycles. The relationships between these facilitating and the precipitating preictal states and how they interact to produce a seizure in an individual remain largely unknown. This makes more complicated a better understanding of the dynamical basis of ictogenesis.

EPILEPSY AS A DYNAMICAL DISEASE

Historically, Babloyantz and Destexhe (47) were the first to demonstrate that the nonlinear analysis of EEG recordings from patients with epilepsy can provide new perspectives regarding epileptogenesis. They estimated the dimensionality and the largest Lyapunov exponent (the mean rate of divergence of initially neighboring states) of scalp EEG signals recorded during a human absence seizure. They found that the value of D_2 for seizure activity is of considerably lower value than for normal activity, whereas a positive value was estimated for the largest Lyapunov exponent. These findings support the hypothesis

that the generation of ictal activity in the brain corresponds with a specific dynamical state that is clearly different from normal ongoing activity. The different values of the nonlinear quantities suggest a *decreased level of complexity* in neuronal networks involved in the epileptic process. In a comparable study, Pijn et al. (48) analyzed epileptic seizures in an animal model of epilepsy (limbic kindling in the rat). The decrease in the D_2 value was most pronounced in the primary epileptogenic area and gradually decreased with increasing distance from the focal area, suggesting a reliable relation between location of neuronal complexity and seizure outcome. In good agreement with the animal model, Lehnertz and Elger (49) presented a moving-window nonlinear analysis of intracranial EEG in 20 patients with unilateral medial temporal lobe epilepsy (MTLE). The onset of a seizure was characterized by an abrupt decrease in D_2 most pronounced in the area of ictal onset, so a spatial identification of the epileptogenic focus by nonlinear quantities appears possible. These findings are in line with the work of Iasemidis and Sackellares (50), who described similar variations in the largest Lyapunov exponent. Perhaps the most exciting observation, first reported by these authors, was that spatiotemporal variations of this nonlinear measure precede the seizure by several minutes. These changes appear to evolve in characteristic patterns, defined as the entrainment of the nonlinear quantities of the epileptogenic hippocampus, the contralateral hippocampus, as well as the ispi- and contralateral temporal and frontal neocortex. Nevertheless, these results were based on a few recordings and had no statistical validation of the significance of the nonlinear measure; this made it difficult to draw definite conclusions.

How the transition from interictal state to the ictal state occurs was explored at the same time by our group (22) and the Bonn group (17). We estimated the correlation integral (which is a measure of the average density in phase space and the fundamental statistic used to determine $D_{2)}$ from intracranial EEG recordings 20 min before the seizure onset in 11 patients with MTLE. Our objective was to follow, by this nonlinear indicator, the transitions to seizures within the epileptogenic focus (defined by the earliest EEG signs of seizure activity) by using surrogate data as statistical control. We demonstrated that in most cases (90%), changes toward long-lasting states occurred before the seizure (mean, 2.5 min) and were more pronounced compared with maximal changes occurring during interictal states, thus enabling us to define a *preictal state*. This phenomenon could not be detected by visual inspection of the original signal or by other more traditional methods of signal processing. Lehnertz and Elger (17) confirmed these findings in a comparable group of 16 MLTE patients. Similar results also were obtained from the spatiotemporal evolution of the largest Lyapunov exponent (50,51), from the spectral analysis of nonlinear fluctuations (52), and by recurrent neuronal network (53).

Taken together, this converging evidence suggests that the dynamical properties of the interictal, preictal, ictal, and postictal states are clearly different. The seizure might be interpreted as the "tip of the iceberg" in the sense that it is just the climax of a process of changes that starts long before. This transition or route toward the seizure seems to reflect a process from "disorder to order" and argues that epilepsy belongs to *dynamical diseases* (54). Despite some scepticism about some interpretations of the results (see the next section for a critical point of view), the reported findings have unambiguously demonstrated that the nonlinear analysis carries a great potential for the detection of subtle changes in brain electrical activity before seizure (7).

SHORTCOMINGS OF NONLINEAR ANALYSIS: BRAIN DYNAMICS IS NOT CHAOTIC

We have presented consistent evidence for preictal changes of several minutes before seizure onset. Nevertheless, some difficulties arise in a careful application of nonlinear analysis to brain signals and in the interpretation of the results. The major difficulties result from the indiscriminate application of the mathematical concept of "chaos" (i.e., deterministic dynamics with a few degrees of freedom) to physiological time series before understanding the actual mathematical properties of the signals. Indeed, after an initial euphoric period (47), it is commonly accepted that the existence of chaotic structures underlying neuronal dynamics is difficult or even impossible to prove (55). It has been shown, for example, that low complexity can be found even for random noise (56). Furthermore, in systems in which the exact value of the complexity is theoretically known, application of a low-pass filter and the use of time series of finite length could lead to severe underestimation or overestimation of the dimension. In addition, if the true dimension is 5 or higher, the most commonly used algorithms for studying dynamical behavior produce erroneous results, sometimes spuriously suggestive of low-dimensional dynamics (57). Consequently, measures of system complexity do not, in themselves, give any insights into whether the system under study shows a complexity change in terms of the number of degrees of freedom. Some authors have addressed this issue statistically, by comparing their estimates of biologic data with those of surrogate data with the same statistical properties as the original data but losing all dynamical information (22,48,58). Nevertheless, errors with this method can arise, because the statistical testing assumes data stationarity over the whole epoch. In summary, an increasing awareness of the pitfalls and limitations of the mathematical and statistical techniques has led to doubts about the low complexity of preictal changes.

MEASURING RELATIVE CHANGES OF BRAIN DYNAMICS

In the recent years, our effort differs from previous works in this area by focusing on methods that are sensitive to the *existence of a change and not necessarily to the nature of the change*. For this purpose, we used a relative dynamical measure (comparing across states) rather than absolute index (18,19). The novelty of the approach is based on the comparison between different moments of the time series, rather than comparison by statistical parameters derived for the time series (Fig. 2A). It is then possible to use relative measures that can be interpreted as a distance or degree of dissimilarity (23,59). Note that this idea to use relative measures between segments of a long sequence for nonstationarity testing has been brought up in recent theoretical works (60), showing a greater discriminatory power than previous nonlinear techniques (59). This idea is particularly useful if nonstationarity is given by changes of the shape of an attractor, while dynamical invariants remain effectively unchanged. Furthermore, unlike deterministic approaches aimed at finding low-dimensional chaos, the similarity framework allows sensitivity to a high-dimensional character of the dynamics and the presence of stochastic effects.

Figure 2B gives a representative example of our analysis applied to a 20-min intracranial recording before a spontaneous seizure of temporal lobe origin. The similarity plot (with a reference state taken at the beginning of the recording) decreases over several orders of magnitude, indicating a transition to a sustained preictal state ~3 min before seizure onset. After this sustained preictal state, the actual seizure induces a second decrease to the lowest values. Postictally, the similarity increases again to the initial level found before the seizure. In this example, a positive detection is defined by a sustained deviation. The anticipation time is defined as the point when the similarity reaches a critical level and remains at or above this fixed deviation threshold k during a time length D. The threshold values (k, D) were determined empirically for our dataset of seizure/subjects to avoid any false positives and still anticipate the actual seizure. In our work, we chose $k = 5$, corresponding to a p value of 0.04, and D = 150 s. With these criteria, we estimated in our example an anticipation time of 3 min. The results obtained from a homogeneous group of 13 patients with TLE confirmed our previous findings that the extraction of dynamical properties allows, in most of the cases, seizure anticipation several minutes in advance (mean, 5.5 min) (18). This new method provides a substantial improvement of our previous anticipation times (22). With a comparable measure of dissimilarity (L_1 distance and statistic between two phase spaces), Hively et al. (61) and Savit et al. (23) confirmed the discriminating power of this strategy for the detection of EEG changes.

ANTICIPATION FROM STANDARD SCALP EEG

To make seizure anticipation practical in real life conditions and to study types of epilepsy that do not warrant intracranial electrode implantation, applications to scalp-EEG recordings is fundamental. However, it is well known that neuronal activity generated within the brain is spatially filtered between neocortex and scalp. This occurs because of the physical separation of the electrode from the nearest neuronal sources (~1 cm) and the "smearing" effect of the skull, which has an electrical resistivity estimated to be roughly 80 times that of cortical tissue (62). Aside from signal attenuation and poor spatial resolution, scalp EEG is well known to be subject to noise or artifacts, which may render delicate and even questionable the detection of changes with current nonlinear measures.

In a recent study (20), we evaluated on scalp EEG recordings our nonlinear strategy based on measure of similarity to determine whether changes in brain dynamics can be detected early enough to anticipate the seizure onset. Analyses were performed on 26 scalp-EEG recordings, including 60 min. before seizure, obtained from 23 patients with TLE. In a subgroup of five patients, we validated our analysis on simultaneous scalp and intracranial recordings. Our results indicated that preseizure changes in brain dynamics can be detected from recordings of scalp EEG activity (Fig. 3A). In most cases (25 of 26), measurement of nonlinear changes in EEG signals allowed the anticipation of the seizure by several minutes (mean, 7 min). Furthermore, these preictal changes in the scalp EEG corresponded well with concurrent changes in depth recordings (Fig. 3B). Therefore, scalp EEG recordings retain sufficient dynamical information that can be used for the analysis of preictal changes leading to seizures.

These findings are surprising in that they suggest that quantitative changes in scalp electrical activity are comparable to those detected from intracranial recordings. However, the relation between activities recorded with intra- and extracranial electrodes is more complex than a simple decrease in the signal-to-noise ratio because of cortical convolutions, anatomic anisotropies, and the orientation, shape, and extension of the underlying generators. In addition, electrical potentials produced by neocortical structures and recorded from scalp electrodes also may be driven by events in deeper cerebral regions. For instance, changes in the hippocampal activity may cause secondary activation of several neocortical areas, producing large synchronized local field potentials. Further studies are required to identify the extent of generators giving rise to the global dynamics ultimately detected on the scalp, in particular, with more extensive intracranial sampling or source-localization methods.

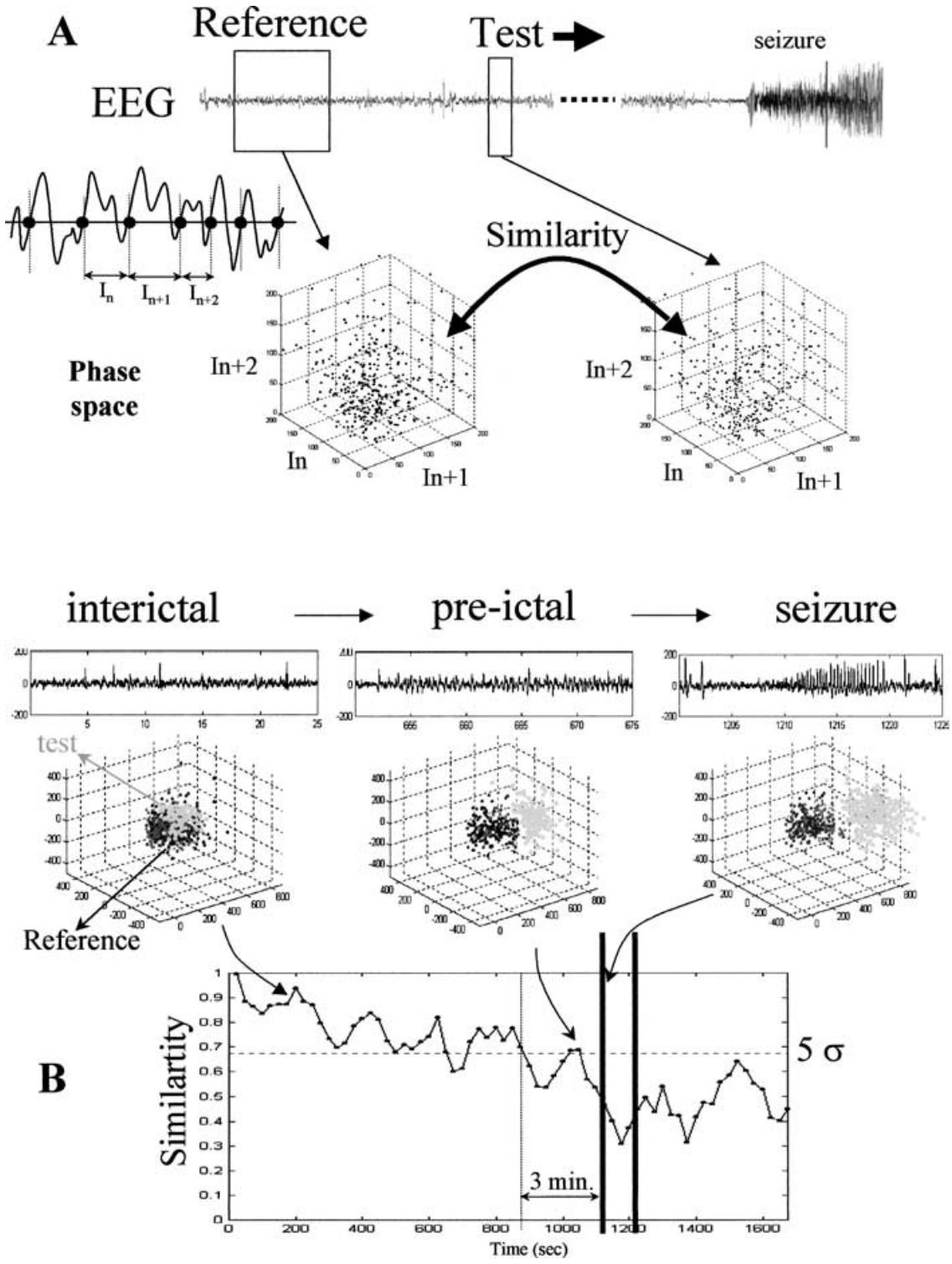

FIG. 2. A nonlinear method for characterizing dynamical EEG changes. **A:** Our strategy first reduces the EEG signal to sequences of time intervals I_n between each successive zero-crossings. The second step is to define a multidimensional reconstruction of the dynamics by a time-delay embedding of the intervals $(I_n, I_{n+1}, \ldots, I_{n+m-1})$ where m is high dimensional in our computations, but here $m = 3$ for a schematic representation. In the 3D space, he dynamics of each window is represented by a cloud of points of which the density fluctuates in time. The third step is to quantify a similarity index measuring the closeness between the reference and test dynamics. The similarity can be viewed as the average number of common points between these reference and test clouds. If the signal is stationary, the similarity index yields a value close to 1. Conversely, if changes in the dynamical state occur, the similarity index between the two clouds decreases to <1. **B:** A representative example of our analysis applied to a 20-min intracranial recording of an epileptogenic hippocampus before a spontaneous seizure. We define the preictal state when the similarity index remains 5 standard deviations under the reference state. With this criterion, we identified a sustained preictal state $\sim$3 min before seizure onset.

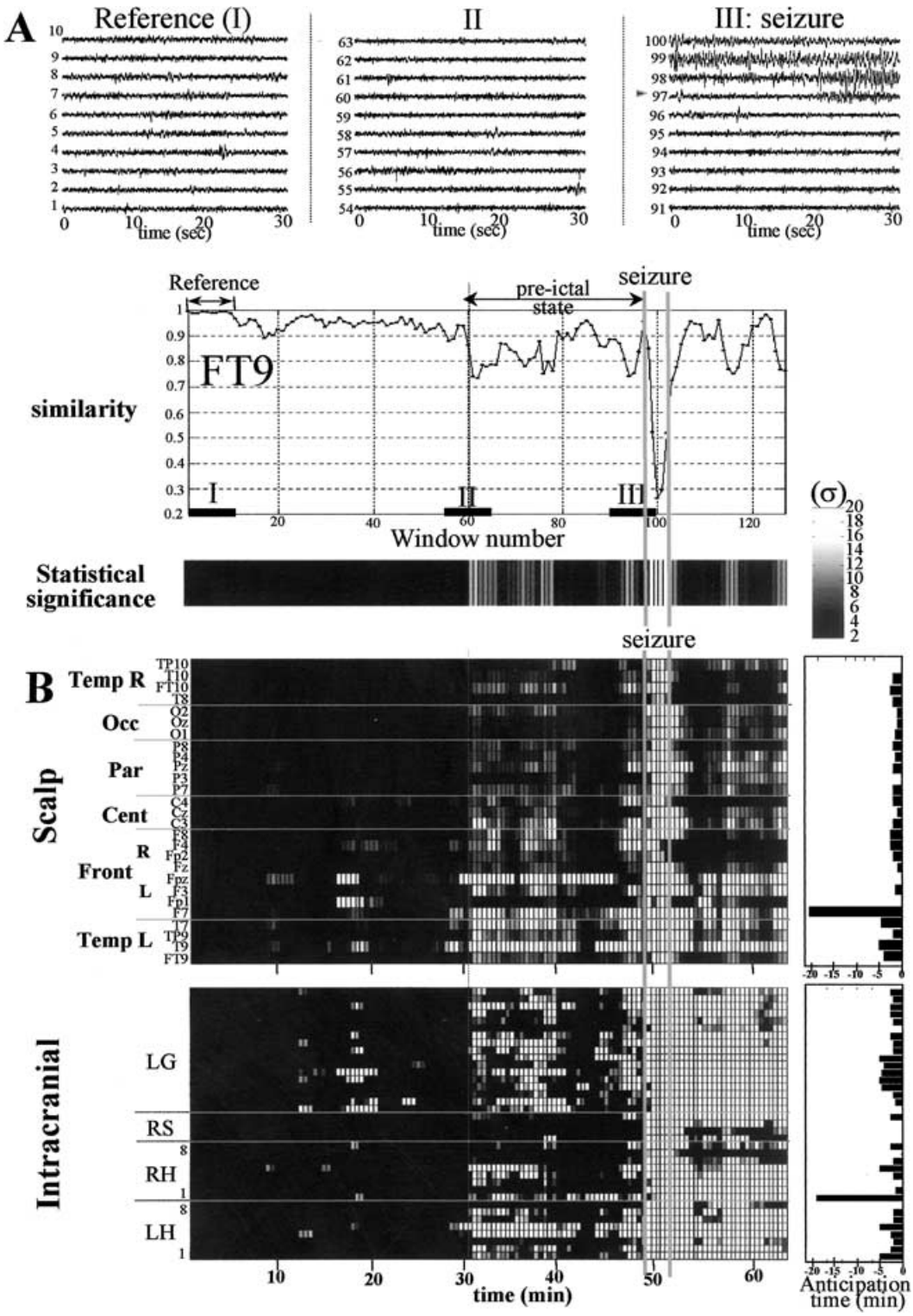

FIG. 3. Anticipation from scalp EEG. **A:** Analysis of 50 min of a scalp-EEG channel (FT9) before a temporal lobe seizure. **Top:** Examples of consecutive windows of 30-s duration in the recording. The seizure onset occurs at window 97. **Middle:** The similarity profile from a long "reference period" chosen here from windows 1 to 10. A sustained preictal state is identified 18 min before seizure onset. **Bottom:** The statistical significance of the preictal changes is quantified by the deviation of the test window from the reference state, here depicted in standard deviations by using a color scale. **B:** Complete spatiotemporal picture of preictal dynamics. The changes from the reference state for each contact are quantified in standard deviations. The corresponding anticipation times are indicated on the right side. Long-lasting decreases ~18 min before seizure were found at a large number of the recording sites. R-L, right-left. For the scalp electrodes, Temp, temporal; Front, frontal; Cent, central; Par, parietal; Occ, Occipital (extended International 10–20 System). For the intracranial electrodes, H, intrahippocampal electrodes with 1, amygdala, 2–3, hippocampus; G, subdural grid; S, subdural strip.

NEW WAYS TO ANTICIPATE SEIZURES: THE ANALYSIS OF NEURONAL SYNCHRONIZATION

In the studies described so far, we tracked the temporal evolution of nonlinear measures at different recording sites, thus considering no spatial interactions during the transition to the ictal state. Recently, measures of synchronization revealed new insights into the spatiotemporal characteristics of the epileptogenic state (63–65). In a more general context, processes of synchronization on various levels of brain organization, from individual pairs of neurons to much larger scales (within one area of the brain or between different parts of the brain) are necessary to attain normal neuronal activity (45).

Detection of synchrony in the brain is a great challenge. Most commonly, synchronizations are characterized by means of traditional cross-correlation (or coherence) techniques. Unfortunately, these classic tools for measuring coherence (66) based on Fourier analysis are highly dependent on the stationarity of the measured signal, which is far from being the case in the brain. The use of time–frequency estimations, which do not assume stationarity, can improve this limitation toward estimating a stable, instantaneous coherence as well as synchrony between two concurrent brain signals. A second and very different limitation is that classic coherence is a measure of spectral covariance, and thus does not separate the effects of amplitude and phase in the interrelations between two signals. Because we are interested in exploring the explicit hypothesis that *synchrony as phase-locking* is the relevant mechanism of brain interactions, coherence provides only a partial and indirect measure.

A direct study of phase relations in the brain requires tools with which the phase component can be obtained separately from the amplitude component for a given frequency range, which can be quite unstable or even uncorrelated (67). Recently we introduced a new method for this purpose on the basis of wavelet analysis (35). Independently, an alternative method based on the Hilbert transform was introduced by Tass et al. (68). Both techniques give similar results applied to neuroelectrical data (32).

With this technique, we analyzed the synchronization between intracranial recordings from eight patients with neocortical focal epilepsy being evaluated for epilepsy surgery (33). Figure 4A depicts a representative example of the temporal evolution of the synchrony near the epileptogenic focus before a seizure. Our main findings were that we consistently observed a preictal decrease in synchrony within the 10- to 25-Hz range (the so-called beta 1 band) in 77% of the seizures, independent of whether the patient was awake or asleep. This decrease is the exact converse of phase-locking, and is best described as *phase-scattering*, in which the probability of finding synchrony between two electrodes decreases well below the interictal level. Interestingly, these changes occurred on a large time scale, sometimes hours before the actual seizure (33,65), and showed recurrent spatial patterns that were more pronounced over the regions near the epileptogenic focus.

Although preliminary, these results reinforce the findings of nonlinear changes before an impending seizure. Nonlinear analysis essentially measures the number of degrees of freedom of the underlying neural dynamics, which are directly related to the degree of local synchronization (69). Furthermore our results provide new insights into the pathophysiologic mechanisms underlying the preictal process. In particular, the preictal period may reflect the activity of a specific population of neurons in relation to the epileptic focus that can induce *dyssynchronization*—their participation in normal synchronization processes is reduced, resulting in a state of increased susceptibility to sudden pathological synchronization. Two related processes with different time scales seem to be involved: (a) a long-lasting decrease in synchrony over minutes, creating conditions favorable for the appearance of seizures; our findings suggest that neuronal populations surrounding the epileptic focus are of crucial importance in this process, determining whether a seizure is likely to occur and spread; and (b) a fast hypersynchronization process giving rise to the seizure onset. Following the hypothesis of Wyler et al. (70), the synchronization of a critical mass of neuronal populations is at this step the necessary condition for the seizure initiation.

THE NEXT STEPS

The specificity/sensitivity ratio

Our findings were obtained mainly from retrospective studies in selected patients. Seizure anticipation can be demonstrated only by validation of the methods on out-of-sample data, in which the presence of seizures is unknown to the tester. In all the works performed in this field, the term *seizure anticipation* is weaker and refers to the time between identification of a preseizure state and the time at which a well-trained clinician can pick up evidence by visual inspection of the EEG. Furthermore, we selected spontaneous seizures, excluding seizures preceded by classic precipitating factors (hyperventilation and photic stimulation) and occurring during stable state of vigilance, as validated by reviewing videotapes. Indeed, as pointed out by others (37), state changes in the interictal dynamics induced by different physiologic states of the brain (like the wakefulness-to-sleep transition) may contribute to spurious detection of preseizure changes, whatever the type of analysis. Therefore, a study over longer periods is clearly the next step to evaluate the specificity and sensitivity of the methods. It should be determined whether the changes observed in preictal activity are unique to this period, or whether they are cyclic and

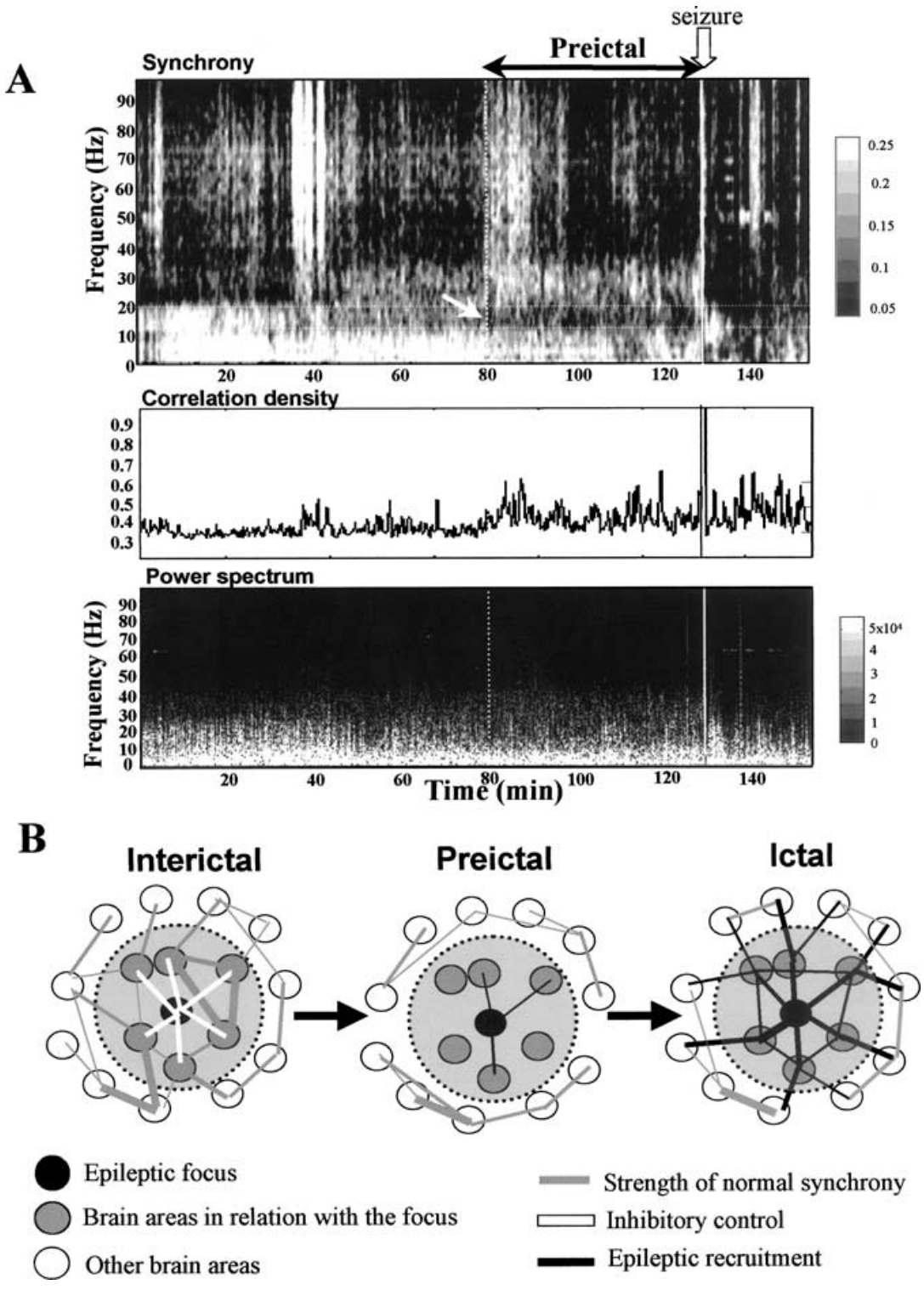

FIG. 4. **A:** Preictal loss of synchrony. Time–frequency chart of *synchrony* **(top)** and *power spectrum* **(bottom)** of signals from a pair of electrodes near an epileptic focus. A sustained decrease from the baseline level of synchrony occurred in the beta range (10–15 Hz) ~70 min before the seizure. Changes in phase synchrony are directly related to modifications in complexity detected by the nonlinear measure. This was not the case for the power spectrum. **B:** Possible mechanisms for ictogenesis. The preictal loss of synchrony might suggest the following mechanisms. During the interictal state, the neuronal population in relation to the epileptic focus are implicated in large-scale dynamics of normal brain functioning. During the preictal state, this population loses the synchronization with other cortical areas and with themselves. This condition isolates the epileptic pacemakers from the ongoing large-scale brain influences and facilitates the development of a focal hyperexcitable state. This condition also provides an "idle" population of neurons that become easily recruited into the epileptic process. Additionally, during this preictal state, the inhibitory control of the epileptogenic zone can progressively break down. Seizure activity will be initiated when a critical mass is recruited.

can occur at periods remote from ictal events. Probably periods of dynamical changes are not followed by a seizure. They may correspond to a real modification of the epileptic activity, but they also can be unrelated to the epileptic condition. The influence of antiepileptic drugs (AEDs) also must be taken into account.

The spatial distribution of preictal changes

Another issue for further research concerns the spatial distribution of the preictal changes. Are they focal, strictly restricted to the area of seizure onset, or are they more extensively distributed? We have examined the transition from interictal to ictal state for a wide range of intracranial recording locations within the epileptogenic area and remote brain regions (19). Our analysis revealed that the spatial distribution of preictal dynamical changes implies a diffuse network, involving the epileptogenic area, but seems not always confined to the restricted ictal-onset region. Several different regions may be implicated, often located at widely separated sites, with a topography more widespread than that of the ictal-onset zone and not spatially congruent with the interictal spiking area. This observation is strengthened by previous works (71) showing widespread functional, cognitive, electrical, and structural abnormalities in MTLE, often suggesting a regional extent of the dysfunctional network with frequent contralateral temporal lobe involvement and, to some degree, a more diffuse process, eventually reflecting secondary epileptogenesis (72). Nevertheless, our observation contrasts with the previous results of Lehnertz and Elger (17), reporting that relevant preictal dynamical changes remain confined to the site where the first focal electrical changes are detected.

The type of epilepsy

An important point to keep in mind is that these results have all been obtained in patients with MTLE. In spite of some degrees of variability in the electroclinical presentation (73), they share as common features that the first signs of seizure activity are recorded at the amygdalohippocampal structures, mainly associated with hippocampal sclerosis and a secondary electrical involvement of the temporal and frontal neocortical areas. The amygdalohippocampal complex plays the key role, in terms of both generation and propagation, and other types of partial epilepsies may exhibit different dynamical behaviors. Whether similar findings can be obtained for seizures originating in neocortex is now under investigation.

Putative neuronal mechanisms of the preictal changes

Although the present findings are still limited and do not provide a robust physiologic mechanism, some hypotheses can nevertheless be made. From our analysis of preictal synchronizations (previous section), we hypothesize that the preictal changes probably refer to a decrease of the interaction between the primary epileptogenic area and its surroundings. Several mechanisms may be distinguished to explain this phenomenon (Fig. 4B): First, desynchronization may functionally isolate pathologically discharging neurons of the epileptic focus from the influence of large-scale brain activity, so facilitating the development of local pathological recruitments. Second, this condition may provide an "idle" population of neurons, which may be more easily recruited into the epileptic process. Finally the preictal loss of synchrony could reflect a depression of synaptic inhibition in areas surrounding the epileptogenic focus, as demonstrated in experimental models of epilepsy (74). Possible changes in inhibitory signaling are especially interesting because inhibitory interneurons are believed to underlie the generation of synchronizations in a specific frequency range (75,76). Furthermore, synchronies have been suggested to play a major role in normal brain function, in particular in the establishment of large-scale links between neuronal groups (45,77). Therefore, the large-scale synchronization could be related to mechanisms that may limit or prevent seizures (78). Animal models will be useful to understand further the mechanisms underlying these preictal dyssynchronization and are under investigation.

FUTURE PERSPECTIVES

What might be done with the information about preictal changes? The ability to anticipate seizures by using the intracranial or scalp EEG may have considerable practical implications for the large population of patients with uncontrolled epilepsy:

1. *Patients warning*: A system of early warning about a seizure would be of great help for numbers of patients and relatives. Such a system would reduce medical consequences of seizures and improve the quality of life of persons with epilepsy by decreasing the risk of injury and the sense of helplessness fostered by the unpredictability of the disease. Nevertheless, it must be stressed that before reaching this stage, we must make two major advances. First, the analysis of specificity and sensitivity in realistic conditions (hospitalized or ambulatory patients) must be pursued with diligence, until a safe margin can be achieved for most patients and the most common types of epilepsy. Second, the process of miniaturization of a device must be accomplished and the kinds of electrodes to be used thoroughly explored. Although both these objectives are surmountable, they have yet to be concretely accomplished before the public is given hopes for such a new clinical application.
2. *Ictal SPECT procedure*: Implementing a bedside system of seizure anticipation in a video/EEG unit would be of considerable help for efficient seizure monitoring and for the injection of the radioactive

tracer in ictal SPECT examinations. Optimally the tracer must be injected at seizure onset as soon as possible. Very often this procedure is not informative enough due to a late injection, tens of seconds after the onset, which marks the areas of propagation more than the actual epileptogenic zone. Considerable resources could be spared by an efficient anticipation of the seizure.

3. *Interventions for seizure abortion*: The perspective opened by the ability to anticipate a seizure several minutes in advance would provide a time window during which therapeutic measures may be taken to avoid the risk of seizure occurrence. In this context, pharmacologic control may be possible by using rapidly acting AEDs with a quick delivery procedure. Probably better adapted to real-time therapy are electrical stimulations. Direct brain stimulations for the control of epileptic seizures have been already tested, although several questions have not been answered: where and when should the stimulations be applied? Should they be done regularly or only in relation to emergence of epileptic activity? In this second option, seizure anticipation offers, in principle, the possibility of delivering precise electrical stimulations to direct the epileptogenic activities away from its route toward the seizure. This has been already done in rat's hippocampal slices by using nonlinear control (79) or adaptive electric field (80).
4. *Self-control*: An important alternative is that a patient could learn to discriminate early signs of the preictal activity and subsequently generate cognitive/behavioral responses to suppress the epileptogenic processes. In this case, seizure anticipation might serve as the introduction of learning paradigms, and subsequent behavioral interventions on the seizure may be assessed by the research with EEG feedback and instrumental conditioning of EEG patterns (78,81). One difficulty in determining prodromic sensations is that the patient could well experience a warning signal but may have difficulty in remembering this symptom because of postictal amnesia. A recent study, however, showed that detailed self-observation achieved a significant reduction of seizures and can contribute to improving long-standing intractable epilepsies (82).

CONCLUSION

Although the field of seizure anticipation is still in its infancy, there is good reason to be optimistic about the development of robust method for seizure anticipation. The findings are promising to characterize in formal terms the preictal state, and thus to determine the necessary conditions for the occurrence of a seizure. Of course, longer time scales may be useful for better characterization and understanding of mechanisms of generation and timing of epileptic seizures. Nevertheless, on the basis of the present results, our understanding of the mechanism that underlies the generation of seizures has progressed to the point where it is clear that most seizures are unlikely to arise from random fluctuations from the background brain activity. Seizures cannot be regarded in isolation but require a process of changes in brain dynamics that starts long before its manifestation. In particular, our analysis of preictal synchronizations reaffirms the point that epileptic seizures do not occur in a behavioral vacuum, but that the integrated, normal functioning of the brain before the seizure occurs is critical. Seizure foci are surrounded by pools of neurons functioning in a local and large-scale interactions and are "pulled" into the seizure discharge once the seizure has started. From our recent observations, we hypothesize that the preictal period may reflect the dyssynchronization of a specific population of neurons. They are not fully incorporated into normal synchronization processes and define a state of increased susceptibility for pathologic synchronization, which acts as a route to the seizure. Developments of nonlinear techniques that can identify the directionality of information flows (64,83) are expected to contribute further to an improved understanding of spatial extension of the preictal phenomena.

REFERENCES

1. Buck D, Baker GA, Jacoby A, et al. Patients' experiences of injury as a result of epilepsy. *Epilepsia* 1997;38:439–44.
2. Devinsky O, Vickrey BG, Cramer J, et al. Development of the quality of life in epilepsy inventory. *Epilepsia* 1995;36:1089–104.
3. Engel J. *Seizure and epilepsy: contemporary neurology series*. Philadelphia: FA Davis, 1989.
4. Duckrow RB, Spencer SS. Regional coherence and the transfer of ictal activity during seizure onset in the medical temporal lobe. *Electroencephalogr Clin Neurophysiol* 1992;82:414–22.
5. Rogowski Z, Gath I, Bental E. On the prediction of epileptic seizures. *Biol Cybern* 1981;42:9–15.
6. McKeown MJ, McNamara JO. When do epileptic seizures really begin? *Neuron* 2001;30:1–3.
7. Schiff SJ. Forecasting brain storms. *Nat Med* 1998;4:1117–8.
8. Abarbanel H, Rabinovich MI. Neurodynamics: nonlinear dynamics and neurobiology. *Curr Opin Neurobiol* 2001;11:423–30.
9. Freeman WJ. *Neurodynamics*. New York: Springer, 2000.
10. Schmidt G, Morfill GE, Barthel P, et al. Variability of ventricular premature complexes and mortality risk. *Pacing Clin Electrophysiol* 1996;19:976–8.
11. Pezard L, Nandrino JL, Renault B, et al. Depression as a dynamical disease. *Biol Psychiatry* 1996;39:991–9.
12. Röschke J, Mann K, Fell J. Nonlinear EEG dynamics during sleep in depression and schizophrenia. *Int J Neurosci* 1994;75:271–84.
13. Pritchard WS, Duke DW, Coburn KL, et al. EEG-based, neural net predictive classification of Alzheimer's disease versus control subjects is augmented by nonlinear EEG measures. *Electroencephalogr Clin Neurophysiol* 1994;91:118–30.
14. Stam CJ, Jelles B, Achtereekte HA, et al. Investigation of EEG nonlinearity in dementia and Parkinson's disease. *Electroencephalogr Clin Neurophysiol* 1995;95:309–17.
15. Iasemedis LD, Sackellares JC, Zaveri HP, et al. Phase space topography and the Lyapunov exponent of electrocorticograms in partial seizures. *Brain Topogr* 1990;2:187–201.

16. Jerger K, Netoff TI, Francis JT, et al. Early seizure detection. *J Clin Neurophysiol* 2001;18:259–68.
17. Lehnertz K, Elger CE. Can epileptic seizures be predicted? Evidence from nonlinear time series analysis of brain electrical activity. *Physiol Rev Lett* 1998;80:5019–22.
18. Le Van Quyen M, Martinerie J, Baulac M, et al. Anticipating epileptic seizure in real time by a nonlinear analysis of similarity between EEG recordings. *Neuroreport* 1999;10:2149–55.
19. Le Van Quyen M, Adam C, Martinerie J, et al. Spatio-temporal characterizations of nonlinear changes in intracranial activities prior to human temporal lobe seizures. *Eur J Neurosci* 2000;12:2124–34.
20. Le Van Quyen M, Martinerie J, Navarro V, et al. Anticipation of epileptic seizures from standard EEG recordings. *Lancet* 2001;357:183–8.
21. Litt B, Esteller R, Echauz J, et al. Epileptic seizures may begin hours in advance of clinical onset: a report of five patients. *Neuron* 2001;30:51–64.
22. Martinerie J, Adam C, Le Van Quyen M, et al. Epileptic seizures can be anticipated by non-linear analysis. *Nat Med* 1998;4:1173–6.
23. Savit R, Li D, Zhou W, et al. Understanding dynamic state changes in temporal lobe epilepsy. *J Clin Neurophysiol* 2001;18:246–58.
24. Lennox WG. *Science and seizures*. New York: Harper, 1946:258.
25. Rajna P, Clemens B, Csibri E, et al. Hungarian multicentre epidemiologic study of the warning and initial symptoms (prodrome, aura) of epileptic seizures. *Seizure* 1997;6:361–8.
26. Novak V, Reeves AL, Novak P, et al. Time-frequency mapping of R-R interval during complex partial seizures of temporal lobe origin. *J Auton Nerv Syst* 1999;77:195–202.
27. Penfield W. The evidence for a cerebral vascular mechanism in epilepsy. *Ann Intern Med* 1933;7:303–10.
28. Weinand ME, Carter LP, El-Saadany WF, et al. Cerebral blood flow and temporal lobe epileptogenicity. *J Neurosurg* 1997;86:226–32.
29. Baumgartner C, Serles W, Leutmezer F, et al. Pre-ictal SPECT in temporal lobe epilepsy: regional cerebral blood flow is increased prior to electroencephalography-seizure onset. *J Nucl Med* 1998;39:978–82.
30. Qu H, Gotman J. A seizure warning system for long term epilepsy monitoring. *Neurology* 1995;45:2250–4.
31. Osorio I, Frei M-G, Wilkinson SB. Real-time automated detection and quantitative analysis of seizures and short-term prediction of clinical onset. *Epilepsia* 1998;39:615–27.
32. Le Van Quyen M, Fouchez J, Lachaux JP, et al. Comparison of Hilbert Transform and wavelet methods for the analysis of neuronal synchrony. *J Neurosci Methods* 2001;111:83–98.
33. Le Van Quyen M, Navarro V, Martinerie J, et al. Characterizing neurodynamic changes before seizures. *J Clin Neurophysiol* 2001;18:191–208.
34. Wieser HG. Preictal EEG findings. *Epilepsia* 1989;30:669.
35. Lachaux JP, Rodriguez E, Martinerie J, et al. Measuring phase-synchrony in brain signal. *Hum Brain Mapp* 1999;8:194–208.
36. Lange HH, Lien JP, Engel J, et al. Temporo-spatial patterns of pre-ictal spike activity in human temporal lobe epilepsy. *Electroencephalogr Clin Neurophysiol* 1983;56:543–55.
37. Katz A, Marks DA, McCarthy G, et al. Does interictal spiking rate change prior to seizure? *Electroencephalogr Clin Neurophysiol* 1991;79:153–6.
38. Lieb JP, Woods SC, Siccardi A, et al. Quantitative analysis of depth spiking in relation to seizure foci in patients with temporal lobe epilepsy. *Electroencephalogr Clin Neurophysiol* 1978;44:641–63.
39. Gotman J, Ives J, Gloor P, et al. Changes in interictal EEG spiking and seizure occurrence in humans. *Epilepsia* 1982;23:432–3.
40. Elbert T, Ray WJ, Kowalik AJ, et al. Chaos and physiology: deterministic chaos in excitable cell assemblies. *Physiol Rev* 1994;74:1–47.
41. McKenna TM, McMullen TA, Shlesinger MF. The brain as a dynamic physical system. *Neuroscience* 1994;60:587–605.
42. Le Van Quyen M, Martinerie J, Adam C, et al. Unstable periodic orbits in a human epileptic activity. *Physiol Rev E* 1997;56:3401–11.
43. Takens F. *Lecture notes in mathematics: dynamical systems and turbulence*. Berlin: Springer Verlag, 1981.
44. Grassberger P, Schreiber T, Schaffrath C. Nonlinear time series analysis. *Int J Biffurc Chaos* 1991;1:521–47.
45. Varela F, Lachaux JP, Rodriguez E, et al. The brain web: phase synchronization and large-scale integration. *Nat Rev Neurosci* 2001;2:229–39.
46. Méndez M, Radtke RA. Interactions between sleep and epilepsy. *J Clin Neurophysiol* 2001;18:106–27.
47. Babloyantz A, Destexhe A. Low dimensional chaos in an instance of epilepsy. *Proc Natl Acad Sci U S A* 1986;83:3513–7.
48. Pijn JP, Neerven JV, Noest A, et al. Chaos or noise in EEG signals: dependence on state and brain site. *Electroencephalogr Clin Neurophysiol* 1991;79:371–81.
49. Lehnertz K, Elger CE. Spatio-temporal dynamics of the primary epileptogenic area in the temporal lobe epilepsy characterized by neuronal complexity loss. *Electroencephalogr Clin Neurophysiol* 1995;95:108–17.
50. Moser HR, Weber B, Wieser HG, et al. Electroencephalograms in epilepsy: analysis and seizure prediction within the framework of Lyapunov theory. *Physiol D* 1999;130:291–305.
51. Sackellares JC, Iasemidis LD, Shiau DS, et al. Epilepsy: when chaos fails. In: Lehnertz K, Elger CE, eds. *Chaos in the brain*? Singapore: Word Scientific, 1999.
52. Cerf R, Ouasdad H. Spectral analysis of stereo-electroencephalograms: preictal slowing in partial epilepsies. *Biol Cybern* 2000; 83:399–405.
53. Petrosian A, Prokhorov D, Homan R, et al. Recurrent neural network based prediction of epileptic seizures in intra- and extracranial EEG. *Neurocomputing* 2000;30:201–18.
54. Mackey MC, Glass L. Oscillation and chaos in physiological control system. *Science* 1977;197:287–9.
55. Theiler J, Rapp PE. Re-examination of the evidence for low-dimensional nonlinear structure in the human electroencephalogram. *Electroencephalogr Clin Neurophysiol* 1996;98:213–23.
56. Osborne AR, Provenzale A. Finite correlation dimension for stochastic systems with power-law spectra. *Physiol D* 1989;35:357–81.
57. Hernandez J, Valdes PA, Vila P. EEG spike and wave modeled by a stochastic limit cycle. *Neuroreport* 1996;7:2246–50.
58. Andrzejak RG, Widman G, Lehnertz K, et al. The epileptic process as nonlinear deterministic dynamics in a stochastic environment: a evaluation on mesial temporal lobe epilepsy. *Epilepsy Res* 2001;44:129–40.
59. Schreiber T. Detecting and analyzing nonstationarity in a time series with nonlinear cross-prediction. *Physiol Rev Lett* 1997;78:843–46.
60. Manuca R, Savit R. Stationarity and nonstationarity in time series analysis. *Physiol D* 1996;99:134–61.
61. Hively LH, Protopopescu VA, Gailey PC. Timely detection of dynamical change in scalp EEG signals. *Chaos* 2000;10:846–75.
62. Nunez PL, Srinivasan R. Implications of recording strategy for estimates of neocortical dynamics with electroencephalography. *Chaos* 1993;3:257–66.
63. Le Van Quyen M, Adam C, Baulac M, et al. Nonlinear interdependencies of EEG signals in human intracranially recorded temporal lobe seizures. *Brain Res* 1998;792:24–40.
64. Le Van Quyen M, Martinerie J, Adam C, et al. Nonlinear analyses of interictal EEG map the brain interdependences in human focal epilepsy. *Physiol D* 1999;127:250–67.
65. Mormann F, Lehnertz K, David P, et al. Mean phase coherence as a measure for phase synchronization and its application to the EEG of epileptic patients. *Physiol D* 2000;144:358–69.
66. Carter GC. Coherence and time delay estimation. *Proc IEEE* 1987;75:236–55.
67. Rosenblum M, Pikovsky A, Kurths J. Phase synchronization of chaotic oscillators. *Physiol Rev Lett* 1996;76:1804–7.
68. Tass P, Rosenblum MG, Weule J, et al. Detection of n:m phase locking from noisy data: application to magnetoencephalography. *Physiol Rev Lett* 1998;81:3291–4.
69. Glass L. Synchronization and rhythmic processes in physiology. *Nature* 2001;410:277–84.
70. Wyler AR, Fetz EE, Ward AA. Spontaneous firing patterns of epileptic neurones in the monkey motor cortex. *Exp Neurol* 1973;40:567–85.

71. Spencer SS. Substrates of localization-related epilepsies: biologic implications of localizing findings in humans. *Epilepsia* 1998;39:114–23.
72. Morrell F. Varieties of human secondary epileptogenesis. *J Clin Neurophysiol* 1989;6:227–75.
73. Adam C, Clemenceau S, Semah F, et al. Variability of presentation in medial temporal lobe epilepsy: a study of 30 operated cases. *Ann Neurol Scand* 1996;94:1–11.
74. Matsumo H, Ajmone Marsan C. Cortical cellular phenomena in experimental epilepsy: ictal manifestations. *Exp Neurol* 1964;9:305–26.
75. Kopell N, Ermentrout GB, Whittington MA, et al. Gamma rhythms and beta rhythms have different synchronization properties. *Proc Natl Acad Sci U S A* 2000;97:1867–72.
76. Traub RD, Whittington MA, Buhl EH, et al. On the mechanism of the gamma to beta frequency shift in neuronal oscillations induced in rat hippocampal slices by tetanic stimulation. *J Neurosci* 1999;19:1088–105.
77. Von Stein, Rappelsberger P, Sarnthein, et al. Synchronization between temporal and parietal cortex during multimodal object processing in man. *Cereb Cortex* 1999;9:137–50.
78. Sterman M, Bowersox SS. Sensorimotor EEG rhythmic activity: a functional gate mechanism. *Sleep* 1981;4:408–22.
79. Schiff S, Jerger K, Chang T, et al. Controlling chaos in the brain. *Nature* 1994;370:615–20.
80. Gluckman BJ, Nguyen H, Weinstein SL, et al. Adaptive electric control of epileptic seizures. *J Neurosci* 2001;21:590–600.
81. Birbaumer N, Elbert T, Canavan A, et al. Slow potentials of the cerebral cortex and behavior. *Physiol Rev* 1990;70:1–41.
82. Schmid-Schönbein C. Improvement of seizure control by psychological methods in patients with intractable epilepsies. *Seizure* 1998;7:261–70.
83. Palus M. Synchronization as adjustment of information rates: detection from bivariate time series. *Physiol Rev E* 2001;63:46211–6.