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Seizure Prediction and its Applications

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Abstract

Epilepsy is characterized by intermittent, paroxysmal, hypersynchronous electrical activity, that may remain localized and/or spread and severely disrupt the brain's normal multi-task and multi-processing function. Epileptic seizures are the hallmarks of such activity and had been considered unpredictable. It is only recently that research on the dynamics of seizure generation by analysis of the brain's electrographic activity (EEG) has shed ample light on the predictability of seizures, and illuminated the way to automatic, prospective, long-term prediction of seizures. The ability to issue warnings in real time of impending seizures (e.g., tens of minutes prior to seizure occurrence in the case of focal epilepsy), may lead to novel diagnostic tools and treatments for epilepsy. Applications may range from a simple warning to the patient, in order to avert seizure-associated injuries, to intervention by automatic timely administration of an appropriate stimulus, for example of a chemical nature like an anti-epileptic drug (AED), electromagnetic nature like vagus nerve stimulation (VNS), deep brain stimulation (DBS), transcranial direct current (TDC) or transcranial magnetic stimulation (TMS), and/or of another nature (e.g., ultrasonic, cryogenic, biofeedback operant conditioning). It is thus expected that seizure prediction could readily become an integral part of the treatment of epilepsy through neuromodulation, especially in the new generation of closed-loop seizure control systems.

Keywords

Spatio-Temporal Dynamical Analysis of EEG; Ictogenesis; Seizure Prediction; Closed-Loop Seizure Control

1. Introduction

Epilepsy is considered a window to the brain's function and is therefore an increasingly active, interdisciplinary field of research [1–2]. The “sacred” or “divine” disease is among the most common disorders of the nervous system, second only to stroke and Alzheimer's disease, and affects 1–2% of the world's population [3, 4]. While epilepsy occurs in all age groups, the highest incidences occur in infants and in the elderly [5–7]. This high incidence

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The author has nothing to disclose.

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of epilepsy stems from the fact that it occurs as a result of a large number of causes, including genetic abnormalities, developmental anomalies, febrile convulsions, as well as brain insults such as craniofacial trauma, central nervous system infections, hypoxia, ischemia, and tumors.

The hallmarks of epilepsy are recurrent seizures and epileptic spikes. If seizures cannot be controlled, the patient experiences major limitations in family, social, educational, and vocational activities. These limitations have profound effects on the patient's quality of life [8]. Epileptic seizures and spikes are due to sudden development of pathological, synchronous neuronal firing in the cerebrum and can be recorded by scalp, subdural and intracranial electrodes. Seizures may begin locally in portions of the cerebral hemispheres (partial/focal seizures) with a single or multiple foci, or simultaneously in both cerebral hemispheres (generalized seizures). After a seizure's onset, partial seizures may remain localized and cause relatively mild cognitive, psychic, sensory, motor, or autonomic symptoms, or may spread (secondarily generalized) to cause altered consciousness, complex automatic behaviors, or bilateral tonic-clonic convulsions. Even though seizures typically run their course (seconds to minutes) and the brain subsequently recovers by itself, there are cases where recovery is accomplished only through external intervention (i.e., high doses of anti-epileptic drugs), as for example in status epilepticus (SE), a life-threatening condition [9–10]. Finally, the brain does not recover by itself also in the event of sudden unexplained death in epilepsy (SUDEP), where external intervention is unfortunately not available. SUDEP is a relatively less frequent than SE condition, seemingly unpredictable, and hence extremely difficult to monitor [11–12].

One of the most debilitating aspects of epilepsy is that seizures seem to occur without warning. Until recently, the general belief in the medical community was that epileptic seizures could not be anticipated. Seizures were assumed to occur abruptly and randomly over time. However, hypotheses on the mechanisms of ictogenesis and predictability of seizures had been postulated in the past based on reports from clinical practice (e.g., existence of auras) and scientific intuition (e.g., theory of reservoir) [13–14]. In 1970s, attempts to show that seizures are predictable also had been undertaken via computer analysis of the EEG [15]. Despite those early attempts, the results were not encouraging. Systematic and robust detection of a preictal period across seizures in the same patient, as well as across patients, remained illusive. It was clear that the essential features of the brain's transition to epileptic seizures were not captured, and a theoretical framework for seizure development that could lead to definition and subsequent detection of such preictal features was missing [16, 17].

It was in the 1980s that new signal processing methodologies emerged, based on the mathematical theory of nonlinear dynamics and chaos for the study of spontaneous formation of organized spatial, temporal or spatio-temporal patterns in physical, chemical, and biological systems [18–29]. These methodologies quantified the complexity and randomness of the signal from the perspective of invariants of nonlinear dynamics and represented a drastic departure from the signal processing techniques based on linear systems analysis (e.g., Fourier analysis). Since the brain is inherently a nonlinear system, the then developed general concept was that seizures represented transitions of the epileptic brain from its "normal", less ordered (chaotic) state to an abnormal, more ordered state and back to a "normal" state along the lines of chaos-to-order-to-chaos transitions [30]. We will see below how this concept, when applied to the EEG in epilepsy, eventually changed some long-held beliefs about seizures and their dynamical causes. Within this framework, systematic mathematical analysis of long-term EEG recordings that included seizures started in the mid-1980s at the University of Michigan (U of M), creating at the time the largest worldwide database of digitally stored peri-ictal EEG recordings with seizures. The

existence of long-term preictal periods (order of minutes) was shown in 1988 by nonlinear dynamical analysis of EEGs recorded by subdural arrays from patients undergoing phase II monitoring of their seizures at the U of M Hospital's Epilepsy Monitoring Unit (EMU) [31].

2. Existence of a preictal period: Seizure Predictability

Among the important measures of the dynamics a linear or nonlinear system exhibits are the Lyapunov exponents that measure the average information flow (bits/sec) the system produces along local eigendirections in its state space [32–33]. Positive Lyapunov exponents denote generation of information while negative exponents denote destruction of information. A chaotic nonlinear system possesses at least one positive Lyapunov exponent, and it is because of this feature that its behavior looks random, even if it is deterministic in nature. Methods for calculating these measures of dynamics from experimental data have been published [34].

The brain, being nonstationary, is never in a steady state in the strictly dynamical sense, at any location. We have shown that, in the case of a nonstationary system with transients like epileptic spikes, the use of the short-term maximum Lyapunov exponent (STL_{max}) constitutes a more accurate characterization of the rate of the average information flow [35] than the traditional maximum Lyapunov (L_{max}) exponent [36]. STL_{max} is estimated from sequential EEG segments of 10 sec in duration per recording site to create a set of STL_{max} profiles over time. Analysis of scalp, subdural or depth EEG from patients with focal (temporal and frontal lobe) epilepsy at the University of Michigan, and subsequently at the University of Florida and Arizona State University, showed that the STL_{max} profiles at brain sites systematically and progressively converge to similar values tens of minutes before a seizure and remain entrained up to the onset of the seizure [37–48]. We have called this phenomenon *preictal dynamical entrainment* (convergence of measures of EEG dynamics long prior to a seizure onset), the involved brain sites “critical sites”, and the corresponding pairs of sites that interact in this dynamical sense “critical pairs”. The focal sites are typically part of the set of the critical sets. Therefore, the following hypothesis was formed that directly relates to mechanisms of ictogenesis: “the epileptic brain is dynamically entrained by the focal sites long before a seizure's occurrence”.

It was further hypothesized that the brain starts malfunctioning due to this loss of relative independence of processing of information at normal brain sites long before a seizure develops. Such a preictal entrainment is illustrated in Figure 1 for a patient with focal epilepsy and EEG recorded by intracranial electrodes (Figure 1(A) and (B)). The STL_{max} profiles of critical sites over time are shown in Figure 1(C). The convergence of STL_{max} profiles of a pair of sites is quantified by the T-index, a statistical measure of the distance between the mean values of the respective time series. Small values of T-index denote small distances between the corresponding STL_{max} profiles, and hence entrainment of dynamics. T-index values over time are estimated within a running window of 10 minutes in duration (60 STL_{max} values) for a pair of STL_{max} profiles. Pairs of sites that are dynamically entrained in the 10 minute period prior to a seizure are characterized as critical pairs. The average T-index profile illustrated in Figure 1(D) represents the average of all T-indices over time across the thus selected critical pairs of sites. From Figure 1(D), it is clear that, if critical pairs of sites are selected (retrospectively) from the immediate preictal period of a seizure, a seizure is predictable. For example, in the seizure depicted in Figure 1(B), a warning could have been issued about 1 hour before its onset, that is, when the average T-index crosses the statistical threshold $T_{th}=2.662$ ($\alpha=0.01$ significance level for convergence of STL_{max} profiles) from above [47].

It is noteworthy that other measures of dynamics, like phase, also exhibit dynamical entrainment in the preictal period, although a bit later than STL_{max} [49-51]. In addition to patients, epileptic rats with chronic epilepsy also exhibit measurable preictal periods in the order of minutes [52-58]. These results demonstrate that seizures are not abrupt transitions in and out of an abnormal ictal state, but instead they follow a dynamical transition that may evolve over minutes to hours. During this preictal dynamical transition, multiple regions of the brain progressively approach a similar dynamical state. Because such spatio-temporal transitions are progressive over time, it has been suggested that, in addition to preictal periods, seizure susceptibility periods could also be identified from analysis of corresponding profiles of brain dynamics [59].

3. Resetting of brain dynamics at seizures

Seizures typically reset the preictal dynamical entrainment and lead to the disenitainment of dynamics of the focus from the rest of the brain. We can observe this important conjecture by comparing the average T-index values and their trend in the preictal versus the postictal period. For example, after seizure's onset in Figure 1(D), we observe a trend towards disenitainment of the preictally entrained pairs of sites (T-index moves rapidly towards higher values above T_{th} and towards ones it exhibited before the beginning of the preictal period). Figure 1(C) shows the same trend at the level of STL_{max} profiles of individual brain sites. We have called this reversal of dynamics *brain resetting at seizures* and we have observed it in focal as well as generalized seizures, within and across patients [60-66]. We also have observed it using other measures of brain dynamics [67]. Furthermore, the observed dynamical resetting in patients with epilepsy is significantly ($p < 0.0001$) specific to seizures at the $\alpha = 0.05$ statistical significance level [64]. Other groups have independently observed similarly reversal trends using classical methods of signal processing [68, 69]. This observation may reflect a passive mechanism (e.g., high electrical activity during a seizure depletes critical neurotransmitters and thus deactivates critical neuroreceptors in the entrained neuronal network). An alternative explanation is an active mechanism, that is, seizure activity releases neuropeptides that may subsequently contribute to the temporary repair of a pathological feedback network (see section on control of seizures below) that allows the dynamical entrainment to occur and last for tens of minutes. Such an explanation is analogous to mechanisms attributed to seizures associated with electroconvulsive therapy (ECT) [70-71].

Given the observed resetting of the brain's dynamical entrainment with the focus at seizures, one would expect that seizures in status epilepticus (SE) fail to reset such pathology of brain dynamics. That is exactly what we have observed after a similar dynamical analysis of the EEG from SE patients in the emergency room (ER), intensive care unit (ICU) or the EMU [72, 73]. Successful anti-epileptic drug (AED) administration, that interrupted SE seizures in rats and humans, resulted to resetting of brain dynamics. Unsuccessful AED administration in humans and/or no AED administration in SE rats failed to reset the brain dynamics with lethal consequences. Thus, resetting of dynamics could be used to monitor treatment of SE by AEDs, as well as for the evaluation of current and possibly the design of new AEDs. Finally, psychogenic non-epileptic seizures do not appear to reset the brain dynamics, and the phenomenon of resetting could thus be utilized as a tool for differential diagnosis between epileptic and psychogenic non-epileptic seizures [74].

4. Seizure prediction

The ability to identify a mathematically defined preictal period from dynamical analysis of EEG from seizure predictability studies has constituted the basis for implementation of algorithms for prospective prediction of epileptic seizures [75-83]. A major difficulty

encountered in the attempt to prospectively versus retrospectively predict an impending seizure is illustrated in Figure 2. In this figure, the T-index created from dynamically entrained critical pairs of sites over 10 minutes before 3 different time instants (1.45 hours, 0.57 hours and 0 hours before seizure onset) is shown for another typical seizure from the same patient as in Figure 1. It is evident that if critical pairs are selected far away from that seizure (Figure 2(A)), they may not be the relevant ones for prediction of this seizure. For example, critical pairs selected from 1.45 hours prior to seizure onset become disentrained before the seizure's occurrence, whereas pairs selected from within the preictal period of this seizure are kept entrained until the seizure occurs to disentrain them. [Preictal period is defined as in section 2, that is, from the average T-index profile of critical pairs selected retrospectively at 0 hours before seizure onset – see also Figure 2(C).] The participation of the epileptogenic focus in the critical sites in each case is illustrated in Figure 3. Visual inspection of Figures 3(A) and 3(B) shows that participation of the focus (right hippocampus in this patient) in the entrainment of normal sites becomes prominent as the seizure approaches. Thus, monitoring the T-index profile of the relevant critical pairs of sites is of paramount importance for prospective seizure prediction. The solution we have given to this problem is adaptive optimal estimation of critical sites (first generation seizure prediction algorithms [80]) or pairs of sites (second generation seizure prediction algorithms, independent from user input and without optimization from training datasets, that is, ready to run anytime on any patient without need of any a priori information on the patient [81]). In each case, pre-determined rules are applied for adaptive selection of the critical sites or pairs of sites over time by the algorithms, from present and past T-index values. These seizure prediction algorithms, applied to scalp and/or intracranial EEG from epilepsy patients or animals, have achieved a sensitivity above 80% (that is, more than 80% of seizures are predicted), fair specificity (false prediction rate of 0.12 to 0.17 per hour, that is, 1 false positive per 8 to 7 hours respectively) and average prediction time above 45 minutes per seizure (that is, issue of a warning for an impending seizure 45 minutes prior to its occurrence). Interestingly, sensitivity and specificity did not depend on seizure rate or the recording modality of the EEG.

Following our first findings on seizure predictability, there has been an explosion of investigations by many other research groups worldwide over the last 20 years. References, chronologically cited herein from 1990 to 2010, are indicative of these investigations [84–183]. A variety of methods have been used in analysis of short and long-term EEG, parametric (model-based) or nonparametric (transform-based), linear or nonlinear, reference dependent (e.g. using baseline EEG segments from interictal periods) or independent, at the microscopic (neuronal) or macroscopic (network) level. In general, these investigations have pointed to seizure predictability with varying degrees of success and criticism. Methods for statistical evaluation of their performance, sensitivity and specificity-wise on training and testing EEG datasets, against periodic or pseudo-random warning time series, use of surrogate data to account for spurious values and noise in the EEG, have been developed too [184–205]. However, with respect to seizure prediction (prospective analysis) very few investigations have been performed. Seizure prediction, what is actually needed in medical applications, is very different from and more difficult to achieve than seizure predictability, as we have argued and shown above. A most recent investigation in seizure prediction was performed by Schulze-Bonhage's group, a group that was very skeptical in the past with respect to feasibility of seizure prediction schemes [206]. These investigators reported a maximum mean sensitivity of 43.2%, at false seizure prediction rate of 0.15 per hour. Training on each patient's EEG data is required before a prospective run of the algorithm on a patient. The interval that a seizure was predicted ahead of time was not clearly reported but should be in the range of 10 to 60 minutes. Although this performance is almost half of what we have reported in the past even with our first generation seizure prediction algorithms

[80], it is an additional independent evidence that seizures may not only be retrospectively predictable but prospectively predicted too.

5. Application of seizure prediction to seizure control

Incorporation of seizure prediction algorithms to neuromodulation schemes for abatement of seizures is one important area of application in the modern treatment of epilepsy (e.g., in DBS) [207, 208]. Our findings from analysis of long-term EEG dynamics in the domains of seizure predictability, prediction and resetting, in animals and patients with various types of epileptic seizures and EEG recordings (scalp and intracranial), led us to formulate the following hypothesis about ictogenesis in terms of basic principles of control in adaptive linear or nonlinear dynamical systems: “Epileptic seizures may occur due to pathological alterations in the global and/or local internal feedback loops in the brain, normally responsible for keeping the spatial correlations (interactions, synchronizations, entrainment) within strict limits (time-wise and space-wise) in order to support the brain’s fast multi-processing and multi-task function”.

Employing neuronal population models that are capable of exhibiting seizure-like behavior, we have shown that entrainment (disentrainment) of the populations’ STL_{max} with increased (decreased) coupling between populations, resembles the observed preictal dynamical entrainment (postictal disentrainment) of the STL_{max} at critical sites in the epileptic brain [209, 210]. In agreement with burst phenomena in adaptive systems, “seizures” in these models occur if the existing (internal to the models) feedback loops are pathological, in the sense that they lack the ability to compensate fast enough for excessive increases in the network coupling. This situation eventually leads to seizure-like transitions in those models. Motivated by these findings, we postulated the existence of an internal pathological feedback action in the epileptic brain; subsequently, using a control-oriented approach, we developed a functional model for an external seizure controller. During periods of abnormally high synchrony (entrainment), the developed control scheme provides appropriate “desynchronizing feedback” to maintain “normal” synchronization levels between neural populations (homeostasis of dynamics). This closed-loop feedback control view of epileptic seizures, and the developed seizure control strategies, we have called *feedback decoupling* and have then validated them on coupled chaotic oscillator models and biologically plausible neurophysiologic models [211–225].

Within the context of closed-loop real-time on-line control of seizures, seizures are anticipated with relatively good sensitivity and specificity from dynamical analysis of EEG, and effective external intervention is applied to change the pathological brain dynamics (long-term entrainment) in a timely manner and prevent a seizure from occurring. Towards this end, we utilized our adaptive seizure prediction algorithm in the feedback branch of a closed-loop electrical stimulation scheme for seizure control. The lithium-pilocarpine (LP) model of acute SE in rats was chosen as the animal model for chronic epilepsy. Male Sprague-Dawley rats were used for the study. Three to four weeks after induced SE, rats were implanted with a six microwire monopolar electrodes targeted to four cortical and two hippocampal locations; two Teflon-coated tungsten bipolar twisted stimulating electrodes were implanted in the centromedial thalamic nucleus. Our second generation seizure prediction program was used to predict on-line and real-time the developed seizures (see Figure 4) and trigger an A-M Systems Model 2300 stimulator unit (Calsborg, WA) at seizure warnings. At a seizure warning, a train of square pulses was delivered in a charge-balanced bipolar cathodic fashion (see Figure 5).

Results from this experiment are shown in Figure 6.3The experiment consisted of weeks-long just-in-time (closed-loop) stimulation (phases A to D in Figure 6) and periodic (open-

loop) stimulation (phase E in Figure 6). Weeks of dramatic reduction of seizures (see panel 3) followed just-in-time adaptive stimulation of the epileptogenic focus (left hippocampus; localized by analysis of the EEG by focus localization algorithms [226, 227]) until resetting of dynamics is achieved (phase D), while less reduction of seizures followed just-in-time stimulation of the thalamus (phases A and B). No reduction of seizures compared to baseline followed open-loop periodic (period equal to the inverse of the mean of seizure rate in baseline) stimulation of the focus (phase E). These results imply that closed-loop, focal stimulation schemes are superior to closed-loop, non-focal ones, which in turn are superior to open-loop, focal ones. The demonstration of the importance of incorporating seizure prediction algorithms in closed-loop control schemes (just-in-time), as well as of the location of stimulation, for online seizure abatement was one goal of this experiment. The importance of stimulus form for seizure abatement, such that it ensures resetting of the entrainment of dynamics, was another goal (use of long stimuli until dynamics are reset resulted to further reduction of seizure rates; compare phases A versus B, and C versus D). These results are in broad agreement and better than the ones we reported in [225], the epileptogenic focus identification and adaptive stimulation of the focus (hippocampus) versus thalamus more probably having contributed a lot to the observed drastic improvement in seizure abatement.

6. A look into the future

The results from investigations into seizure prediction over the last 25 years have established firm foundations for direct clinical applications to epilepsy [228]. The concepts delineated in this review constitute the basis for a dynamical interpretation of ictogenesis and lead to long-term prediction of seizures well prior to their clinical or electrographic onset, detection of seizure susceptibility periods, epileptogenic focus localization, and the development of innovative treatments for epilepsy through timely interventions to control seizure occurrence (e.g., via electrical stimulation and/or in situ drug delivery). We have shown that timing of intervention is critical for successful control of seizures, and that seizure prediction algorithms can now provide this important information on line and in real time making them an important component of future brain pacemakers for epilepsy.

Seizures appear to be the end result of a progressive recruitment of brain sites by the focus towards an abnormal synchronization of dynamics. The onset of such recruitment occurs on the order of minutes with respect to seizure prediction, on the order of hours and days with respect to seizure susceptibility. Resetting of this pathological preictal dynamical recruitment occurs at seizures. In cases that seizures are unable to reset this pathology of dynamics (e.g., in status epilepticus) external intervention (e.g., via AEDs) may do it.

In light of the above, a dynamical systems perspective of the epileptic brain can also be formulated. Seizures could result from the inability of internal feedback mechanisms to provide timely compensation/regulation of coupling (entrainment) between brain sites, and hence seizure control may be achieved by preictally decoupling the pathological sites via externally provided appropriate feedback. Such optimal feedback decoupling has been found to be a function of both the EEG and the coupling between respective brain sites [217–218, 223–224]. According to this hypothetical dynamical scheme of ictogenesis, the following series of events are conjectured: a) brain in spatiotemporal chaos, b) internal or external stimulus enters the system and changes the spatial coupling between two or more brain sites, c) spatial coupling produces spatial correlations, possibly storing the information about the stimulus and/or initiating action, d) spatial correlations activate an internal compensating feedback mechanism, e) compensation tries to remove (or assimilate) the developed spatial correlations, f) the system returns to spatiotemporal chaos if step (e) is successful. In the “normal brain”, the correlations in the network must lie within a “normal” range and vary

quickly in response to a stimulus, which implies that the internal feedback path should be well-tuned and able to track changes of the coupling over time reasonably well. In the epileptic brain, step (e) involves pathologic (poorly tuned) internal feedback paths. The observed long-term dynamical entrainment prior to seizures can then be interpreted as an indicator of pathology in the internal feedback of the network. According to the theory of adaptive systems control, such pathology can exhibit large errors in the estimation of the coupling, and in turn cause local destabilization and bursting of the network (seizures). This rationale can easily be applied to explain the mechanisms of “reflex” epilepsies, with external stimuli as inputs to the system causing enduring entrainment, and seizures following to reset it.

It should not be surprising that a dynamical global view of seizures in epilepsy, an interdisciplinary avenue of research between engineering, neuroscience and medicine, can generate such refreshing results and novel hypotheses. It would be to the benefit of the epilepsy patient to pursue and test them further.

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Figure 1.

Detection of long preictal periods and resetting of brain dynamics at seizures. **(A)** The electrode montage utilized for recording of intracranial EEG. **(B)** A typical electrographic onset of seizures for a patient with focal, temporal lobe epilepsy (25 seconds of EEG is shown around a seizure's onset, band-pass analog filtered between 0.5 and 70Hz, and then sampled at 200Hz and stored digitally on hard drive). The seizure was secondarily generalized and lasted for 2.5 minutes. The epileptogenic focus was determined as RTD (right hippocampus). **(C)** STL_{max} profiles from 2 hours before to 1 hour after seizure's onset at: RST4 (right subtemporal - solid line), LOF2 (left orbitofrontal - dotted line), RTD8 (right hippocampus - dashed line), and LTD9 (left hippocampus - dotted/dashed line) electrodes. **(D)** The average T-index profile was estimated by averaging the T-indices of the critical electrode pairs (in this seizure, 119 out of a total of 435 possible electrode pairs). The critical pairs selected are the ones that are dynamically entrained 10 minutes prior to the electrographic seizure's onset (retrospective calculation – test of seizure predictability). Values of T-index below the horizontal dotted line at 2.662 in the T-index plot denote dynamical entrainment (statistical convergence of the corresponding pairs of the STL_{max} profiles at the $\alpha=0.01$ significance level). The vertical dotted lines in panels (C) and (D) denote the seizure's onset (at about 2 hours into the recording). It is clear that a) preictal entrainment of critical brain sites was reversed to disentrainment following seizure onset, and b) if we had prospectively followed those critical electrode pairs since the beginning of the recording, we would be able to issue a warning for the impending seizure about 1 hour prior to its occurrence.

Figure 2.

Selection of relevant critical brain sites/pairs is important for seizure prediction. **(A)** Average T-index profile from critical pairs (all pairs that were identified to be statistically entrained with respect to their STL_{max} measures of dynamics) within a 10 minute interval about 1.45 hours (left vertical dotted line in this panel) before the onset (right vertical line) of a second seizure from the same patient as in Figure 1. The number of critical pairs thus identified was 120 and did not all remain entrained up to the seizure. **(B)** Average T-index profile from critical pairs of brain sites within a 10 minute interval about 0.57 hours (left vertical dotted line in this panel) before the onset (right vertical line) of the seizure. The number of critical pairs thus identified was 161, remained entrained up to the seizure, and were disentrained postictally. **(C)** Average T-index profile from critical pairs of brain sites within a 10 minute interval immediately prior to the seizure's onset (left and right vertical lines are therefore in this panel identical). The number of critical pairs thus identified was 168 and, looking back (retrospective evaluation), they became entrained about 40 minutes prior to this seizure's onset. From this figure, it is clear that a) there are different critical

pairs entrained at different times prior to a seizure, b) a progressive entrainment of critical sites can be observed as a seizure approaches only if relevant critical sites are selected, and c) for a seizure prediction scheme to be successful, adaptive estimation of relevant to the upcoming seizure critical brain sites has to be performed over time.

Figure 3.

Topography of preictal dynamical entrainment: Network connectivity maps from analysis of brain dynamics at “instances” long before a seizure. In these maps, two brain sites are shown as connected if they are dynamically entrained for 10 minutes prior to the “instance” the map is generated at. Since our measures of dynamics (STL_{max}) are estimated every 10 sec, connectivity maps can be produced every 10 sec. (A) Brain connectivity map generated at 1.45 hours before the seizure in Figure 2, that is still in the interictal period according to Figure 2(A). (B) Brain connectivity map generated at 0.57 hours before the seizure, that is, in the preictal period according to Figure 2(B). The seizure focus is the right hippocampus (right vertical column in the graphs) and it appears that, as seizure approaches (transition from interictal to preictal period), the pathological right takes over the more “normal” left hippocampus in the dynamical entrainment of the rest of the brain.

Figure 4.

Real-time on-line prediction of seizures. A snap shot on the screen of a PC that runs real-time our second generation adaptive seizure prediction program on simultaneously recorded EEG from a rat with chronic epilepsy. The two waveforms displayed on top are respectively the STL_{max} and average T-index profiles generated from automatically determined critical sites over time [81]. The profile that includes the seizure warnings and seizure occurrences is displayed in the next row (scale in hours). The on-line real-time recorded EEG is displayed in the last row (scale in seconds).

Figure 5.
Flow diagram of a closed-loop just-in-time seizure control system.

Figure 6.

Real-time control of seizures in an epileptic rat via closed-loop and open-loop deep brain stimulation (DBS). In the closed-loop seizure control scheme (just-in-time), electrical stimulus was administered at seizure warnings that were issued by our online second generation seizure prediction program [81] according to the flow diagram described in Figure 5. In the open-loop seizure control scheme (periodic), electrical stimulus was delivered periodically without using any feedback/knowledge of the state of the concurrent brain dynamics. Both control schemes used the following traditional predefined electrical stimulus: train of periodic biphasic pulses of 130Hz in frequency, and each pulse of 200 μ sec in duration (pulse-width) and 200 μ A in amplitude. The experiment consisted of the following 5 different phases of stimulation, each one including recording of about 3 weeks of EEG with stimulation OFF and 3 weeks with stimulation ON. The 5 different phases are schematically depicted in PANEL 1 of this figure: (A) Just-in-time closed-loop stimulation of the thalamus for 1 minute right after issue of a seizure warning. (B) Just-in-time closed-loop stimulation of the thalamus after a seizure warning for as long as it takes (up to an upper limit) to reset the entrained critical pairs. (C) Just-in-time closed-loop stimulation of the focus (left hippocampus) for 1 minute after each seizure warning. (D) Just-in-time closed-loop stimulation of the focus (left hippocampus) after a seizure warning for as long as it takes (up to an upper limit) to reset the entrained critical pairs. (E) Periodic open-loop focal (hippocampal) stimulation for 1 minute at a time, with frequency equal to seizure frequency of the preceding to phase E baseline. The seizure frequency (#seizures per day) over time is shown in PANEL 2 (middle panel). The frequency of stimulation (#sets of stimulations per day) over time is shown in PANEL 3 (bottom panel) and, as expected, was variable over time for phases A to D, and constant for phase E. It is clear that the most successful stimulation schemes in reducing seizure frequency were schemes C and D in which seizure frequency was even reduced to zero for days at a time. The worst seizure control scheme was the periodic scheme E.