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Epilepsies as Dynamical Diseases of Brain Systems: Basic Models of the Transition Between Normal and Epileptic Activity

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Summary: *Purpose:* The occurrence of abnormal dynamics in a physiological system can become manifest as a sudden qualitative change in the behavior of characteristic physiologic variables. We assume that this is what happens in the brain with regard to *epilepsy*. We consider that neuronal networks involved in epilepsy possess multistable dynamics (i.e., they may display several dynamic states). To illustrate this concept, we may assume, for simplicity, that at least two states are possible: an *interictal* one characterized by a normal, apparently random, steady-state of ongoing activity, and another one that is characterized by the paroxysmal occurrence of a synchronous oscillations (seizure).

Methods: By using the terminology of the mathematics of nonlinear systems, we can say that such a bistable system has two attractors, to which the trajectories describing the system's output converge, depending on initial conditions and on the system's parameters. In phase-space, the basins of attraction corresponding to the two states are separated by what is called a "separatrix." We propose, schematically, that the transition between the normal ongoing and the seizure activity can take place according to three basic models:

Model I: In certain epileptic brains (e.g., in absence seizures of idiopathic primary generalized epilepsies), the distance between "normal steady-state" and "paroxysmal" attractors is very small in contrast to that of a normal brain (possibly due to genetic and/or developmental factors). In the former, discrete *random* fluctuations of some variables can be sufficient for the occurrence of a transition to the paroxysmal state. In this case, such seizures are not predictable.

Model II and model III: In other kinds of epileptic brains (e.g., limbic cortex epilepsies), the distance between "normal steady-state" and "paroxysmal" attractors is, in general, rather large, such that random fluctuations, of themselves, are commonly not capable of triggering a seizure. However, in these brains, neuronal networks have abnormal features characterized by *unstable parameters* that are very vulnerable to the influence of endogenous (model II) and/or exogenous (model III) factors. In these cases, these critical parameters may gradually change with time, in such a way that the attractor can deform either gradually or suddenly, with the consequence that the distance between the basin of attraction of the normal state and the separatrix tends to zero. This can lead, eventually, to a transition to a seizure.

Results: The changes of the system's dynamics preceding a seizure in these models either may be detectable in the EEG and thus the route to the seizure may be predictable, or may be unobservable by using only measurements of the dynamical state. It is thinkable, however, that in some cases, changes in the excitability state of the underlying networks may be uncovered by using appropriate stimuli configurations before changes in the dynamics of the ongoing EEG activity are evident. A typical example of model III that we discuss here is photosensitive epilepsy.

Conclusions: We present an overview of these basic models, based on neurophysiologic recordings combined with signal analysis and on simulations performed by using computational models of neuronal networks. We pay especial attention to recent model studies and to novel experimental results obtained while analyzing EEG features preceding limbic seizures and during intermittent photic stimulation that precedes the transition to paroxysmal epileptic activity. **Key Words:** Epilepsy—Electroencephalography—Nonlinear dynamics—Seizures—Phase-coherency index—Models—Signal processing, computer assisted.

THE CONCEPT OF EPILEPSY AS A DYNAMICAL DISEASE

In essence the sudden occurrence of an increase in synchronous activity within relatively large neuronal networks underlies epileptic manifestations. This widespread synchronous state disturbs the normal working of the brain. It may be triggered by some changes in network's parameters and/or inputs, although this may not be evident to an observer. In a normal brain, such changes would not cause more than a transient and harmless modification of brain activity; but in the epileptic brain, they can cause disastrous massive synchronous discharges. This is the essence of a paroxysmal disorder. Why and how paroxysmal episodes occur is difficult to apprehend, based only on current knowledge of pathophysiology, because of the complexity of the factors that jointly are responsible for

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their occurrence. The main purpose of this article is to show that to understand this kind of phenomenon, it is useful to apply concepts derived from the mathematics of nonlinear complex systems to the analysis of the working of neuronal networks. Likewise such concepts are necessary to understand other complex phenomena of nature, such as in hydrodynamics, in meteorology, or in the physics of plasmas (1).

In this context, we assume that in the epileptic brain, some neuronal networks can display different kinds of dynamical states because they possess an abnormal set of control parameters. In other words, they may have bi(multi) stable properties. This means that, in addition to a normal steady state, they also have an abnormal one characterized by widespread synchronous activity, and that the transition between these two states may occur abruptly. This accounts for the two main characteristics of epilepsy: (a) that an epileptic brain can function apparently normally between seizures (i.e., during the interictal state; and (b) that the seizures occur in a paroxysmal way, thereby impairing brain functioning to a lesser or greater extent. In this sense, epileptic disorders may be considered especial cases of the large class of dynamical diseases, meaning those pathophysiologic states characterized by the occurrence of abnormal dynamics, a theoretical concept proposed by Glass and Mackey (2) that we have used in the context of epilepsy (3) and others thereafter (4).

The theory of nonlinear dynamics offers the possibility to understand, in formal terms, how the occurrence of the manifestations of dynamical diseases takes place. In the case of epilepsy, the basic question is how changes in the dynamics of a neuronal network may occur such that paroxysmal widespread synchronous oscillations abruptly emerge.

NONLINEAR DYNAMICS, ATTRACTORS, AND EPILEPSY

We briefly present some general notions with respect to the dynamics of complex nonlinear systems that are useful to better understand the models that we propose here. An important notion in the dynamics of such cases is the fact that systems are characterized by the presence of attracting sets, or *attractors*, in the phase space. An attractor may be seen as a state toward which a system tends to evolve over time. For example, in a damped harmonic oscillator, a typical trajectory in phase space spirals into its point of origin, as illustrated in the examples of Fig. 1A. In this case, the system has the origin as attractor (i.e., it has a point attractor). In the example of Fig. 1B, the attractor is a closed curve, called the limit cycle. In these cases, the attractors have simple forms. However, in more complex systems, the attractor has an intricate geometric structure, called a *manifold*. The latter are characteristic of high-dimensional systems with so-called chaotic dynamics. These complex manifolds are commonly called *fractals*, if they consist of noninteger dimensions. An attractor that is a fractal is called a *strange attractor*. These systems display sensitive dependence on initial conditions. As time evolves, small fluctuations in some parameters may drastically change the behavior of the system. One calls the part of the phase space within which the characteristic trajectories of the system converge to the attractor the *basin of attraction*. A complex nonlinear system may have more than one attractor, and therefore more than one *basin of attraction*. In phase space, the basins of attraction occupy distinct spaces and are separated by a closed curve, the *separatrix*. Examples obtained by using our model are shown in Fig. 2.

The transition from one to another kind of attractor in a nonlinear complex system may not occur abruptly, but it may show an intermittent character when an approximately periodic behavior is intermittently interrupted by bursts in which the system's trajectory behaves in a different manner. Several forms of intermittency transition from a stable periodic attractor to chaos may occur (1). Transitions from interictal EEG activity to seizure activity often occur in ways that are reminiscent of such intermittency behavior. In general, a dynamical system has a relatively small number of parameters that can modify its overall dynamical structure, such that the system may make a transition from one to another attractor. We then say that a *bifurcation* has taken place (for details of physiological applications, see refs. 5 and 6). Thus, a bifurcation represents a qualitative change and depends on a set of critical parameters that define the operating regime of the system. An epileptic seizure may occur when some critical parameters of a neuronal network change in such a way that a bifurcation to a low-dimensional attractor occurs. Whether the latter is a chaotic attractor is difficult to determine by using real EEG signals in most cases. The neuronal network's behavior may often approach a limit cycle, as illustrated in Fig. 1B. The basic set of critical parameters of such a neuronal network is reflected in the balance between excitatory and inhibitory processes, both intrinsic and synaptic.

NEURONAL NETWORKS, SYNCHRONY, AND OSCILLATORY BEHAVIOR

The main factors that condition, in general, the basic phenomenon of synchronous oscillations in neuronal assemblies are (a) the intrinsic membrane properties of the neurons, (b) the structure of the interconnectivity between the network elements, (c) the synaptic processes related not only to specific inputs but also to the existence of feedback and feedforward connections, and (d) the modulating influences from neurotransmitter systems.

It has been frequently assumed that cellular "pacemakers" might determine oscillations in neuronal networks.

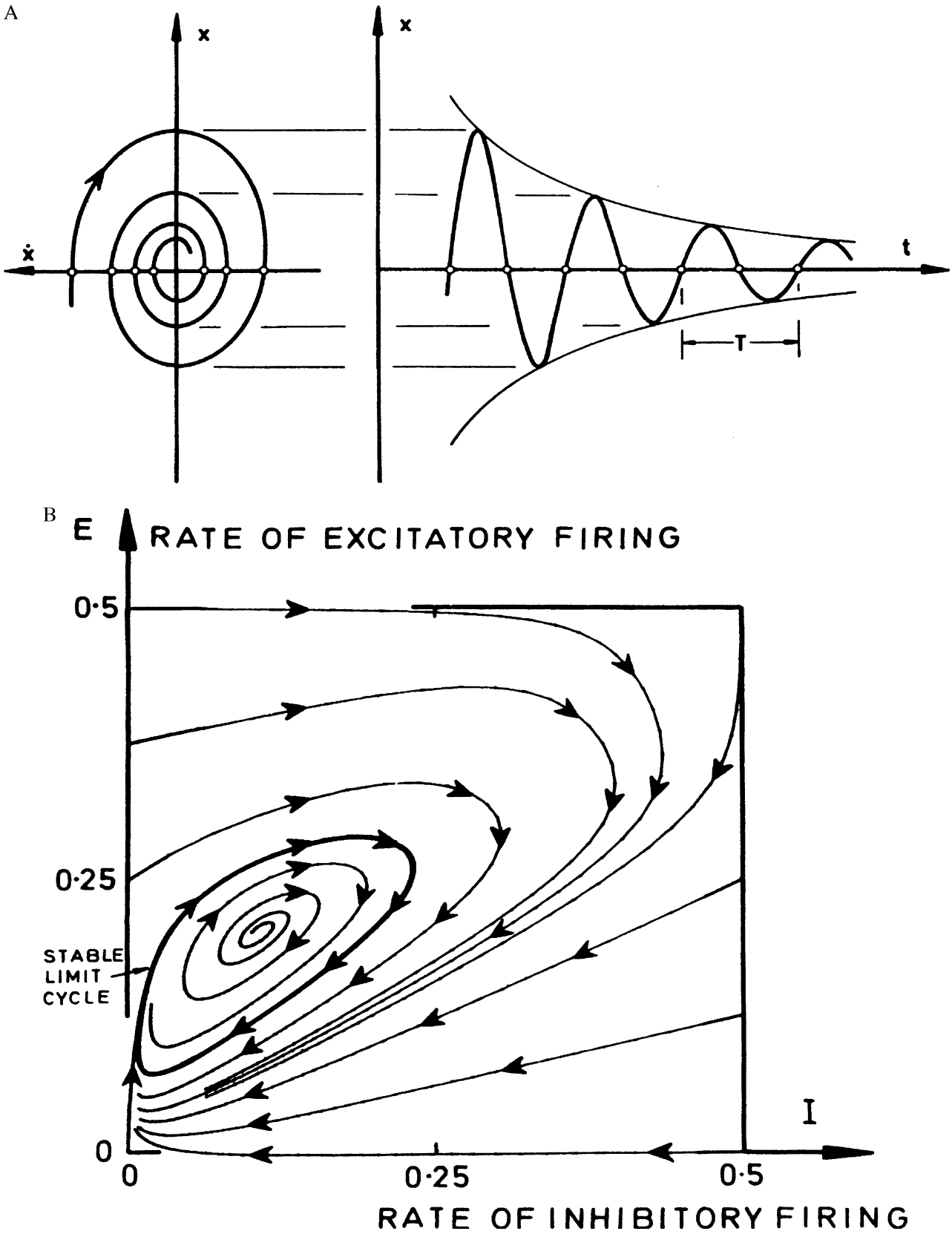

FIG. 1. Examples of attractors. **A:** Response of a damped linear oscillator on the right and phase plane showing the convergence of the trajectory to a point attractor. **B:** Stable limit cycle in the phase space of a neural computer simulation. The limit cycle represents the attractor as a function of the firing rates of the excitatory and the inhibitory populations (adapted from 70).

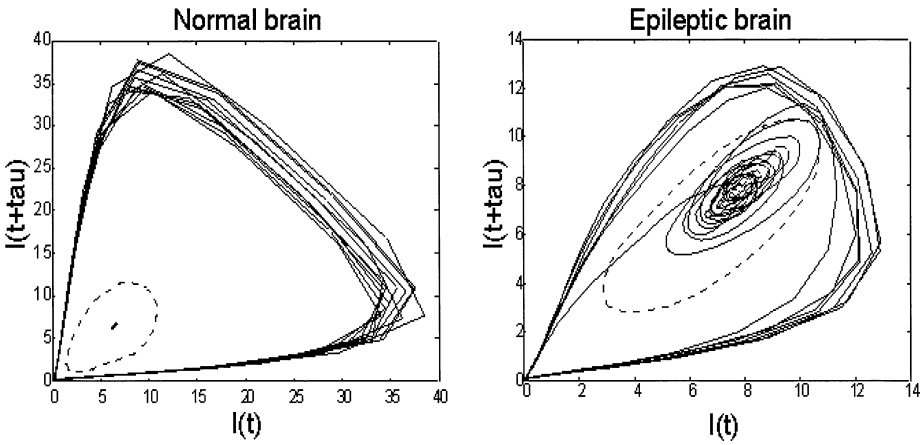

FIG. 2. Phase-plane representation of the attractors obtained by way of computer simulations with two models. **Right:** This model has parameters representing a "normal brain." **Left:** This model has parameters of an "epileptic brain." In the "normal brain," a large distance exists between the "normal attractor," having a concentrated basin of attraction and the possible "seizure attractor," so that a transition to the latter will practically never occur. Conversely, the "epileptic brain" **(right)** shows a very small distance between the two attractors, such that any fluctuation of critical parameters can give rise to a transition to the "seizure attractor." The separatrix between the two basins of attraction is represented by the dotted line (adapted from Suffczynski et al., unpublished data).

In this context, it has been shown that some types of thalamic neurons may display oscillatory behavior in vitro, even after blocking synaptic transmission (7,8). Given the appropriate initial conditions, such neurons can generate intrinsic membrane oscillations mainly in the frequency range of 6–10 Hz. The question is whether these oscillations are really autonomous, as in the case of a genuine "pacemaker" in some populations of heart cells. This is difficult to prove. Studies of the ionic conductances of thalamic neurons, both thalamocortical and reticular nucleus neurons (9–11), showed that these neurons may present oscillations, but only under specific initial conditions. Such neurons may switch from a nonoscillatory to an oscillatory mode, and even from one to another preferred frequency within the latter, depending on the level of membrane potential. Thus, these neurons tend to oscillate at 10 Hz when their membrane potential is more depolarized than at rest, and at ~6 Hz when they are relatively more hyperpolarized than the resting potential. In between, they do not appear to behave in a continuous oscillatory state. This is why they do not behave as true (i.e., autonomous and continuous) "pacemaker" cells. They react to the input conditions that modulate their membrane potential by shifting from one mode to another. For instance, the 10-Hz oscillatory mode requires that the membrane potential shift in the depolarizing direction, which has to be achieved by an appropriate synaptic input. Similarly the 6-Hz mode requires that the membrane be first hyperpolarized by an inhibitory γ-aminobutyric acid-ergic (GABAergic) synaptic input. The same authors showed that the thalamic nuclei do not generate spindle oscillations after being disconnected from the reticular nucleus (RE) of the thalamus (12). Nevertheless, although the neurons of the latter may show oscillatory spindles on their own, the mechanism underlying these oscillations probably depends on a change in driving forces (13,14). This means that in the intact brain in vivo, the initial conditions and control parameters that are responsible for different behavioral modes are supplied by specific and modulating synaptic inputs. Therefore, these initial conditions and control parameters depend on the activity of other neuronal elements of the local network and/or on that of distant neuronal populations (e.g., cholinergic, monoaminergic, and/or peptidergic) that act as modulating systems. This implies that when discussing the mechanisms responsible for rhythmic behavior in neuronal networks, we must emphasize the dynamics of synaptic interactions (feedforward and feedback connections), taking into consideration the intrinsic membrane properties of the different neuronal types (15,16). The latter are certainly important in setting the initial conditions that are necessary for the occurrence of specific oscillations. We next present a general model of how oscillations of large amplitude and relatively low frequency (3–4 Hz), typical of some forms of epilepsy, may emerge from a state characterized by low-amplitude oscillations around 7–14 Hz, as seen during alpha rhythms and sleep spindles, that in a first approximation may be taken together, although these two kinds of rhythmic activities differ in a number of properties.

In addition to the relatively low-frequency oscillations described earlier, remarkable high-frequency oscillations also can be recorded in the EEG or magnetoencephalogram (MEG). During visual stimulation, high-frequency synchrony between series of action potentials is evident during specific behavioral states (17–19). The discharge of these neurons is typically oscillatory in the high-frequency range (20–70 Hz, usually called beta and gamma bands). In some cases, phase-locking of oscillatory trains of action potentials occurs at a distance as great as 7 mm over the cortical surface (20,21). Most interestingly, in cats trained to pay attention to a visual stimulus cue, precise synchronization occurred between populations of neurons

of different cortical areas: the visual, parietal, and motor cortex, with a millisecond precision (22). At the same time, although oscillatory bursts with a frequency of ~20 Hz were found in area 5, the oscillatory bursts in area 7 had a lower frequency. These relatively high frequency synchronous oscillations at the neuronal level are likely to correspond to the local cortical beta/gamma EEG rhythmic activities recorded in freely behaving animals, particularly during attentive visual states (23–25) and in humans (26,27). Both neurophysiologic and computational studies showed that oscillations in the gamma frequency range in hippocampal and neocortical networks may be caused by changes in the dynamics of inhibitory neuronal populations (28–33).

From these experimental findings, we may conclude that neuronal networks can display different states of synchrony, with oscillations at different frequencies with specific dynamics. We described (24) that it is possible to record alpha or beta/gamma oscillations from the same cortical areas, depending on the level of alertness, but that the low-frequency rhythms are much more generalized in space, whereas the higher frequency oscillations are localized to restricted cortical areas and can vary in dominant frequency among closely spaced areas. In this respect, it also has been shown that oscillations in the beta frequency range (12–29 Hz) have a different dynamical structure than gamma oscillations (30–70 Hz) and that the former involve cortical areas at longer distances than the latter (30). The transition between both types of oscillations depends on the system's parameters (on the strength of excitatory recurrent synapses and of intrinsic slow K^+ conductances). Thus, when neuronal populations display resonant behavior (i.e., they present oscillations), the latter tend to recruit neurons in larger cortical areas in the case of low frequencies and to be more spatially restricted in the case of higher frequencies. Under these circumstances, the cortex appears to be functionally organized as a mosaic of differently active neuronal assemblies that may display a large variety of oscillations with distinct dominant frequencies.

Basic mechanisms of thalamocortical oscillations and paroxysmal spike-and-waves

The basic mechanisms of oscillations, of the ~3-Hz spike-and-wave kind, can best be understood with the help of computational models of the electrical activity of thalamocortical networks. In these networks, two main types of oscillations can occur, depending on specific conditions: the spindles found in certain stages of sleep and the ~3-Hz spike-and-wave (SW) oscillations characteristic of absence seizures of idiopathic primary generalized epilepsy. Spindles are defined as waxing and waning waves between 7 and 14 Hz, grouped in sequences that last for 1.5–2 s and that recur periodically with a slow rhythm of 0.1–0.2 Hz (10). The thalamic origin of these spindle waves is well known (34). Experimental studies in vivo (9), in vitro (35–37), as well as computational modeling (38) clarified the cellular and network mechanisms underlying spindle rhythmicity. It is currently considered that spindle oscillations result from reciprocal interactions between thalamocortical relay (TCR) and thalamic RE cells (Fig. 3). The RE cells receive excitatory input from TCR cells and project back to relay nuclei via inhibitory synapses. The TCR cells can fire occasionally rebound bursts of spikes after recovery from hyperpolarization induced by inhibitory postsynaptic potentials (IPSPs) of RE origin. RE cells tend to fire bursts of action potentials in response to excitation from thalamocortical and corticothalamic cells. In both types of cells, the ability to generate bursts is provided by a low-threshold (I_T) calcium current (7,39–43) that needs a period of membrane hyperpolarization to deinactivate it. This hyperpolarization can be caused by GABAergic inhibition. The cellular activity during the alpha rhythms recorded during wakefulness is still unknown, but it is hypothesized that it might resemble some general mechanisms responsible for the 7- to 14-Hz spindle activity, although alpha rhythms and sleep spindles differ quantitatively and qualitatively in several respects (44).

The cellular mechanisms of the generation of spindle oscillations during sleep appear to be related to those for the generation of the ~3-Hz SW complexes (45) that are associated with classic absence seizures in idiopathic primarily generalized epilepsy. This was clearly in evidence in ferret geniculate slices. In this preparation, the pharmacologic block of $GABA_A$ can result in the paroxysmally occurring transformation of spindle waves into ~3-Hz SW ictal activity. A remarkable property of these paroxysmal SW oscillations is that they are suppressed by $GABA_B$-receptor antagonists (35–37). Although this SW activity in vitro may differ from that observed during absence seizures in patients (46,47), the activation of $GABA_B$ receptors in the thalamic relay nuclei seems to be essential in both cases. In animals with genetic absence-type seizures, thalamic injection of selective agonists of $GABA_B$ receptors results in SW discharges, whereas administration of $GABA_B$-receptor antagonists diminishes the occurrence of SW in a dose-dependent manner. The long duration of $GABA_B$ receptor–mediated hyperpolarization is effective in removing the inactivation of the low-threshold calcium current. Therefore, activation of the $GABA_B$ receptors results in rebound bursts of action potentials in a large proportion of thalamocortical neurons. These facilitated TCR cell discharges strongly excite RE cells, which can result in the generalization of paroxysmal activity. A major role of the low-threshold Ca^{2+} currents in the pathophysiology of absence-type seizures is suggested by the observation that the "antiabsence seizure" drugs ethosuximide (ESM) and trimethadione (TMO) exert their therapeutic effect by antagonizing low-threshold calcium currents in the thalamus (48–50).

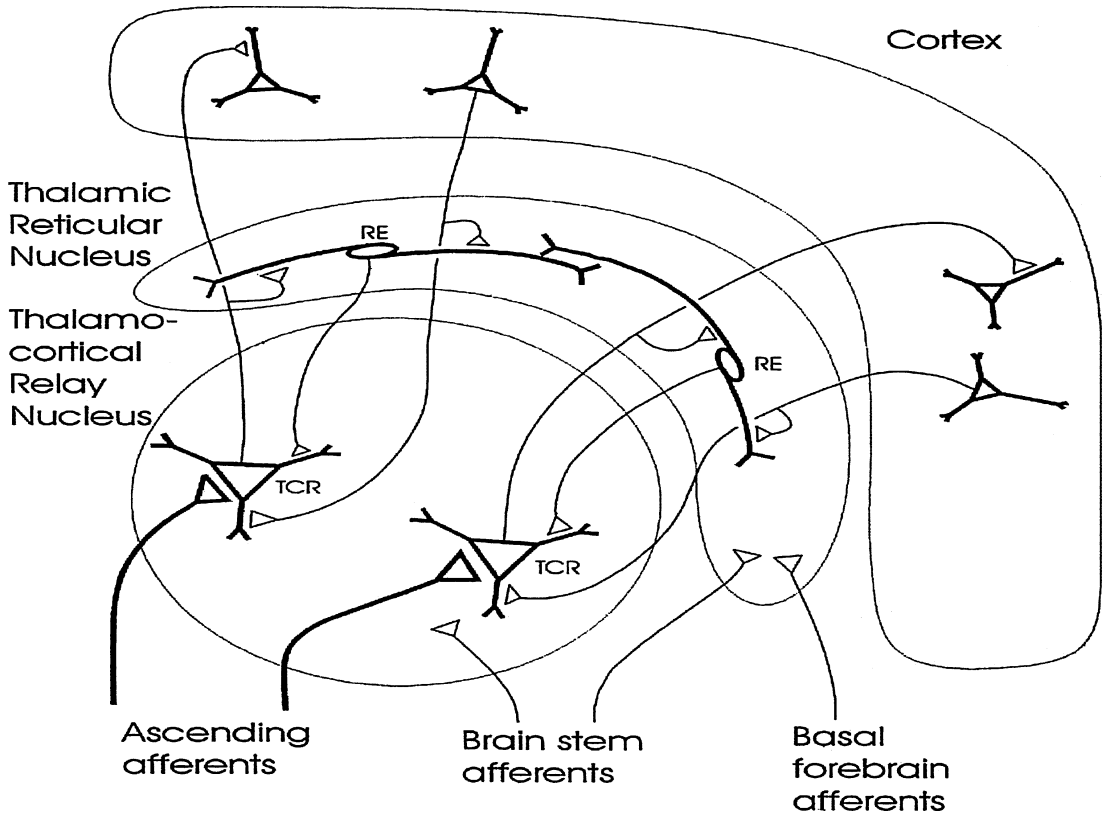

FIG. 3. Schematic diagram showing two simplified thalamocortical modules. Each module consists of a thalamocortical neuronal population (TCR), the corresponding population of reticular neurons (RE), and the cortical pyramidal neurons. The TCR neurons receive afferents from specific sensory sources as well as modulating inputs from the brainstem and basal forebrain. Note the existence of feedback loops between TCR and RE neurons and between the thalamic and the cortical neurons. The two modules are interconnected by lateral connections between neighboring RE neurons.

Thus, it is clear that both GABA synaptic transmission, mediated by A or B receptors, and low-threshold Ca^{2+} currents play a role in the transition from the alpha spindle activity mode to the 3-Hz SW bursts mode. The interplay between these factors is complex, and they cannot be considered isolated from another important control factor, the level of the membrane potential of the main neuronal population. The latter is modulated by a number of inputs (cholinergic, monoaminergic, peptidergic) arising from the brainstem and forebrain. To obtain a better understanding of how these different factors condition the two main modes of activity in this neuronal network, and the transition between both, we constructed a computational model (Fig. 4). In this way, it is possible to analyze in a quantitative way, albeit by means of computer simulations, the conditions by which the thalamocortical networks display different dynamical states that characterize the normal oscillatory activity in the alpha frequency range and the transition to the paroxysmal SW oscillations.

Model I: how bifurcations between distinct oscillatory states can take place in a thalamocortical network

A number of detailed, distributed models of thalamic and thalamocortical networks were recently developed (51–53). These models can give insight into basic neuronal mechanisms. However, 3-Hz SW absence-type seizures reflect the dynamical properties of neuronal populations at the macroscopic level. Therefore, in a previous study (54), we approached this problem at an intermediate level (i.e., we did not simulate the explicit behavior of individual neurons but rather modeled the populations of interacting neurons lumped together). With this approach, we were able to simulate that thalamocortical networks can display distinct oscillatory modes (Fig. 5). This means that these networks have distinct attractors. This can best be visualized by way of phase-space plots, as illustrated in Fig. 2. A separatrix between the two basins of attraction in phase space can be defined. It also can be shown that this dynamical system presents hysteresis and jump phenomena (i.e., the system's dynamics may jump abruptly from one oscillatory mode to another). One mode corresponds to the normal oscillatory state, the typical alpha rhythm, whereas the other corresponds to the SW mode characteristic of the absence-type seizure of idiopathic primary generalized epilepsy.

In analogy, the basic difference between a normal brain and that of an epilepsy patient with idiopathic primary generalized epilepsy during absence seizures is that,

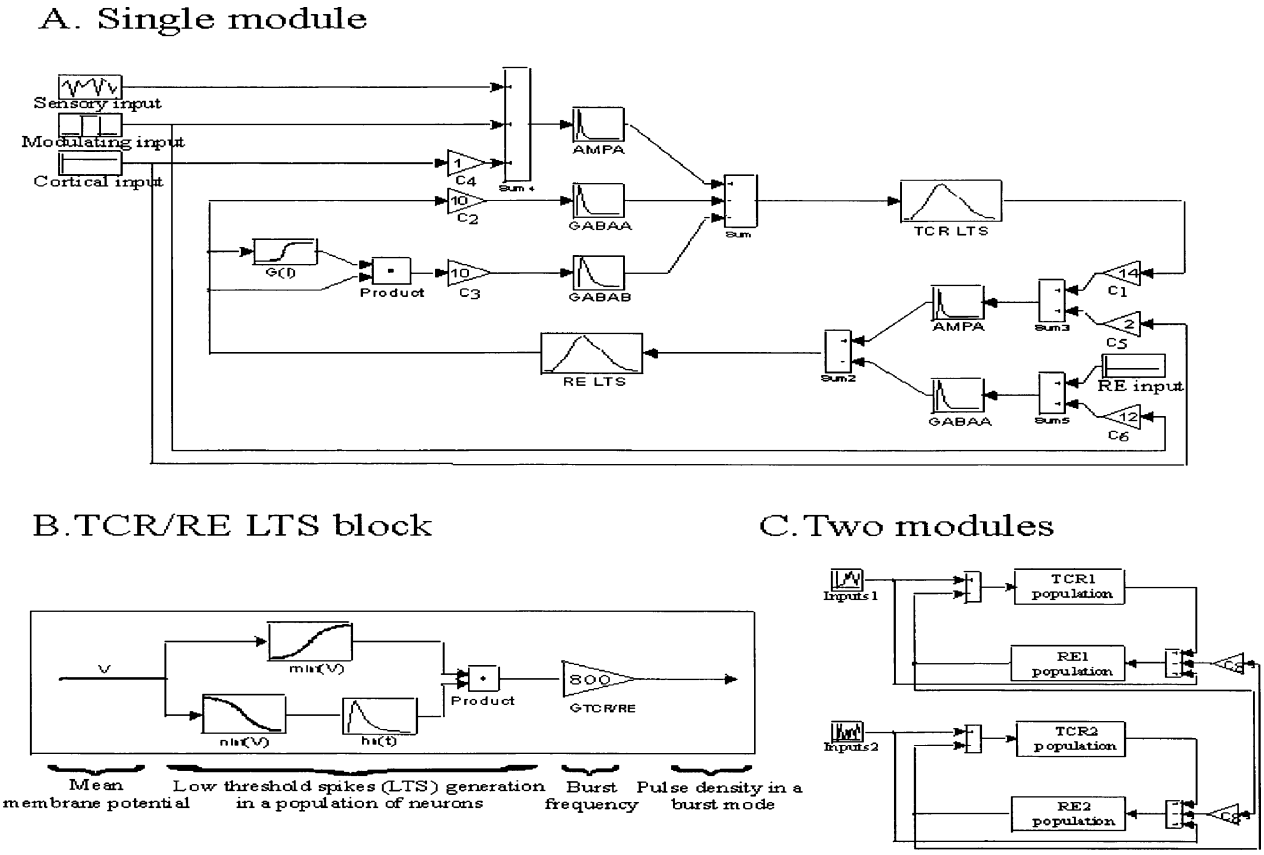

FIG. 4. **A:** Block scheme of the lumped model used to simulate the transition between normal ongoing EEG activity and spike-and-wave seizures. Each module represents a TCR population with three inputs: a one glutamatergic (AMPA) and two γ-aminobutyric acid (GABA)ergic (**A**, **B**), with the corresponding synaptic transfer functions. The summed activity is the input to a nonlinear transfer function that represents the generation of impulses, including the low-threshold spikes (LTSs), as shown in **B**. **C:** The two modules are interconnected (54).

in the former, the basin of attraction under all circumstances of everyday life is very distant from the separatrix, and thus from the attractor corresponding to the ~3-Hz SW oscillatory mode, whereas in the latter, this distance is very small (Fig. 2). This feature of this kind of epileptic brains is likely determined by the existence of abnormal neuronal parameters, affecting for example the low-threshold Ca^{2+} channels and/or the $GABA_B$ receptors, because of genetic and/or developmental defects.

According to this model, discrete *random* fluctuations of some variables can be sufficient for the occurrence of a transition to the ictal state. Therefore, in this pathophysiologic case, any small fluctuation of parameters or inputs may flip the system's trajectory over the separatrix such that it can enter the basin of attraction of the ~3-Hz SW paroxysmal mode. If random fluctuations in a bistable network are responsible for the sudden onset of the absence seizures in idiopathic primary generalized epilepsy, it seems reasonable to assume that occurrence of those seizures cannot be predicted, as fluctuations are by definition unpredictable. This conclusion is consistent with the long-standing axiomatic clinical observation, "If warning occurs, the diagnosis of *petit mal* may be questioned" (55).

Model II: Experimental evidence for a gradual change in network parameters and EEG dynamics preceding limbic epileptic seizures

We may assume that in a class of epileptic seizures (e.g., limbic cortex epilepsies), the pathophysiology of the epileptogenic network is characterized by a set of cellular/molecular changes rendering certain control parameters (deemed essential in maintaining stability of the neuronal networks) extremely vulnerable to the influence of exogenous and/or endogenous factors. In these cases, the distance between the basins of attraction of the normal steady-state oscillatory behavior of the interictal state and the separatrix to the ictal oscillations is commonly large enough such that random fluctuations do not lead to a seizure. However, this distance may gradually become smaller because of certain changes of some critical unstable parameters, in such a way that a transition to a seizure eventually occurs. Accordingly we may assume that in this case, changes of dynamics preceding the seizure may be detectable in the EEG. The question is whether such

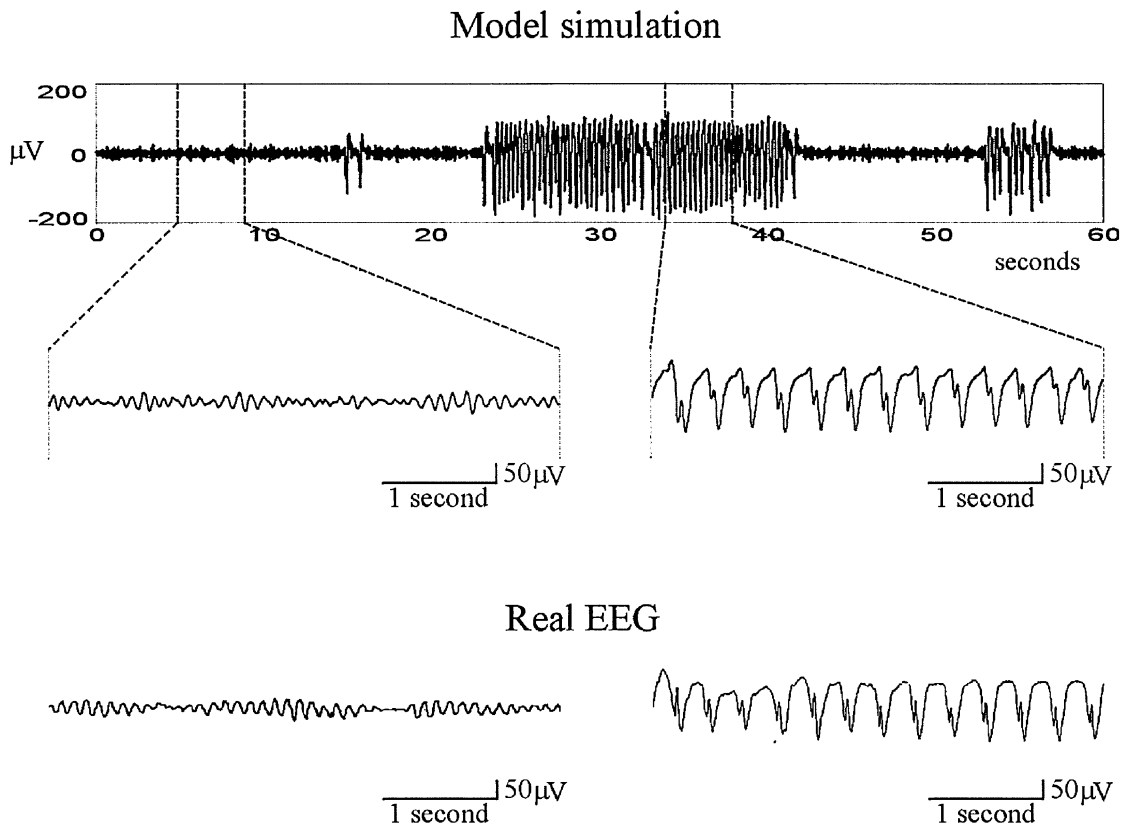

FIG. 5. Above: Result of the simulation of an EEG from a network that is in a state close to the separatrix between the "normal" ongoing EEG activity attractor, characterized by a relatively low-amplitude predominant alpha activity, and the "seizure" attractor with the typical 3-Hz spike-and-wave oscillations of large amplitude. **Below:** Two epochs of real EEG signals recorded from a patient with absence-type seizures.

changes in the dynamical properties of the underlying system may be detected by using the current methods of signal analysis, even before the seizure becomes manifest. Should such changes occur and be detectable by using the mathematical tools derived from the theory of nonlinear dynamical systems, one would be able to predict the occurrence of seizures. This assumption would be of potential clinical significance. An affirmative answer to this question was obtained in a number of studies showing decreased values of correlation dimension in interictal EEGs preceding epileptic seizures (56). Others described that a decrease of the value of the largest Lyapunov exponent occurring simultaneously in a number of EEG channels appears to precede an epileptic seizure (57,58). In yet other studies, a method based on the correlation dimension and surrogate signals was reported to anticipate seizures several minutes before seizure onset (59). In a follow-up study (60), the same group was able to anticipate epileptic seizures on both scalp and intracerebrally recorded EEG signals by using a measure of nonlinear similarity. In our experience with a modified method of computing the correlation dimension, we also found that changes of this statistic may precede seizures by several minutes. However, these methods appear to have a rather weak specificity (i.e., similar changes may be detected although no seizure occurs within a reasonable interval). Nevertheless we cannot simply consider such events "false positives," because they may just correspond to changes in the dynamical state of neuronal networks that are not directly reflected in electrographic seizures and/or electroclinical ictal events. Recent reports in the literature indicate that use of more traditional signal-analysis methods may identify changes in interictal intracranial EEG recordings preceding seizure occurrence in TLE patients (61). This raises the intriguing question, which of all measurable changes in the dynamical state of neuronal networks do actually lead to an epileptic seizure? Is this a question of the duration and magnitude of the dynamical change, and/or of the extent of the neuronal networks involved? Of course, current methods of analysis may still be too limited to capture all relevant features of the dynamical changes reflected in the EEG signals that precede epileptic seizures. A precise answer to these questions requires a profound analysis of electroclinical seizures along with more comprehensive experimental and theoretical models of the dynamics of neuronal networks. In any case, the relation between EEG statistical measures, like the correlation dimension, and the neurophysiological substrate must be better understood to be able to grasp mechanisms responsible for the transition from the ongoing interictal

to the seizure activity. In this respect, some preliminary data of our group appear relevant because they show that changes in the excitatory/inhibitory balance within neuronal networks of the hippocampal formation occurring minutes before a limbic epileptic seizure can be put in evidence by probing the status of the neuronal networks with appropriate stimulations and recording the resulting local field potentials.

Model III: Experimental evidence for the existence of specific features of EEG/MEG signals preceding the transition to SW discharges in photosensitive epilepsy

In a mixed model, the distance between the normal steady state and the separatrix may be very small, as in model I, but in addition, the network's parameters also can change gradually as in model II, but now under the influence of specific external stimuli. This may occur in general in reflex epilepsies. Recently we found experimental evidence for such a possibility in the photosensitive absence type of epilepsy. The observation that in photosensitive epilepsies, the intermittent light at a given frequency after a number of stimuli can elicit the transition to the paroxysmal SW oscillations characteristic of classic absence-type seizures led us to search for features of the neural activity that would indicate the change in network parameters. Without entering into methodologic details published elsewhere (62), we note that we were able to find features in the MEG/EEG signals of patients before the transition to the paroxysmal epileptiform activity mode that appear to be significantly associated with the probability that such a transition will really occur some seconds later. The most significant feature in this respect is a decrease of the phase dispersion, or increase of the phase coherency index, of frequency components in the gamma frequency range that are harmonically related to the fundamental frequency of the intermittent light stimulation (Fig. 6). It should be noted that in the normal functioning of the brain, the formation of dynamic links mediated by synchrony over multiple frequency bands has been proposed (63) as the mechanism involved in large-scale integration of distributed anatomic and functional domains of brain activity to enable the emergence of coherent behavior and cognition. We may hypothesize that the mechanisms involved in this large-scale synchronization may be disturbed in some brains such that they became unstable and, eventually, may undergo a transition to another pathophysiologic oscillatory state, resulting in a seizure.

How can these MEG/EEG-evoked activities with an enhanced phase synchrony at specific high-frequency bands be generated? To understand these phenomena, we should take into consideration that a flickering light of the kind used to trigger epileptiform paroxysms in photosensitive epilepsy patients causes the generation of higher harmonics, and sometimes also subharmonics, of the fundamental stimulation frequency. These nonlinear properties of the visual pathways are well documented (64,65). In addition we note that during visual stimulation, high-frequency synchrony between series of action potentials is evident, as indicated earlier (17–21), and that in the awake attentive state, domains of beta and gamma oscillations are present in the neocortex of animals (22–25), and humans (27). Furthermore it has been demonstrated that cortical

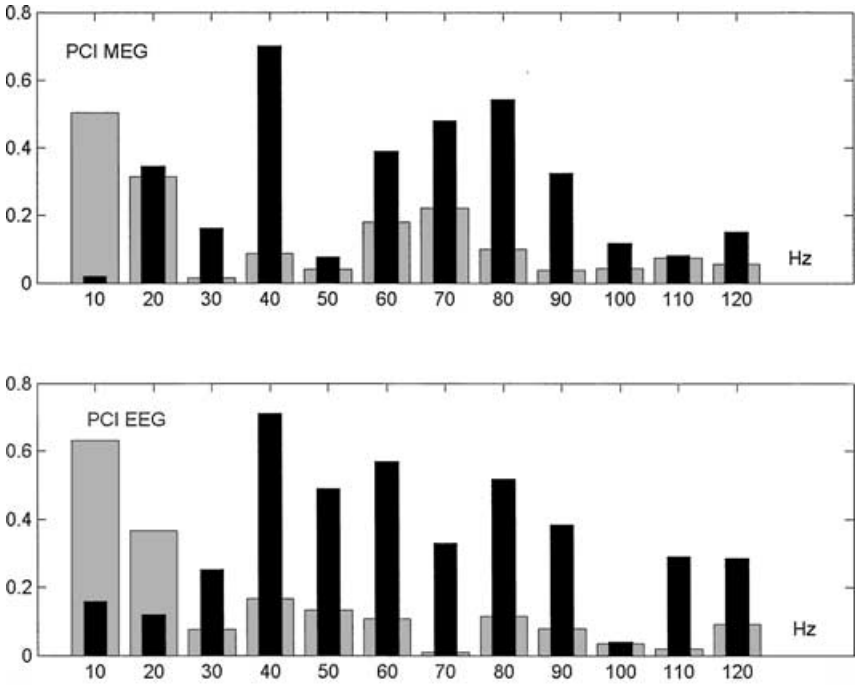

FIG. 6. Histograms showing the value of phase coherency index (PCI) of one MEG **(above)** and one EEG **(below)** channel as function of frequency. Trials performed with intermittent photic stimulation (IPS) at 10 Hz. The PCI values are shown for this frequency and higher harmonics. Wide grey bars: PCI values in the condition that no seizure occurred. Thin black bars: PCI values in the case a seizure occurred. The PCI values were averaged over a time window of 5 s during IPS and before the transition to seizure was detected. Note the much larger PCI values (both in MEG and EEG), particularly in the gamma frequency range (30 to 90 Hz), in the case in which a seizure followed the IPS, as compared with the case in which this did not occur.

networks may display gamma oscillations even in vitro, and the neurophysiologic conditions that may be responsible for the generation of such oscillations have been put in evidence both experimentally (29,31,66) and in model studies (67). Taking these different observations together, we may assume that cortical populations of neurons may display an intrinsic tendency to oscillate in the beta/gamma frequency range under appropriate behavioral conditions. These populations may oscillate at different dominant frequencies, although within the same frequency range, as encountered experimentally. Intermittent photic stimulation that causes the occurrence of higher harmonics within the beta/gamma frequency range appears to lead to the entrainment of such intrinsic oscillatory populations. Thus, the finding of the enhancement of phase coherency within this same frequency range in the photosensitive epilepsy patients (68) may be interpreted as evidence for such an entrainment. The observation that this increased phase coherency is much enhanced in the cases in which the intermittent light stimulation leads to the transition to SW dynamical state implies that, in these cases, a stronger tendency exists for the occurrence of the entrainment of beta/gamma oscillators. Experimental data (69) show that human subjects stimulated with flickering light at frequencies from 1 to 100 Hz exhibit event-related potentials with steady-state oscillations at all frequencies up to $\geq$90 Hz. Interestingly, the steady-state potentials exhibited clear resonance phenomena around 10, 20, 40, and 80 Hz. How these physiologic properties relate to the pathophysiologic enhancement that we found in patients, as described earlier, is discussed elsewhere in more detail (62).

CONCLUSIONS

We present our view of what we may call the basic mechanisms of the routes to epileptic seizures. Our main assumption is that these processes cannot be understood just on the basis of currently accepted pathophysiologic concepts, or even stronger, of current neurobiologic knowledge. To achieve this aim, it is necessary to combine concepts of the neurophysiology of neuronal networks with those of the mathematics of nonlinear systems. The reason is that neuronal networks, in general, behave as nonlinear systems with complex dynamics. This essential feature must be taken into account to understand how neuronal networks can have bi(multi)-stable states and can display bifurcations between such states, sometimes displaying intermittency, depending on changes of the values of some critical parameters. The latter, even if minute, may have enormous consequences. Such dynamical features are characteristic of how epileptic seizures may occur. We developed a framework to account for different routes that can lead a neuronal network to change from its normal mode of activity to a seizure mode within the context of these theoretical considerations. We were able to construct three basic models of routes to epileptic seizures and to define under which circumstances the transition from the ongoing (interictal) activity mode to the ictal (seizure) mode may or may not be predictable. We draw the conclusion that either situation is possible, depending on the dynamical state of a given neuronal system. Whether in some cases seizures may be essentially unpredictable, as most often in absence-type seizures of idiopathic primary generalized epilepsy, in others, it is likely that the actual seizure is preceded by a gradual change in dynamics that, in principle, may be detectable some time before the seizure becomes manifest. This has been already demonstrated in a number of studies, mostly with analysis methods derived from the theory of nonlinear dynamics. In addition we stress the need for a more comprehensive analysis of the dynamical states of neuronal networks based on a combination of basic neurophysiology and computer model studies.

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