Forecasting Seizures: Not Unthinkable Anymore

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"Prediction is very difficult, especially about the future."

Niels Bohr, Nobel Prize in Physics in 1922

Summary

Epilepsy is a cyclical brain disorder par excellence: Single or clusters of spontaneous seizures recur with relatively fixed symptom-free intervals. This temporal structure of epilepsy is a fascinating phenomenon that likely has an endogenous basis. Over the past decades, seizure prediction has been a niche endeavor for a few epileptologists and scientists acquainted with non-linear systems and equipped with the necessary statistical background. Today with the rapid development of wearables and implantable devices, the idea is gaining terrain in the clinical epileptology community. Aided by synergetic developments in machine learning and the accumulation of massive amounts of epilepsy data, the field can transform this once vague idea into a practical tool for the broader drug-resistant epilepsy population. We make the prediction that forecasting seizures is soon-to-be a reality.

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Keywords: Seizure prediction, chronobiology, circadian rhythm, multidien rhythms

La prédiction des crises d'épilepsie n'est plus impensable

L'épilepsie est une maladie cyclique par excellence : des crises spontanées isolées ou en grappe surviennent à intervalles relativement fixe. Cette structure temporelle de l'épilepsie est un phénomène fascinant qui a probablement une base endogène. Au cours des décennies passées, les tentatives de prédiction de crises ont été le terrain de jeux de quelques épileptologues et scientifiques connaissant bien les systèmes non-linéaires et les outils statistiques. Aujourd'hui, avec le développement rapide des appareils « wearable » et implantables, l'idée gagne du terrain au sein de la communauté épileptologique. Avec l'aide de développements en « machine-learning » et l'accumulation de quantités de données sur l'épilepsie, notre branche peut transformer cette idée autrefois vague en un outil pratique pour le bénéfice des patients. Nous prédisons que la prédiction des crises est une réalité à venir.

Mots-clés : prédiction des crises, chronobiologie, rythme circadien, rythmes multidien

Anfallsvorhersage: Nicht mehr undenkbar

Epilepsie kann als typisches Beispiel einer „zyklischen Hirnerkrankung" betrachtet werden: Einzelne Anfälle oder Gruppen von Anfällen wechseln sich mit erstaunlich konstanten anfallsfreien Zeitperioden ab. Dieses faszinierende Phänomen hat mit hoher Wahrscheinlichkeit endogene Ursachen. Während der letzten Jahrzehnte hat die Anfallsvorhersage ein Nischendasein gefristet, hauptsächlich betrieben von einer Gruppe von Epileptologen und Naturwissenschaftlern, die über das notwendige anspruchsvolle Wissen über nichtlineare Systeme und statistische Methoden verfügten. Mit der heutigen raschen Entwicklung von

trag- oder sogar implantierbaren Geräten stösst die Idee der Anfallsvorhersage nun aber auf zunehmend breiteres Interesse und Akzeptanz in der klinischen Epileptologie. Unterstützt durch die synergetische Entwicklung des maschinellen Lernens und die Entstehung umfassender Datenmengen, generiert durch zunehmend mobilere Epilepsiediagnosegeräte, besteht erstmals die Möglichkeit, die einst noch unscharfe Vision einer Anfallsvorhersage in die Praxis umzusetzen, zum Nutzen aller Patienten mit pharmakoresistenter Epilepsie. Wir sagen voraus, dass die Vorhersage von Anfällen schon bald Realität sein wird.

Schlüsselwörter: Anfallsvorhersage, Chronobiologie, circadianer Rhythmus, Multidien-Rhythmen

Introduction

Epilepsy is characterized by the seemingly random occurrence of spontaneous seizures. Yet, any neurologist has been confronted with individual patients' seizure diary revealing striking regularity (**Figure 1**). Over the course of history, this regularity in seizures has been attributed to devil intervention, phases of the moon – epilepsy patients were once called "lunatics" in reference to their behaviors influenced by the moon – or other obscure forces. Centuries of observation have only formally identified a handful of triggers (**Table 1**) for epileptic seizures, and none that is considered causal of the disorder. An underexplored endogenous modulation may be underlying rhythmicity in epilepsy.

Historical aspects

In the 19th century, Gowers already recognized groups of epilepsy patients having exclusively nocturnal (22%) or diurnal (45%) episodes or a mix of both (33%) [1]. At the beginning of the 20th century, colonies for epilepsy patients were organized, motivated by the rationale that work in the fields was beneficial for their health. One such example is the Lingfield colony, in the London countryside, where more than 100 boys and men were living in community. Through constant surveillance, and meticulous charting of the time and date of seizure occurrence, a number of facts regarding rhythmicity in epilepsy were established. In the 1920s, Langdon-Down and Brain [2] showed the circadian modulation beyond vigilance stages of 2'524 major seizures (mostly convulsive). A decade later, this was confirmed by Griffith and Fox [3] in extended analyses based on no less than 39'929 seizure occurrences. They showed that seizures tended to recur at the same time of the day across patients, with preferential times being 6 a.m., noon and midnight. They also showed that seizures are interspersed with relatively constant seizure-free intervals in given patients. The duration of this interval varied from patient to patient, for example weekly, bi-weekly, monthly or longer, including rare examples of seasonal epilepsy. Their landmark paper points to a patient-specific endogenous multidien (multi-day) rhythmicity in epileptic activity that is key to determining seizure timing.

As epilepsy patients regained their status of community dwellers, access to that information was partially lost, due to the pervasive inaccuracy of self-reported events. Nevertheless, Bercel [4] published in the 1960s a series of 1105 male and females cases of which 10% displayed regular cycles of 2 weeks, 4 weeks, or several months. He also made the comment that "The

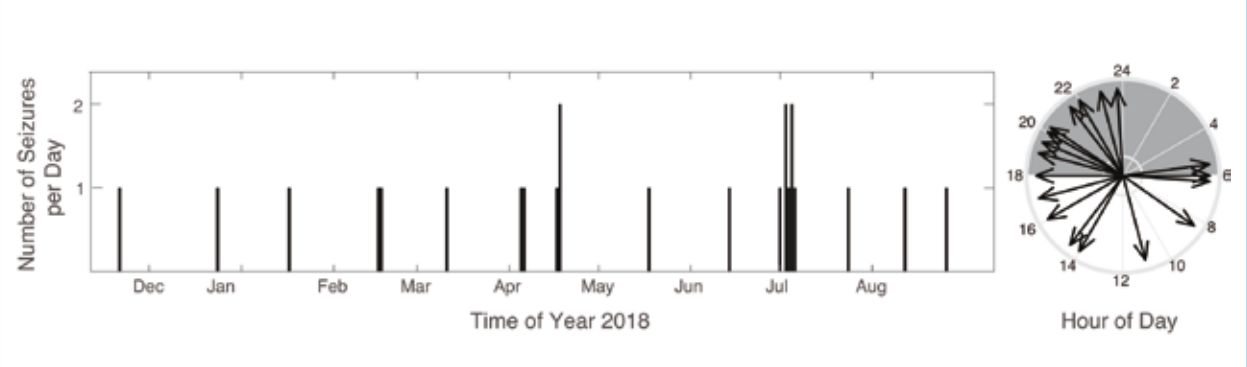

Figure 1: Example of a seizure diary kept during about a year by a patient followed at the University Hospital of Bern (Inselspital, courtesy of PD Dr. med. Heidemarie Gast). Left: note the striking regularity with which single seizures or clusters occur. Yet, the average periodicity of 23 days is slightly variable. In July, seven seizures occurred over the course of 5 days, representing a prolonged cluster.
Right: Each arrow represents one seizure and is pointing to its time of occurrence on the 24-hour clock. Note a tendency for seizure to occur in the afternoon and evening, with a second smaller cluster around six o'clock. Without access to continuous recordings of interictal epileptiform activity, rhythmicity is apparent, but only partially characterized.

Table 1: Factors influencing the timing of seizures

Triggers	Cyclical modulation
Medication non-compliance	Circadian cycle (time of day)
Alcohol or drugs	Sleep-wake cycle (brain states)
Stress	Multidien cycles (multiple days)
Sleep deprivation	Hormonal cycles (for example: menstrual)
Fatigue	Unknown modulating factors
Flashing lights (rarely)	
Reflex seizures (rarely)	

time structure of epileptic rhythms has not yet been studied by means of computer technics, which leaves a good many male epileptics with 28-day periodicity still staring at the moon for an answer". Although the study of seizure timing by means of computer technics has advanced our statistical understanding of the phenomenon, the biological explanation for these rhythms is still lacking entirely and an influence of lunar cycles has not formally been excluded. One fact is established: Rhythmicity in epilepsy is to be found in women, men and children alike.

Temporal structure in epilepsy

Historical knowledge on temporal patterns of seizure recurrence has been rediscovered over the past few years through the lens of technology. Data from chronic EEG (i.e. many months) in ambulatory patients represent an invaluable source of information to broaden our knowledge on the topic. Electrographic documentation is one objective measurement of seizure timing that can fully supplant patient-based seizure calendars, notorious for being unreliable and inaccurate in many cases [5].

To this day, two datasets of chronic EEG recordings have been investigated: the *NeuroVista* and the *NeuroPace* data. The *NeuroVista* data comes from a trial of an implanted seizure warning system in 15 patients over three years (see below) and represents to date the only continuous raw EEG data recorded over many months. The *NeuroPace* data comes from a responsive neurostimulation device implanted, to this date, in more than 1500 patients for therapeutic purposes in the US. As opposed to the *NeuroVista* data, the *NeuroPace* data does not provide access to continuous raw EEG but instead counts of detected epileptiform events. Despite this limitation, data accumulated for up to 10 years provides an important source of information.

In a recent study [6], epileptic activity was shown to be regulated at multiple temporal scales. First, the sleep-wake and circadian cycles were shown to influence the rate of interictal epileptiform discharges. Second, the study unraveled that ictal and interictal activity was modulated in multidien cycles with periodicity of several days specific to each patient. This observation positions the interictal epileptiform activity as an excellent biomarker to monitor epileptic brain activity over time. Indeed, interictal epileptiform activity can be used to "partition" time into periods of low and high risk for epileptic seizures [7].

The pro- and pre-ictal states

The feasibility of seizure forecasting crucially relies on the existence of two pathophysiological phenomena that are known to clinicians: a pro-ictal state on the scale of days and a pre-ictal state on the scale of minutes to hours. The pro-ictal state relates closely to the circadian and multidien rhythms described in the previous paragraph. Due to pro-ictal states lasting a few days, seizures tend to occur in clusters during these recurring periods of high seizure risk (**Figure 2**). Clinical evidence for a pre-ictal state is to be found in some patients (~6%) who feel "something building up" as non-specific premonitory symptoms (that are different from an aura), minutes to hours before the occurrence of a

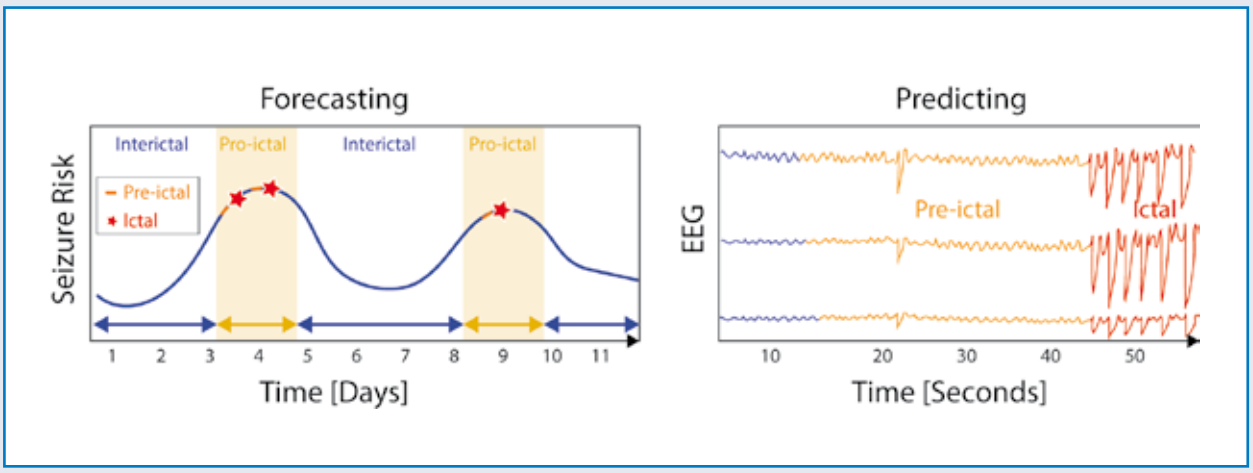

Figure 2: Depiction of the different states of the epileptic brain over time.
Left: Seizures happen for the most part during pro-ictal states and can be forecasted by extrapolating the expected next cycle. Right: Seizure prediction seconds or minutes before seizure onset, based on the detection of a pre-ictal state in the EEG. Future algorithms for the anticipation of seizures will combine information at both temporal scales for improved performance.

seizure, including restlessness, malaise and headaches [8]. There is also mounting electrophysiological and neuroimaging [9] evidence that changes in the brain are detectable, minutes before the onset of seizures.

While a consensus definition is lacking, the field usually refers to seizure prediction in the sense of warnings of impending seizures based on the detection of a pre-ictal state. Based on recent understanding of the temporal structure of epilepsy, we propose that seizure-risk forecasting can be defined as establishing the probabilistic forecast of seizures over the course of a few days, akin to weather forecasting. These two concepts are not antagonist but complementary and reflect the multiple timescales (days vs. minutes) at which epilepsy operates. In a Bayesian approach, knowing the seizure risk on a given day or hour will help refine the performance of seizure prediction algorithms [10]. An alert (pro-ictal) could be given a few days in advance and confirmed (or not) by a warning of imminent seizure (pre-ictal) a few minutes in advance.

Past trials of seizure prediction

With the development of chaos theory and non-linear system theory in the 1980s, physicists became interested in applying their tools to EEG time series, aiming at understanding the dynamics of the brain switching from one state (normal) to another (seizure). Using intracranial EEG from inpatient epilepsy work-ups, early papers described peri-ictal changes of chaoticity measures, and proposed that the methods from non-linear dynamics could help anticipate seizures [11]. However, the initial enthusiasm was slowed down by several studies reporting negative results or questioning the validity of the methods applied (for an overview see [12]). During the first few international workshops on seizure prediction (Bonn, 2002, Freiburg 2007), none of the participants was able to predict seizures above chance on a dataset available during the meeting.

One consequence of the raising skepticism was that researchers took “one step back” and started to re-investigate and better define the events to be predicted, i.e. the seizures [13]. A better understanding of epileptic seizures can help identify states promoting or impairing their occurrence and ultimately improve prediction. Over the past two decades, the understanding of seizure dynamics, i.e. how seizures begin, how they propagate and how they terminate [14,15], has improved with the use of advanced analytical methods [16 - 20]. Yet, no single biomarker of the preictal state has been identified to date.

As a consequence, in the 2010s the field has turned to multi-variate measures and machine-learning as the default approach to personalizing predictive algorithms on a patient-specific basis. A number of standards were established for the statistical testing of algorithm performance [12]. These developments have been led by contributive efforts of the machine-learning community through competitions open to the public (www.kaggle.com). Rigorous methodology was imposed including training algorithms on a subset of data and testing them on a separate subset of data from the same patients that was not available to the participants [21, 22]. Overall, the results were above chance and very encouraging when based on long-term recordings. The initial issue of low specificity of prediction was overcome. This is key as false warnings can lead to increased stress for patients. Yet, this approach does not help us understand the pathophysiology of epilepsy, as the algorithms typically rely on a number of EEG input features that are difficult to synthesize into one coherent explanation.

First prospective trial of seizure prediction

After a few prospective trials based on inpatient EEG recordings, researchers soon realized that changes in medication and sleep deprivation could confuse the picture. There are clear benefits in attempting seizure prediction in ambulatory patients, on stable medication, in their natural environment. The *NeuroVista* trial is to date the only prospective trial of ambulatory seizure prediction. It took place in Melbourne between 2010 and 2012, enrolling 15 participants. This study relied on chronic intracranial EEG using 16 electrodes, directly in contact with one brain hemisphere. A subclavicular implant was communicating to an external hand-held unit. The system enabled data processing in real time and issued warnings in the form of colored lights: blinking red for impending seizure, white for indeterminate and blue for safe. Across patients, results were mixed, but for a subset of patients (N=9) above-chance warnings could be issued. Interestingly, the blue light (safe) was as valuable as the red light and contributed to decrease stress. Once the study concluded, the *NeuroVista* system was never commercialized due to a lack of investment.

From this trial a number of points were clear: Prediction algorithms need to be patient-specific and require a great amount of data to be trained. Success of prediction also seemed to heavily depend on finding the right algorithm. Even in patients with seizures that were difficult to predict during the trial, offline analysis and algorithm development after the closure of the trial enabled great improvement in predictions, once the correct method was found. This indicates that aside from hardware development (i.e. a recording device), optimization of software is also needed. This pioneering study established that seizure prediction was feasible prospectively, and useful for these patients. This represents a revolution for our field.

Upcoming trials

Enriched by evidence accumulated with chronic EEG, new clinical trials are in preparation. The American Epilepsy Foundation attributed a 3 million dollar grant to a team of scientists to develop a system for seizure forecasting (www.epilepsy.com). Other trials in Europe (Radar-CNS, www.radar-cns.org) have also invested in wearables to better understand epilepsy at a large scale. Yet the most reliable biomarker to date remains brain activity; and in addition to intracranial systems, sub-scalp minimally invasive EEG could be used for similar purposes.

Future of chrono-epileptology

In the coming years, miniaturization of electronics, development of connected devices (« Internet of Things ») and rapid development of know-how in neuro-engineering will continue. Technology will play a major role in neurology in general and in epileptology in particular. EEG is the only established portable technique for investigating the brain in its natural environment. It is far superior to MRI in its applicability to continuous chronic recordings.

It is thus natural to think that the advent of chronic EEG will improve the care for chronic neurological disorders. Today, it is conceivable that patients with epilepsy will track their disease activity and titrate their anti-epileptic drugs, just like patients with diabetes track their glucose and adjust their insulin. Seizure forecasting is not unthinkable anymore [23, 24].

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