Seizure prediction and the preseizure period
Brian Litt\textsuperscript{a} and Klaus Lehnertz\textsuperscript{b}

Beginning in the 1970s engineers designed systems to predict epileptic seizures based upon quantitative changes in the electroencephalogram, which they hypothesized began well in advance of clinical seizure onset. These efforts flourished in the 1990s, as independent laboratories demonstrated evidence of a ‘preseizure period’ up to 20 min prior to clinical symptoms in patients implanted with intracranial electrodes during evaluation for epilepsy surgery. Years later, clinical and laboratory experiments leave little doubt that a preseizure period exists in temporal lobe and perhaps other forms of epilepsy. Its existence, however, raises fundamental questions about what constitutes a seizure, what brain regions are involved in seizure generation, and whether discrete interictal, preictal, ictal and post-ictal physiologies exist, or blend together in a continuous process. Pressing milestones, necessary for clinical utility, are: (1) demonstrating prospective seizure prediction from prolonged human data sets, (2) elucidating mechanisms underlying seizure precursors and (3) implementing these algorithms on implantable hardware platforms. The notion of a preseizure state is catalyzing new clinical and basic science research, which has the potential to dramatically increase our understanding of epilepsy, and to generate exciting new therapies for patients. Curr Opin Neurol 15:173–177. © 2002 Lippincott Williams & Wilkins.

Introduction
Approximately 1% of the world’s population suffers from epilepsy. With today’s available antiepileptic drugs, seizures can be controlled satisfactorily in about two thirds of affected individuals; another 8% may profit from epilepsy surgery. The remaining 25% of epilepsy patients cannot be adequately treated by any available therapy.

One of the most disabling aspects of epilepsy is the seemingly unpredictable nature of seizures. If it were possible to forecast seizures, however, therapeutic possibilities would change dramatically [1]. For example, many individuals who cannot be controlled by medications, or who are not candidates for epilepsy surgery, might be helped by new therapies based upon seizure prediction. Even those who are controlled by antiepileptic drugs might benefit from reduced side effects, if their medications could be replaced by electrical stimulation or drug infusion activated only during the pre-seizure period. Together with other prevention techniques, this would reduce morbidity, mortality, and greatly improve the quality of life for epilepsy patients.

Until recently the interictal-ictal transition was believed to be an abrupt phenomenon, occurring without warning. Converging evidence now indicates that this classical two-state model has to be expanded to include a third ‘pre-ictal’ transitional phase. This phase may be defined as a functional state in which epileptic brain will evolve into a seizure unless some kind of intervention takes place. Evidence supporting the existence of a preseizure (preictal) state is divided into two main areas: (1) non-electroencephalogram-based methods, including clinical patient evaluations, functional imaging and other related biological studies; and (2) EEG-based methods, including quantitative analysis of human clinical and animal laboratory data.

Non-electroencephalogram-based evidence
This work exists primarily in the form of broad observations, or case reports of findings in several patients with temporal lobe epilepsy and will only be briefly summarized here.

Patient reports of non-specific ‘prodromal’ symptoms are relatively common [2]. These symptoms include depressive mood changes, irritability, sleep problems, nausea, or headache, and suggest the presence of precursor events that may wax and wane over time, minutes to hours or even days prior to clinical seizure onset.
There is activation, as measured by increased blood flow and possibly increased oxygenation, in the region of the seizure focus approximately 10 min prior to EEG seizure onset. Activation then ‘spreads’ to the contralateral temporal lobe at least 2–3 min before seizure onset on EEG [3–5].

There are also changes in autonomic regulation of heart rhythm over several minutes prior to EEG seizure onset [6,7].

Electroencephalogram-based evidence
Quantitative analysis of EEG provides the majority of evidence supporting the existence of a preseizure state in temporal lobe epilepsy. The major conclusions from this research to date are:

1. That there are a series of discrete precursor events occurring on different time scales, which are statistically associated with an increased probability of electrical seizure onset.
2. That a variety of nonlinear and linear analysis techniques demonstrate preictal changes up to hours prior to EEG onset of seizures.
3. That clinically useful seizure prediction will likely take the form of forecasting the probability of seizure onset over a given time horizon, and need to utilize multiple EEG features and algorithms tuned to individual patients.

It is important to note that this main section of the seizure prediction literature is both the most exciting to read and the most difficult to interpret. There are a significant number of publications that claim ‘seizure prediction’ based upon analyzing brief epochs of preseizure data, with no reference to control data or baseline data epochs. While some of these reports are of interest, they have been omitted below, due to the inability to validate them. Other reports must be interpreted in light of their design, the amount of data processed and their uniformly retrospective structure. Referenced literature includes peer-reviewed journals, book sections, patents and conference papers by necessity, given that these are common media for conveying results in the quantitative world. In general, abstracts from medical meetings have been omitted.

The earliest ‘engineered’ seizure predictor
The first EEG-based studies were conducted by Viglione et al., in the 1970s [8]. Assuming the existence of a pre-ictal period, these investigators trained a feature extraction and pattern recognition algorithm to distinguish between arbitrarily selected 10-min pre-ictal and non-pre-ictal EEG epochs. Their technique was able to perform the prediction task with ‘reasonable’ results, but by its design was not able to give insight into which aspects of the data were important. Since the published body of this work consists primarily of abstracts, industrial proposals and reports, a clear statistical measure of the system’s performance is difficult to ascertain. The authors coined the term ‘seizure prediction’, and by patenting their work demonstrated a clear understanding of the therapeutic and commercial potential of their research.

Since spikes in the EEG are usually considered the hallmark of an epileptic brain, their possibly altered pre-ictal occurrence was investigated in several studies. In 1978, Sherwin provided more direct physiological evidence of a pre-ictal period [9]. This investigator noted increased correlation of epileptiform activity (spikes) between two adjacent cortical sites in the 15–20 min before EEG onset of focal seizures in a cat model of epilepsy. A few years later, in 1983, Lange et al. demonstrated a similar correlation of interictal epileptiform activity between the side of the seizure focus and the ‘normal’ temporal lobe, 20 min prior to EEG seizure onset in patients with temporal lobe epilepsy [10].

While other authors reported on a decrease or even total cessation of spikes before seizures, re-examination did not confirm this phenomenon in a larger sample [11].

Although these early attempts indicate that pre-ictal EEG changes are detectable at least to some extent, these studies were not successful in defining a pre-ictal period, most likely because the concept of applying classical methods of signal processing and pattern recognition for analysis of the EEG may not be sufficient. With the advent of the physical-mathematical theory of nonlinear dynamics (colloquially termed chaos theory) in the early 1980s, new analysis techniques were developed that can characterize apparently irregular behavior, a distinctive feature of the EEG. Application of these techniques during the last two decades has produced a large body of evidence that seizure prediction is feasible [12*].

Seizure prediction becomes ‘chaotic’
In 1988 and 1990, Iasemidis, Sackellares et al. introduced the idea of using changes in nonlinear dynamical parameters, primarily the largest Lyapunov exponent, for characterizing intracranial EEG recordings [13,14**]. In this novel work they noted premonitory events prior to EEG onset of seizures. The authors later demonstrated these preseizure changes up to 7.5 min before seizure onset in several recordings [15]. This group has steadily expanded this body of work since that time, reporting that a pre-seizure transitional phase may begin hours before seizure onset, that during this phase a gradual ‘spatial entrainment’ of critical cortical sites can be observed, that seizures act as a resetting mechanism, that
seizure precursors can be detected on the scalp, and that they can theoretically be exploited in an implantable device to predict seizures [16**,17–19,20*].

The emphasis of this novel approach on quantitative analysis, rather than standard physiology, makes it less accessible to clinicians and some basic researchers, as is much of the quantitative work in seizure prediction. This work, however, has provided a model for a number of very productive collaborations between quantitative scientists and epileptologists in this field.

‘Neuronal complexity’, seizure prediction and relation to physiology

In 1994, Lehnertz, Elger et al. began to publish findings using nonlinear measures of EEG complexity, such as correlation dimension, to explore the preseizure period. They coined the term ‘ictogenesis’ to describe the process by which seizures are generated, as evidenced by seizure precursors [21]. In 1995, in the most complete study of seizure prediction to that time, the group described intermittent drops in ‘neuronal complexity’, a parameter related to correlation dimension, in preseizure and baseline EEG segments recorded intracranially in 20 patients [22**]. The group was able to lateralize these changes to the epileptic focus, and observed occasional similar changes in the focus region even in data epochs far from seizures in time. In 1998 they provided the first statistical evidence for predictability of seizures in 16 patients, demonstrating that drops in correlation dimension that occurred up to 25 min prior to seizures were significantly more pronounced than those found during interictal periods [23,24**]. These studies have helped to promote acceptance of seizure prediction by nonlinear EEG analysis in the mathematical and physical sciences communities.

In 2000 the group found the first evidence for a preictal drop in synchronization and concluded that an epileptic seizure might be regarded as the climax of a process of changes in brain dynamics that starts long before onset seizure [25*].

Based on the variety of observed phenomena, this group has suggested that multiple derived features will likely be required for clinically acceptable seizure prediction over all patients and seizure types [26,27*] and therefore continues to develop new EEG analysis techniques, steadily increasing the amount of EEG data analyzed and the number of patients investigated.

Dynamical similarity: seizure prediction research gets broad exposure

In 1998 Le Van Quyen, Baulac, the late Francisco Varela et al. published the first of a number of prominent articles describing another nonlinear measure for predicting seizures, one of which they call ‘correlation density’. With this technique the group analyzed intracranial preseizure EEG segments from 19 patients and demonstrated changes associated with oncoming seizures within 10 min of their EEG onset [28**]. To the present, the group has introduced newer nonlinear techniques, such as the ‘dynamical similarity index’. This method computes nonlinear characteristics of a reference EEG window that is then compared with a similar scanning window that are moved forward in time towards known seizure onsets [29,30*]. When statistical differences between the reference and scanning windows reach a significance threshold, a preseizure state is declared. The group has steadily increased the amount of EEG data analyzed, the number of patients investigated, and recently demonstrated the presence of seizure precursors on scalp EEG [31**]. Similar to other groups, the performance of these measures on prolonged baseline data has not been demonstrated in controlled studies. Recently, this group has also started to focus on synchronization phenomena prior to seizures [32*].

This research group contributed the term ‘seizure anticipation’ to the literature, as a way of expressing the idea that there is not yet evidence that the exact time of seizure onset is likely to be predictable. Rather, this concept suggests that seizure-prediction algorithms are more likely to identify periods of time when seizures are generally more likely to occur. An important aspect of this group’s work is that the publication of these studies in journals such as Nature Medicine and The Lancet, have thrust seizure prediction research into the limelight, promoting acceptance by mainstream medical and engineering communities.

The ‘preictal cascade’, probability, multiple features and electrodes

Turning from an emphasis on nonlinear dynamics to physiology-based seizure prediction, Litt, Echauz, Esteller, et al. recently published a series of quantitative observations from intracranial EEG suggesting that there is a cascade of electrophysiological events that give rise to temporal lobe seizures [33**]. This work reports results from quantitative analysis of well-known EEG phenomena as seizures approach, such as bursts of complex epileptiform activity, delta slowing, subclinical seizures, and gradual increases in energy in the epileptic focus. The relative strength of the work is its emphasis on complete, multiday data sets (more than 1 week in some patients), its inclusion of both sleep and awake states, and its attempt to relate seizure precursors to the underlying physiology and terminology used by clinicians and basic scientists working in epilepsy. This research utilizes the same retrospective design employed by other groups occupied with seizure prediction. Initial results build on previous theoretical work on multiple
feature fusion and probabilistic seizure prediction, and on-going efforts to individualize these techniques and elucidate mechanisms underlying seizure generation [34,35*].

What is the pre-seizure state?
The work presented above demonstrates a series of complementary findings indicating that seizure generation in temporal lobe epilepsy likely occurs over minutes to perhaps hours in a series of electrophysiological events that can be quantitatively measured. Despite the different methods employed, the results indicate remarkably similar times of occurrence. The fact that most of the approaches result in different prediction horizons, ranging from minutes to hours to days, indicates that they reflect different aspects of ictogenesis, but none appears to depict the process fully. Seizure precursors may wax and wane, in attempts to ignite a clinical event, but the forces both driving and suppressing seizure generation remain hidden. Seizure precursors may begin locally, and then expand spatially, even ‘entrain’ other brain structures before reaching the critical mass required to initiate a clinical seizure. Patterns appear to be patient-specific, within a finite range of pattern types, and it appears that different quantitative features may be required to predict seizures with clinically useful accuracy in different individuals. This may be a function of individual physiology or potentially confounding variables, such as electrode placement and the amount and speed of medication taper during inpatient video-EEG monitoring. Very focal subclinical seizures that build prior to seizures raise further questions. Are these brief events, lasting 3–6 s, seizures in themselves, or do they reflect different aspects of ictogenesis, but none appears to depict the process fully.

In summary, the pre-seizure state evolves over minutes to hours in a series of electrophysiological events that may wax and wane, in attempts to ignite a clinical event, but the forces both driving and suppressing seizure generation remain hidden. Events on EEG? These and many other related questions may not be fully answered until the mechanisms underlying ictogenesis are understood.

Conclusion
Led by a growing number of active research groups, the field of seizure prediction is moving steadily forward. Current factors limiting progress include (1) a lack of sufficient numbers of standardized, complete, high quality, well-described human intracranial data sets for extensively testing and comparing algorithms; (2) recognized performance standards for assessing and comparing prediction algorithms; (3) minimum testing requirements for seizure prediction methods; and (4) an accepted forum for investigators involved in seizure prediction to exchange ideas and methods. Important milestones ahead are further improvement of sensitivity and specificity of seizure prediction techniques, demonstration of seizure precursors in extratemporal epilepsy, in children, in animal models of epilepsy, and collaboration with industry to implement seizure prediction in implantable therapeutic devices. These efforts, coupled with a strong focus on determining the mechanisms underlying ictogenesis promise to make the field of seizure prediction a productive and promising area of research for many years to come.

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References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as: * of special interest ** of outstanding interest

The evolution with time of the spatial and non-linear indicators of the pre-seizure state. An important paper developing some of the major concepts in seizure prediction from one of the first groups to popularize this scientific approach.

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14 Iasemidis LD, Zaveri HP, Sackellares JC, Williams WJ. Phase space analysis of EEG in temporal lobe epilepsy. In: Proceedings of IEEE Engineering in Medicine and Biology Society 10th Annual International Conference; 4–7 November 1998; New Orleans. pp. 1201–1203. This article is of special interest as one of the first popular publications focused on non-linear dynamics applied to seizure prediction, from one of the first groups to popularize this scientific approach.


