Prediction of epileptic seizures

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For almost 40 years, neuroscientists thought that epileptic seizures began abruptly, just a few seconds before clinical attacks. There is now mounting evidence that seizures develop minutes to hours before clinical onset. This change in thinking is based on quantitative studies of long digital intracranial electroencephalographic (EEG) recordings from patients being evaluated for epilepsy surgery. Evidence that seizures can be predicted is spread over diverse sources in medical, engineering, and patent publications. Techniques used to forecast seizures include frequency-based methods, statistical analysis of EEG signals, non-linear dynamics (chaos), and intelligent engineered systems. Advances in seizure prediction promise to give rise to implantable devices able to warn of impending seizures and to trigger therapy to prevent clinical epileptic attacks. Treatments such as electrical stimulation or focal drug infusion could be given on demand and might eliminate side-effects in some patients taking antiepileptic drugs long term. Whether closed-loop seizure-prediction and treatment devices will have the profound clinical effect of their cardiological predecessors will depend on our ability to perfect these techniques. Their clinical efficacy must be validated in large-scale, prospective, controlled trials.

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Epilepsy affects more than 50 million individuals worldwide—about 1% of the world's population. Two-thirds of affected individuals have seizures that are controlled by antiepileptic drugs. Another 7–8% can be cured by epilepsy surgery. Thus, in about 25% of individuals with epilepsy, seizures cannot be controlled by any available therapy. One of the most devastating features of epilepsy is the apparently unpredictable nature of seizures. Episodes of staring, walking aimlessly, or loss of awareness that might be harmless if they occur at home can be life-threatening if they occur while the patient is driving, crossing a busy street, or swimming alone. The need for new curative treatments is clear. A system able to herald seizures far enough in advance to allow preventive action would reduce morbidity and mortality, and greatly improve the quality of life of many people with epilepsy.

Serious scientific work on predicting epileptic seizures began in the 1970s with the visionary ideas of Viglione and colleagues,[1] but available technology did not begin to catch up with this vision until 20 years later. The explosion of interest since 1990 is due to a confluence of several factors: the discovery of a preictal state before temporal-lobe seizures; the wide acceptance of digital electroencephalographic (EEG) technology; maturation of methods for recording from intracranial electrodes to localise seizures; and the tremendous efficacy, acceptability, and commercial success of implantable medical devices, such as pacemakers, implantable cardiac defibrillators, and brain stimulators for Parkinson's disease, tremor, and pain. There are many important differences between technical requirements for cardiac defibrillators and implantable epilepsy devices, which make implementing the latter much more challenging. These differences have been described in detail elsewhere.[2]

Are seizures predictable?

Clinicians who care for patients with epilepsy have long known that many patients are aware of periods when seizures are more likely, though they can rarely specify an exact time when seizures will happen. There is also physiological support for the idea that seizures are predictable. Rajna and colleagues[3] interviewed 562 patients and found that clinical prodromes or auras occurred in more than 50%. Weinand and co-workers[4] detected a significant increase in blood flow in the epileptic temporal lobe that started 10 min before seizure onset and an increase in both temporal lobes 2 min before seizure onset. Similarly, Baumgartner and colleagues[5] demonstrated increased blood flow in the epileptic temporal lobe in two patients 11 min and 12 min before seizure onset. Preictal changes in other variables, such as R–R interval on the ECG,[6] may be side events related to seizure precursors.

Nomenclature: prediction, anticipation, and detection

There is as yet no clearly accepted nomenclature for the periods of time, both clinically and on the EEG, that are relevant to prediction of seizures. Figure 1 depicts important points in time, identified by our research group, marked on a 10 s epoch of an intracranial EEG recording of a seizure. Although most groups acknowledge that the points in time labeled on this figure are important, there is

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no consensus on how they should be named, their physiological significance, or a definition of exactly when seizures begin. Some uniform nomenclature is important, however, because different studies refer to predicting or detecting different points in time related to either EEG or clinical seizures. As shown in figure 1, the earliest change on the intracranial EEG associated with seizures commonly precedes unequivocal EEG seizure onset by several seconds or more, depending on electrode placement. The unequivocal EEG onset of a seizure generally precedes earliest clinical onset by 7–10 s in temporal-lobe epilepsy, provided that the electrodes are implanted close to the seizure focus. Practically, these times must be marked by a clinical expert and may vary somewhat between experts. Still, we find this conceptual framework useful for comparing methods, studies, and results.

Various terms are used to describe the process of identifying seizure precursors; some, such as anticipation and prediction, are preferred by certain research groups. We think that sensitivity to these preferences is important, but no distinction is drawn between these terms in this review and they are interchanged freely with other synonyms. We prefer the term "epileptic seizure prediction", coined by Viglione in the early 1970s; it is taken to mean identification of a time when seizures are probably approaching, without knowledge of the exact time when they will occur. When other meanings are intended, these are specified.

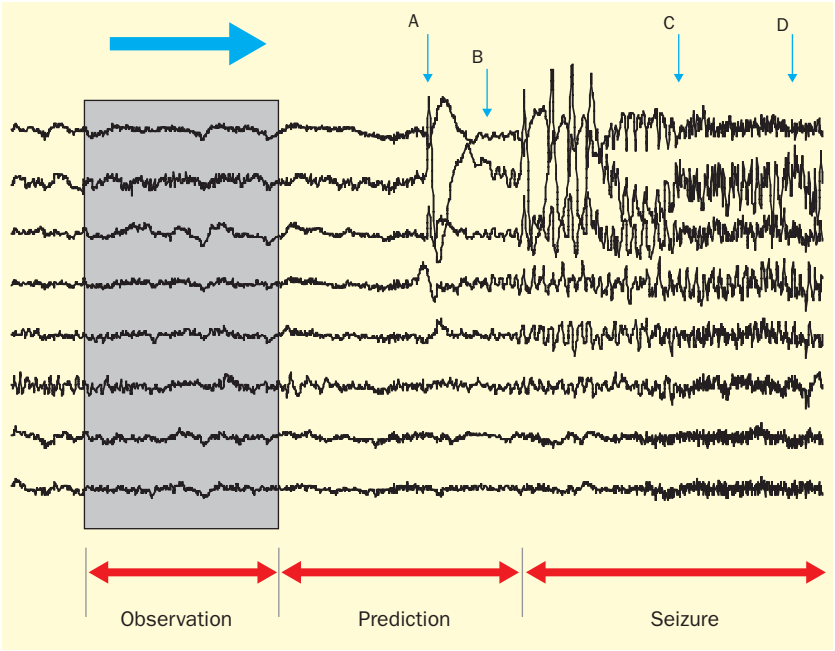

Figure 1. Times of importance to seizure prediction. A 10 s epoch of intracranial EEG from a patient implanted with hippocampal depth electrodes is shown. A is the time of earliest EEG change (EEC) associated with the seizure, compared with the patient's baseline background activity; it is found by moving backward in time from the unequivocal seizure onset until the earliest change from previous background activity is identified. B is the unequivocal EEG onset (UEO) of seizure activity and is the point when a seizure is clearly under way, even without knowledge that a clinical seizure follows. C is the time of earliest clinical change (ECC) from baseline behaviour. D is the time of unequivocal clinical seizure onset (UCO). The observation window is that segment of EEG being analysed. The prediction horizon is the time left from the processing window to the unequivocal EEG onset of the seizure.

Methods

No controlled, prospective studies on prediction of epileptic seizures have been published in peer-reviewed journals to date, though an early effort occurs in abstract form.[7] The reasons for the lack of substantive studies include: the need for long-duration, high-quality datasets from a large number of patients implanted with intracranial electrodes; adequate storage and powerful computers for processing of digital EEG datasets many gigabytes in length; and environments facilitating a smooth flow of clinical EEG data to powerful experimental computing facilities. Virtually all published studies on seizure prediction have been retrospective, in that data are collected and marked, and computed variables for preseizure and baseline data epochs are compared to reveal statistically significant differences associated with oncoming seizures. Seizure-prediction methods fall into several basic categories.

Time-domain analysis

These methods include statistical analysis of particular EEG events and computed characteristics of the data. For example, no evidence has been found that the number of interictal epileptiform discharges on EEG relates to oncoming seizures,[8–10] though the occurrence of spikes and the intervals between spikes become related between the epileptic and normal temporal lobes in patients with temporal-lobe epilepsy from 20 min before seizure onset.[11,12] In another example, we logged the occurrence of energy bursts in the EEG over several days of recording and found that these bursts appeared to increase in number over hours as seizures approached.[2]

Frequency-domain analysis

These techniques decompose the EEG signal into components of different frequencies.[13–16] For example, we have found bursts of activity in the range 15–25 Hz, which build from about 2 h before seizure onset in some patients with temporal-lobe epilepsy.[2] These discharges appear in the form of "chirps" that change their frequency steadily so that they become faster or slower or some combination of the two over time—similar to the doppler effect heard when a train whistle or car horn passes by an observer. Although chirps have long been associated with seizure patterns on the EEG,[17,18] recent work in our laboratory suggests that preictal chirps may reliably anticipate seizures (unpublished observation).

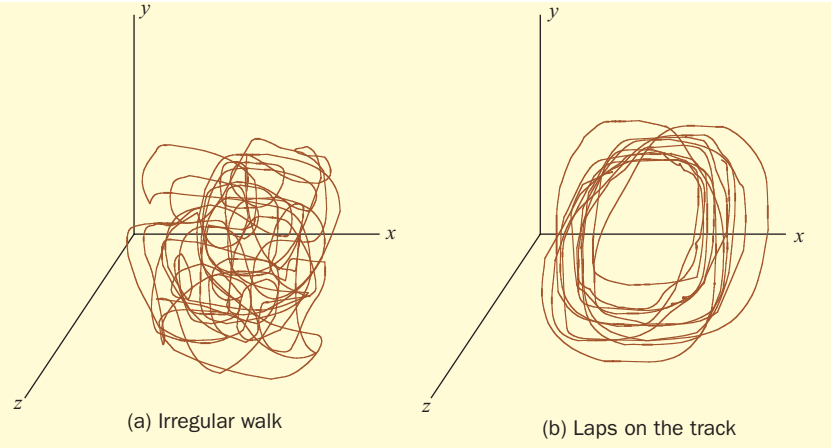

Figure 2. Example of two trajectories, plotted in "phase space" according to the method of delays. In (a), the trajectory is of an apparently random, chaotic process, such as the fly's flight path. In (b), the trajectory is more regular, such as walking laps around a lake or track.

Non-linear dynamics and chaos

Some of the most important early studies showing changes in characteristics of the EEG waveform in the minutes leading up to seizures apply theory from the area of non-linear dynamics.[19,20] These techniques focus on systems with behaviour too complex to be described by a series of equations or a mathematical model.[21,22] Takens' theorem states that the complete dynamics of a system can be reconstructed from a single measurement sequence (such as its trajectory over time), along with certain invariant properties (see later).[23] This scheme gives us a way to pry open the black box that generates these complex signals and analyse some of their properties.

A practical example of a complex non-linear system is the apparently random flight path of a housefly in a kitchen. We can analyse the behaviour of such systems by deriving quantitative parameters from their trajectory, for example by tracing a plot connecting each point of the fly's position (ie, its distance from some reference point) to the next point over time. Although these methods may not be able to predict the fly's exact movements, they are useful in describing its behaviour and enable us to compare one fly with another. Important characteristics quantified by these methods are the complexity of the insect's movements (straight lines or involuted squiggly paths; this complexity correlates with a variable called "fractal dimension" and a related measure, the "correlation dimension"); the regularity of the flight path (is it repeating itself?); and the pattern—does the fly zoom out abruptly from particular points over long distances (such as from the fruit bowl to the window across the room then back to the lemonade glass) in which case the paths diverge rapidly, or does it move in smaller, more regular steps, exploring nearby regions before moving farther out (slow divergence)?

A measure that characterises the divergence of one point in the path from another over time is called the "principal Lyapunov exponent" (PLE). A basic finding shared by investigators who use non-linear techniques to analyse the EEG before seizures is that the trajectory of the EEG seems to become more regular and organised before visible onset of the seizure. This change in the dynamics of the EEG is marked by decreases in the correlation dimension, the PLE, and later the quick (waveform) fractal dimension.[24–29]

Arguably these methods may be more difficult to relate to the neurophysiology of epilepsy than other quantitative tools, but non-linear dynamics account for some of the first descriptions of seizure precursors in human epilepsy and remain a focus of great interest in this area.

The method of delays

A fundamental concept in non-linear dynamics is the "method of delays". In this method, each point in a series of events or measurements is considered in the context of other events or measurements in the same series that are close in time. This approach is like considering each step during a walk in the snow in view of other nearby footprints made during the walk (either the footprints before or after each step can be used). The larger the number of adjacent footprints that are used to describe each step, the better the idea obtained about the nature of the entire walk, up to some limiting number.

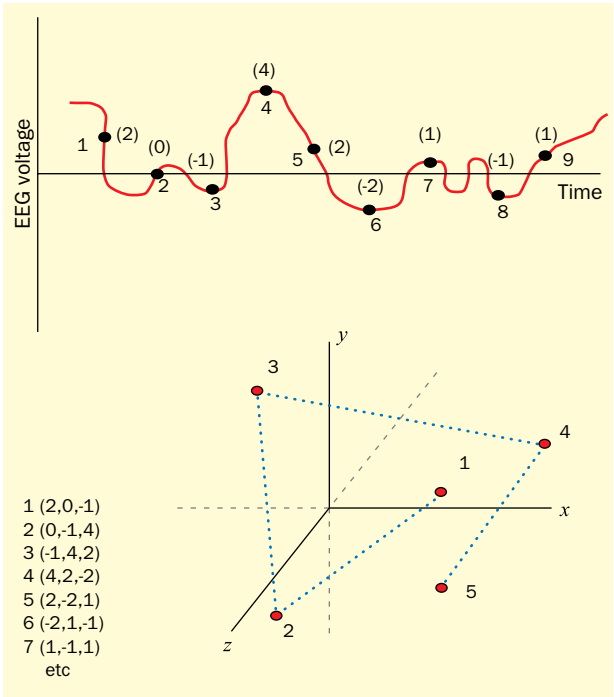

Figure 3. A demonstration of the method of delays applied to a brief segment of analogue EEG sampled at nine points along the waveform. The upper part of the figure shows the EEG tracing sampled at individual points 1–9, with the voltage measurement at each point written beside each sampled point. The lower part shows the coordinates of each point for the plot, using each point and the two that come after it, and the plot of these point coordinates, demonstrating how a trajectory in phase space is reconstructed.

Each step in the walk is marked by its value at that point (for example, the distance from the footprint to home), and the value at each of the other points being considered with it. For example, if a man walks a distance of 1 m away from a house with each of the first few steps, and we choose to describe each step in the walk in light of the two steps that come immediately after it, the coordinates of the first point will be (1,2,3), that is, 1 m away, then 2 m away, then 3 m away. The coordinates of the next point in the trajectory will be (2,3,4), and so on. If the walk is over an irregular path in the forest, it will consist of a series of irregular movements away from and closer to home. The walk, if each step is plotted in three-dimensional space according to the coordinates given to it above, might appear as an irregularly shaped jumbled mass, like a tangled ball of string (figure 2). If the walk is very regular, however, for example laps around a nearby pond, its trajectory will appear as an oval (figure 2). The number of context points chosen to view each step is called the "embedding dimension".

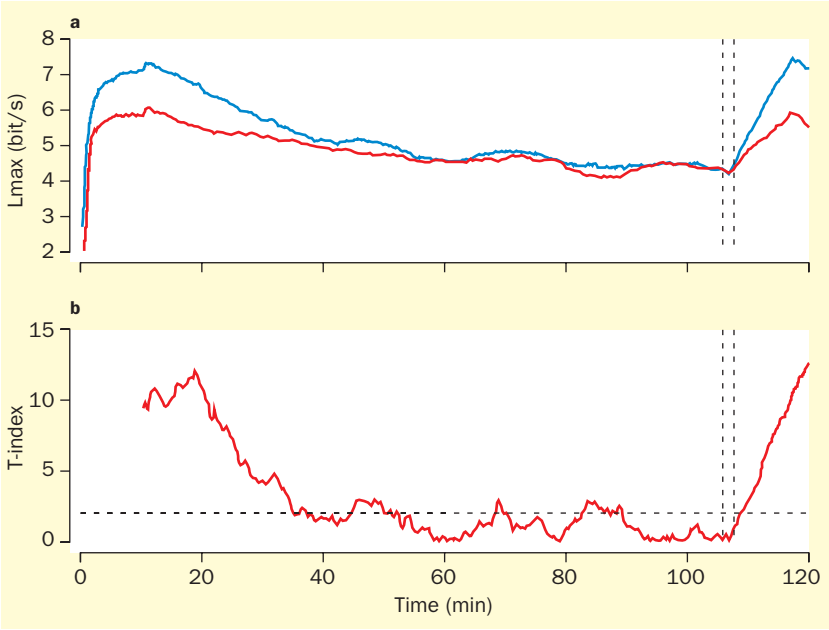

Figure 4. Display of entrainment of two sites—the right temporal depth electrode (red trace), in the seizure focus, and the right orbitofrontal electrode (blue trace) nearby—prior to a temporal lobe seizure. In (a), the principal Lyapunov exponents (PLEs), calculated in overlapping 10 min windows, converge between the sites. In (b) the T-index, a measure of the difference in PLEs between the two electrode sites, is displayed for the same time interval. The horizontal dashed line indicates the seizure prediction threshold. After the seizure (marked by vertical dashed lines), the PLEs again diverge (top trace), and the T-index rises (bottom trace). Reproduced with kind permission of Kluwer Academic Publishers and Leonidas Iasemidis, Department of Bioengineering, Arizona State University, AZ, USA.[48]

Figure 3 shows a close-up of a brief segment of EEG and a plot of the trajectory of the EEG made by the method of delays with two adjacent points used to describe each measurement point on the EEG (a total of three points, or an embedding dimension of three). A plot can then be made which shows each point from the EEG (one point is analogous to one footprint in the example above) connected to the other points, the coordinates of which are derived in the same way. For most EEG studies, embedding dimensions of seven to ten have been used.[30]

In a variation of these methods, called dynamical similarity, the EEG is not directly embedded from all of its digitally sampled points but only the timepoints when the trace crosses the zero voltage axis, and the slope of the voltage curve is upward, are used to reconstruct a trajectory. The trajectory of the EEG signal is calculated (by the method of delays and an embedding dimension of ten) in a 5 min reference window far from seizure onset; it is then compared with computed trajectories in 30 s test data epochs in the EEG as seizures approach. When the difference between these two epochs in time reaches 5 SD, a preseizure state is declared, and the seizure is said to be "anticipated".[31]

Intelligent systems

These methods include mathematical and computer tools, such as neural networks and other artificial-intelligence structures, which can learn to distinguish between preseizure and normal (baseline) states, often by a guided trial and error procedure, after being trained on a subset of the data set aside for this purpose.[32–34] A significant advantage of these systems is that they can learn this task without requiring that specific rules be articulated as to how the program should decide between one class of events and another. Unfortunately, even if the program succeeds in learning to make these decisions accurately, it cannot explain the rules it has discovered back to its creator.

History of seizure prediction

The first serious attempt at seizure prediction was made by Viglione and colleagues in 1970.[1,32] An experiment based on seven seizures from five patients yielded 90% average correct separation between preseizure and non-preseizure epochs of EEG in the training set. Initially, the system was not tested on data that had not been used in training. Further development of the project led to a patent for an electronic warning device for epilepsy.[35] This system had a high correct prediction rate but produced too many false-positive results perhaps due to artefacts in the scalp EEG (A Gevins, personal communication). Work on this system stopped in the mid-1970s, because system training and testing were limited by the computers available and there were concerns about the need for patients to wear EEG electrodes during waking hours.

In 1972, *The Terminal Man*, a novel about an implanted brain-stimulating device to predict and stop seizures, was published.[36] The author, Michael Crichton, is a medical

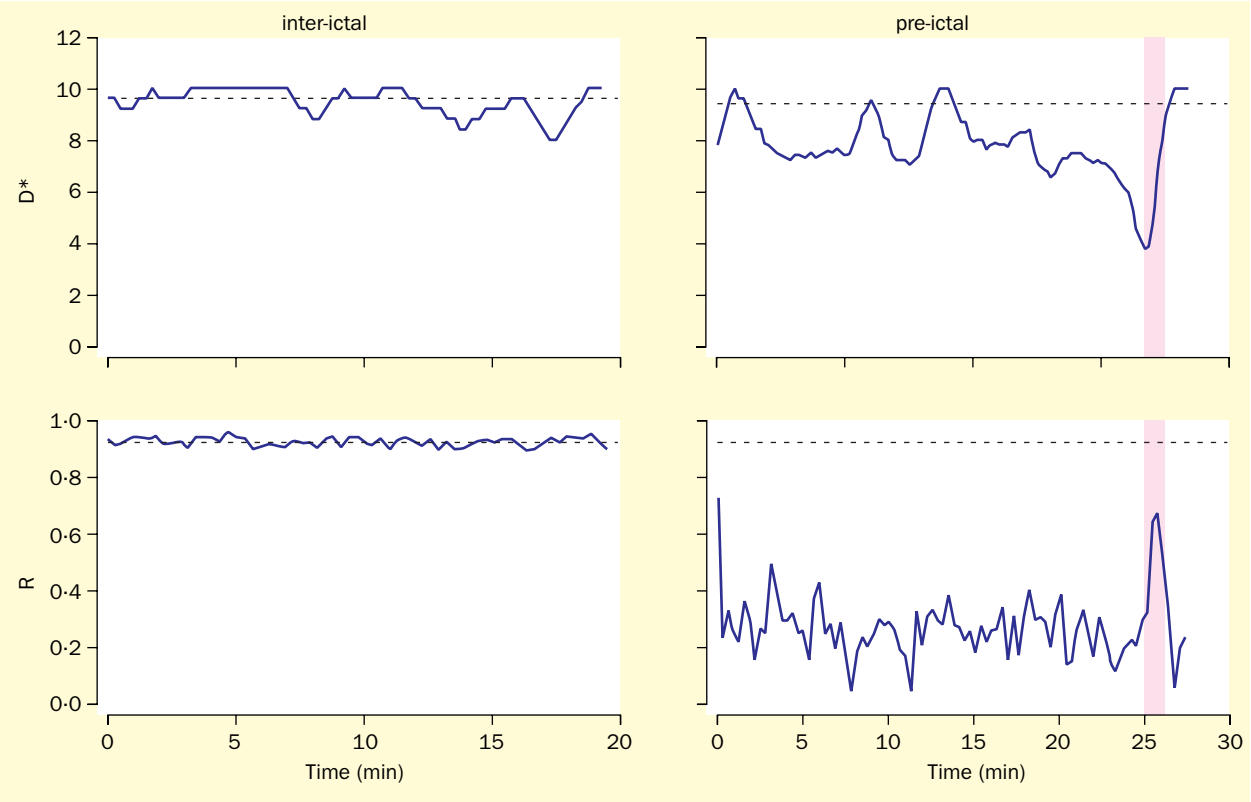

Figure 5. Representative examples of discrimination between the interictal and preictal states in one patient for a univariate measure. An estimate of the correlation dimension (D) is shown in the upper row, and a bivariate measure, the mean phase coherence (R) as a measure of phase synchronisation, is shown in the lower row. Note that changes in D* characteristic of the preseizure state occur about 12 min before seizure onset, whereas those for R occur at least 25 min ahead of the seizure. Dashed lines indicate the mean interictal value for each measure. The grey shaded area indicates the ictal state, from onset to end of electrical seizure activity. Reproduced with permission from Klaus Lehnertz, Department of Epileptologie, University of Bonn, Germany.*

doctor, but we do not know whether any of the ideas for the book's plot came from the work of Viglione and colleagues, or whether the unfortunate consequences of the device in the novel (the central character becomes insane and violent) suppressed work in this area for a time. Two other groups of investigators submitted patents on systems to control epileptic seizures before onset in the 1970s, one using EEG features to trigger a warning to the patient,[37] and the other triggering a sustained biofeedback signal to abort seizures.[38]

Work on seizure prediction in the late 1970s and early 1980s consisted mainly of studies of visible features in the EEG, such as epileptic spikes, and their relation to seizures.[10–12] The discovery that abnormal activity in the epileptic and normal lobes became correlated about 20 min before seizure onset was corroborated by non-linear techniques almost 15 years later.[39]

In 1987, Milton and co-workers[40] postulated that the timing between seizures in a given patient occurred in a predictable pattern. Though they could not verify this idea, others later found varying degrees of predictability in temporal seizure patterns in human beings and animal models of epilepsy.[41–43]

The late 1980s and 1990s saw the application of non-linear dynamics as a technique for predicting seizures. Transient drops in the PLE were described by Iasemidis and colleagues as "a route to seizures" in temporal-lobe epilepsy.[19,44,45] In this work, the investigators proposed that the EEG became progressively less chaotic as seizures approached. This work expanded in 1991 to suggest evidence of a preictal phase transition, beginning 7·5 min before seizure onset.[46] This group later proposed that preictal entrainment of the PLE in a "critical mass" of brain is necessary before seizure onset can occur.[47] Figure 4 demonstrates a sample of the PLE trajectory for a prolonged EEG recording in a single test patient.[48] Further details of these ideas, and methods for implementing them are described elsewhere.[26,48–50]

In 1994, a research group led by Elger and Lehnertz from Bonn, Germany, introduced application of the correlation dimension, another non-linear measure, for use in predicting seizures. This measure showed reproducible decreases in value during seizure generation in a significant number of patients.[51] This group has since shown that a derived measure, neuronal complexity loss, can help identify the ictal onset zone,[20,52] that it can be used to distinguish the epileptic from the non-epileptic temporal lobe,[53,54] and that this variable can be used reproducibly to predict epileptic seizures in many patients.[24,55] In addition, the group has developed techniques that can be used to demonstrate phase synchronisation hours before seizure onset; these methods can be useful in mapping the epileptogenic zone in lesional

and extratemporal epilepsies.[56–58] Figure 5 illustrates an example of neuronal complexity loss and changes in phase coherence in anticipation of EEG seizure onset.

Scott and Schiff[59] found some degree of non-linear predictability in the timing of intervals between spikes in hippocampal slices induced to express epileptiform activity. Geva and co-workers, in 1997, applied intelligent systems, using fuzzy clustering in seizure predictions to analyse recordings from rodents induced to have generalised convulsive seizures by exposure to hyperbaric oxygen. In that study, wavelets (a way of identifying portions of the EEG with certain temporal and frequency characteristics) were used to calculate energy in the EEG signal. The investigators found a reliable increase in wavelet-derived energy an average of 4 min before electrical and clinical seizure onset of generalised seizures in two channels of EEG obtained from each of 25 rats.[33] We do not have space here to devote to other studies of preseizure EEG changes in animal models of epilepsy, which began in the 1960s and have shown a resurgence in recent years.[60–64]

In 1998, a group of investigators led by Baulac and Varela[65] from the Hôpital de la Salpêtrière, in Paris, published evidence of seizure anticipation in preseizure segments (total of 6·3 h of data) using a measure called correlation density. This group has expanded the methods and volume of test data using a method called dynamical similarity.[31,66,67] Figure 6 illustrates the temporal and spatial distribution of changes in similarity index in a patient with temporal-lobe epilepsy during monitoring with intracranial electrodes.[31]

Also in 1998, we established a collaboration between investigators at the Georgia Institute of Technology, University of Pennsylvania (previously at Emory University), and the University of Puerto Rico Mayaguez, applying intelligent-systems techniques to seizure prediction. In this method, many quantitative features are extracted from the intracranial EEG, a subset are chosen that best enable seizure prediction in each individual patient, and the features are fused in an attempt to predict optimally the probability of seizure onset in different time horizons (eg, 10 min, 1 h, 1 day).[34,68,69] Our group has also focused on analysis of standard electrophysiological measures associated with epilepsy, and analysis of long-term recordings. We recently described a cascade of electrophysiological events, which appear to take place over hours, leading to electrical seizure onset. Some of these changes include bursts of long-term energy related to epileptiform activity and slowing, spatially-limited subclinical seizures, and accumulation of energy in an increasing volume of tissue that leads to seizure onset.[2] Figure 7 displays accumulated energy tracings from

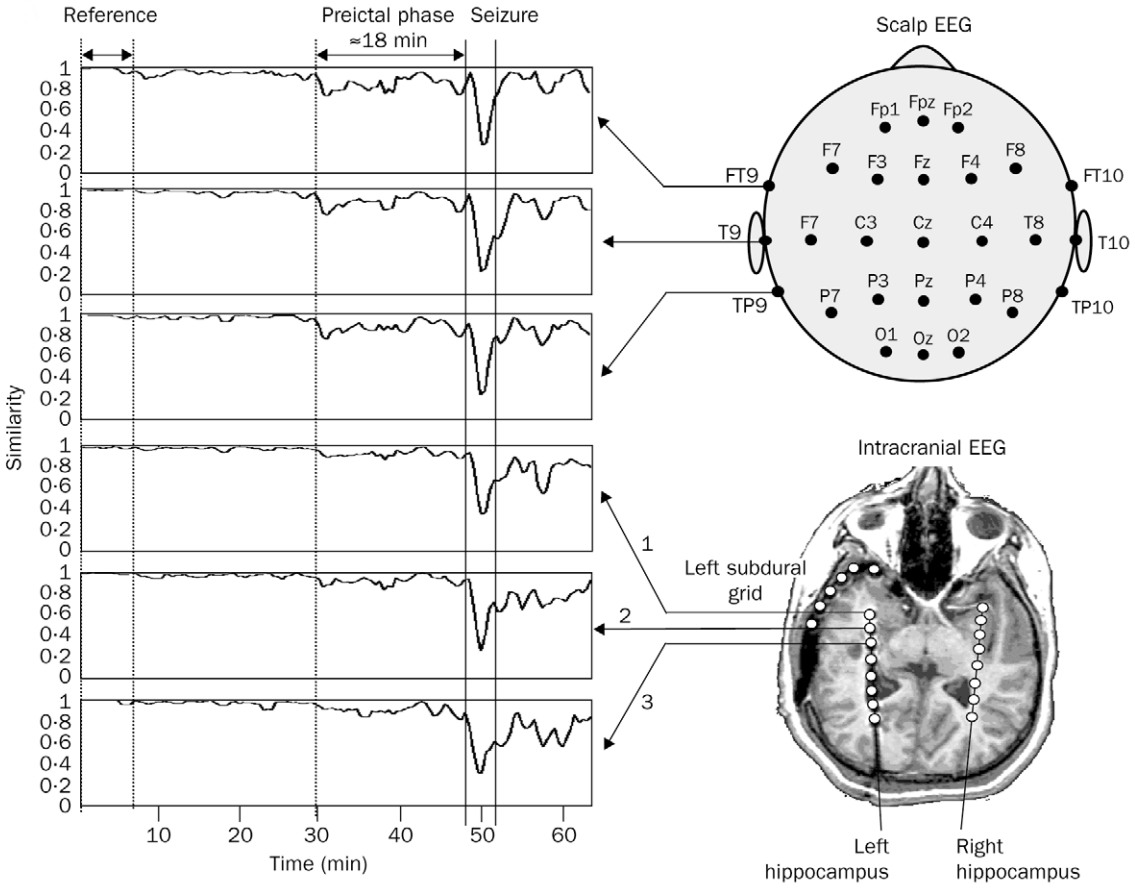

Figure 6. Spatial and temporal changes in similarity index, also including the EEG reference segment used for this running calculation, in a patient with temporal-lobe epilepsy. A diagram of the intracranial electrodes from which the intracranial EEG is recorded is included. Reproduced with permission of The Lancet Publishing Group.[31]

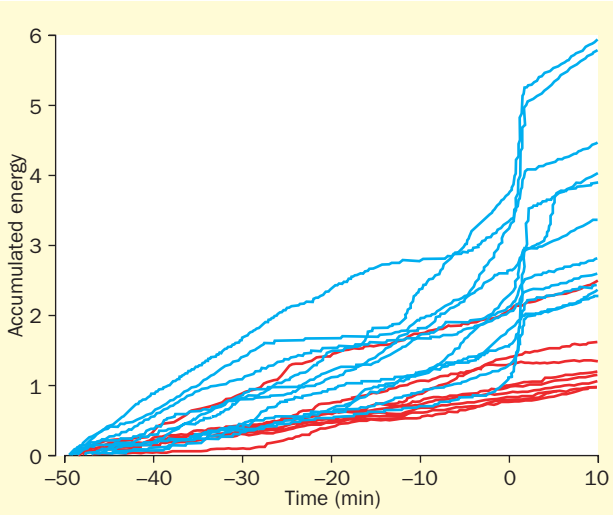

Figure 7. Accumulated energy plot for preictal epochs (blue) and baseline epochs (red) from a patient with temporal lobe epilepsy containing preseizure and baseline records from wakefulness and sleep, normalised and drawn on the same graph. This measure relies on separation of data epochs into primarily asleep or awake periods, given that baseline energy in the EEG increases during sleep.

preseizure and baseline segments from a depth electrode placed within the seizure onset zone of a patient with temporal-lobe epilepsy.

During the past few years, seizure prediction work has branched out. There is awareness that single quantitative techniques are unlikely to predict seizures in all patients. New groups are contributing promising algorithms and processing tools.[70] The last few years have also kindled an interest in methods for predicting seizures from other physiological or non-physiological variables, though most are in early stages of development.

Finally, we should mention dogs that are reported to predict seizures in individual patients, after specific training.[71–73] Although this method of predicting seizures and warning patients is of great interest in the community, there have been no controlled trials to validate the performance of these animals.

The present

Thus, the state of the art in seizure prediction is that there is strong evidence from several methods that seizures in temporal-lobe epilepsy can be predicted at least 20 min before unequivocal electrographic onset and also substantial evidence that other changes that begin 1·0–1·5 h before onset in temporal-lobe epilepsy are highly associated with seizures and may be predictive. There are other changes that occur up to a few hours before unequivocal EEG onset of seizures, such as bursts of long-term energy, changes in phase synchronisation, accumulated energy, chirps, and very focal subclinical seizures on EEG, which may be associated with periods of increased probability of seizure onset. Several different methods have shown that abnormal activity in the hippocampi becomes correlated or "entrained" bilaterally in the 10–20 min before the unequivocal electrical onset of seizures in temporal-lobe epilepsy. This finding implies that the epileptic focus may require coincident activation of other brain regions—cortical, subcortical, or both—to generate clinical seizures.

The future

To sustain research related to quantitative analysis of EEG and seizure prediction, there are some important requirements. First, large, high-quality data archives are needed; this means a source of well-characterised, high-quality, meticulously collected data, representing the breadth and depth of patterns and patients found in human epilepsy. Recordings should be intracranial, because these provide the highest resolution and are the richest kind available for analysis. Since improved neuroimaging and better understanding of epilepsy syndromes are making intracranial monitoring less common in major epilepsy centres, every effort must be made to fund and assemble such data archives and make them available to major research groups as soon as possible.

Second, since epilepsy is such a heterogeneous disorder, with a high incidence in childhood, lessons learned from investigations in medial temporal-lobe epilepsy should be applied to other epilepsy syndromes and seizures arising from other anatomical locations. Individuals with these disorders are in even more desperate need of new treatment options than many with temporal-lobe epilepsy, because their seizures tend to be more difficult to localise and control.

Third, an important milestone will be prospective clinical trials of seizure-prediction algorithms on-line. Demonstration of clinically useful results of this type will stimulate academic efforts and the medical device industry, paving the way for clinical trials of prediction algorithms in implantable devices and intelligent systems that will bolster basic science research in epilepsy.

One of the most useful and exciting recent developments in seizure prediction is the growing momentum toward releasing and testing first-generation intelligent seizure-treatment devices. With hardware platforms well into development, some of them adaptations of neurostimulation devices meant for other purposes (eg, treatment of pain, tremor, and Parkinson's disease), these first-generation units will probably detect unequivocal electrical seizure onset and trigger therapy, either electrical stimulation or local drug infusion, in response. Gradually, over several generations, algorithm development for these implantables is likely to push the prediction horizon back from electrical seizure onset, as reliable prediction algorithms become available. This evolution will have implications for therapy, because farther away from seizures less aggressive therapy may be required to arrest seizure generation. In addition, if this less aggressive therapy has few or no side-effects, a higher false-positive prediction rate can probably be tolerated, and therapy can be activated at lower seizure prediction probabilities far in advance of seizures. Early closed-loop pilot trials are already beginning.

As we delve deeper into this task, many questions will arise, such as what causes seizures to begin, which functional components of the network are necessary for seizure generation, how they can be stopped, and whether we are

really predicting seizures or learning more about a continuous ebbing and flowing process, one that may have its origins years before its first clinical manifestations.

Conclusion

Since 1970, scientists and clinicians have envisioned intelligent, implantable devices to predict seizures and trigger abortive therapy to help the many people worldwide who have medically intractable epilepsy. A confluence of technological innovation and intense interest from clinicians, scientists, and industry seems poised to make this vision a reality. Work to date gives convincing evidence that there are measurable changes in the EEG that take place far in advance of clinical seizures, but no truly prospective studies of long-term data have been done. Evidence suggests that seizure precursors may come and go, as attempts to ignite seizures in the temporal lobe wax and wane, perhaps over days, before some synchronising event propels the process towards electrical and clinical seizure onset. Substantial work remains to take these findings, which seem to vary from method to method and patient to patient, and convert them into reliable on-line systems able to predict seizures prospectively and in real time. The technology necessary for these tasks has only recently become available. If the productivity in intellectual property development and rate of publication in this area are any indication, the pace of development will continue to accelerate. One of the most important ingredients for success in seizure-prediction systems is access to large amounts of continuous, high-quality human intracranial EEG data for analysis, covering all physiological states relevant to seizures. Of course, quantity is not everything. Some studies that appear to analyse smaller pools of data may actually better validate more sensitive seizure-prediction algorithms, because they analyse more preseizure and seizure segments. Other experiments better validate algorithm specificity, analysing data containing fewer seizures, but longer baseline stretches.

Of all the approaches used to predict or anticipate seizures presented above, which is the best? All seem to provide important insight into seizure generation, and they probably constitute different ways of viewing the same thing. Some rarified combination of quantitative features, encompassing parts of many of the methods used by major research groups, will probably be required to carry out reliable seizure prediction tailored to individual patients. As a consequence, real progress may require collaboration between the major research groups involved in this effort, something that has already begun to occur.

Search strategy and selection criteria

Data for this review were gathered from medical, engineering, and patent publications by use of the following search services: USENET, CARL, GTEC, GENL, ENGI, IEEE, INSPEC, NERAC, Current Contents and PubMed (National Library of Medicine), and NTIS. The search terms used were: “seizure”, “prediction”, “forecasting”, “precursors”, “preictal”, “anticipation”, “epilepsy”, “non-linear dynamics”, “chaos”, “digital”, “EEG”, “subdural”, “intracranial”, “scalp”, “depth”, “electrode”, and “intelligent systems”. Abstracts, conference papers, and reports from meetings were included only when they related directly to previously published work. Only papers published in English were reviewed. Whenever possible, we attempted to avoid reference to medical abstracts, unpublished work, or non-peer-reviewed work. There are rare exceptions, in the spirit of giving insight into the cutting edge of work on seizure prediction.

Aside from immediate clinical applications, there are significant scientific implications of recent progress in the area of seizure prediction. Most of the major research groups in the discipline are already applying quantitative methods to analyse signals generated by animal models of epilepsy. Free from the restrictions on recording periods, implantation sites, and inability to control variables such as medications, sleep-wake cycles, and activity, these experiments promise to further our understanding of the neurophysiology of epilepsy and its underlying mechanisms. This work has the potential to promote not only better prediction algorithms, but also better therapies and perhaps even insight into the process by which normal brain becomes epileptic.

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Authors' contributions

Both authors contributed equally to all parts of the text.

Conflict of interest

BL has been awarded a small number of stock options (less than 0·25% of the company's total value) in NeuroPace Inc, resulting from licensure of patents to the company. These patents are all owned, singly or in combination, by the University of Pennsylvania, Georgia Institute of Technology, and Emory University. Potential conflicts of interest have all been managed in strict adherence with the academic policy of each of these institutions. JE is an employee of NeuroPace Inc.

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