Seizure anticipation: from algorithms to clinical practice

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Purpose of review

Our understanding of the mechanisms that lead to the occurrence of epileptic seizures is rather incomplete. If it were possible to identify preictal precursors from the EEG of epilepsy patients, therapeutic possibilities could improve dramatically. Studies on seizure prediction have advanced from preliminary descriptions of preictal phenomena via proof of principle studies and controlled studies to studies on continuous multi-day recordings.

Recent findings

Following mostly promising early reports, recent years have witnessed a debate over the reproducibility of results and suitability of approaches. The current literature is inconclusive as to whether seizures are predictable by prospective algorithms. Prospective out-of-sample studies including a statistical validation are missing. Nevertheless, there are indications of a superior performance for approaches characterizing relations between different brain regions.

Summary

Prediction algorithms must be proven to perform better than a random predictor before prospective clinical trials involving seizure intervention techniques in patients can be justified.

Keywords

methodology, performance, seizure prediction, statistical validation

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Introduction

With a prevalence of approximately 1% of the world's population, epilepsy represents one of the most common neurological disorders, second only to stroke. Two-thirds of patients can benefit sufficiently from medical treatment and another 8% could benefit from resective surgery. For the remaining 25% of patients, no sufficient treatment is currently available.

To epilepsy patients, the sudden, unforeseen way in which seizures strike 'like a bolt from the blue' represents one of the most disabling aspects of the disease. Apart from the risk of serious injury, there is often a severe feeling of helplessness that has a strong impact on the everyday life of a patient. It is obvious that a method capable of predicting or forecasting or anticipating (these terms are used interchangeably) the occurrence of seizures could significantly improve the therapeutic possibilities [1] and thereby the quality of life for epilepsy patients.

A question of particular interest is whether apart from clinical prodromi, which are found only in some patients [2], characteristic and objective features can be extracted from the continuous electroencephalogram (EEG) that are predictive of an impending seizure. If it were possible to reliably predict seizure occurrence from the EEG of epilepsy patients, therapeutic concepts could move from preventive strategies (e.g. long-term medication with antiepileptic drugs) towards an on-demand therapy, for example by excretion of fast-acting anticonvulsant substances or by electrical or other stimulation in an attempt to reset brain dynamics to a state that will no longer develop into a seizure.

Studies on seizure prediction

For a better understanding of the practical problems in this field, we categorize the literature on seizure prediction according to methodological standards. A chronological overview is given in Table 1 [3–32,33•, 34,35••, 36–40,41•,42••,43•,44•,45••,46].

The earliest approaches to seizure predictions in the 1970s and 1980s were based on spectral analysis or pattern detection ([47] and references therein).

Following the advent of the theory of nonlinear dynamics in the 1980s, time series analysts became aware of seizure prediction as a potential field of application. During the 1990s several quantitative EEG studies reported preictal

Table 1 Studies on seizure prediction and their relevant characteristics

Authors	Year	Characterizing measure	Patients	Seizures	Total EEG (h)	Interictal controls (h)	Type of analysis	In-sample parameter optimization	Retrospective best channel selection	Prospec-tive	Assumed preictal period (min)	Sensitivity (%)	False-positive rate (FP/h)	Mean prediction time (min)	Statistical validation of performance
Lehnertz and Elger [3,4]	1998	Correlation dimension	16	16	21	16.9	Statistical	Yes	Yes	No	30	94	0	12	No
Martinerie *et al.* [5]	1998	Correlation density	11	19	13	0	Algorithmic	No	Yes	No	20	89	NA	3	No
Le Van Quyen *et al.* [6]	1999	Similarity index	13	23	15	0	Algorithmic	No	Yes	No	20	83	NA	6	No
Le Van Quyen *et al.* [7]	2000	Similarity index	9	17	11	0	Algorithmic	No	Yes	No	20	94	NA	4	No
Mormann *et al.* [8]	2000	Phase synchronization	2	3	4	1.8	Proof of principle	No	Yes	No	NS	100	0	NS	No
Cerf *et al.* [9]	2000	Correlation integral	7	9	NS	1.8	Statistical	Yes	Yes	No	60	100	0	NS	No
Hively *et al.* [10]	2000	Dissimilarity measures	NS	20	40	0	Algorithmic	Yes	No	No	262.5	100	NA	52	No
Le Van Quyen *et al.* [11]	2001	Similarity index	23	26	26−35	0	Algorithmic	No	Yes	No	60	96	NA	7	No
Iasemidis *et al.* [12]	2001	Dynamical entrainment	5	58	266	53.9	Statistical	Yes	Yes	No	Variable	91	NS	49	No
Litt *et al.* [13]	2001	Accumulated energy	5	30	> 312	50	Statistical	Yes	No	No	180	90	0.12	19	No
Le Van Quyen *et al.* [14]	2001	Phase synchronization	8	NS	NS	NS	NS	NS	NS	No	NS	77	NS	Several min	No
Lehnertz *et al.* [15]	2001	Correlation dimension	59	95	> 145	> 115	Algorithmic	Yes	Yes	No	NS	47	0	19	No
Protopopescu *et al.* [16]	2001	Dissimilarity measure	41	46	261	73.9	Algorithmic	Yes	Yes	No	60	95	0	NS	No
Jerger *et al.* [17]	2001	Seven different measures	4	12	1	0	Algorithmic	Yes	Yes	No	3	100	NA	2	No
Navarro *et al.* [18]	2002	Similarity index	11	41	53−142	12−60[c]	Algorithmic	No	Yes	No	90	83	0.31[c]	8	No
Schindler *et al.* [19]	2002	Simulated neuronal cells	7	15	144	NS	Algorithmic	Yes	No	No	Variable	100	NS	83	No
Mormann *et al.* [20]	2003	Synchronization/correlation	10	14	31	15	Algorithmic	Yes	No	No	240	86	0	86/102[h]	Yes
Mormann *et al.* [21]	2003	Phase synchronization	18	32	117	49	Algorithmic	Yes	No	No	240	81	0	4−221	No
De Clercq *et al.* [22]	2003	Similarity index	12	NS	NS	0	Algorithmic	No	Yes	No	60	0	NA	–	No
Niederhauser *et al.* [23]	2003	Sign periodogram transf.	5[a]	31	336	335	Algorithmic	Yes	Yes	No	2	94	0.08[f]	5−80 s	No
Chávez *et al.* [24]	2003	Phase synchronization	2	6	22	9	Proof of principle	Yes	Yes	No	90	NS	NS	≫ 30	No
Hively and Protopopescu [25]	2003	Dissimilarity measure	41	46	261	73.9	Algorithmic	Yes	No	No	60	88	0.02	35	No
D'Alessandro *et al.* [26]	2003	Feature selection	4	46	NS	160	Algorithmic	Yes	Yes	No[d]	10	63	0.28	3	No
Iasemidis *et al.* [27]	2003	Dynamical entrainment	5	28[b]	214	NS	Algorithmic	No	No	Yes	180	83	0.17[f]	100	No
Winterhalder *et al.* [28]	2003	Similarity index	21	88	588	509	Algorithmic	Yes	Yes	No	30[e]	42	0.15	NS	No
Aschenbrenner-Scheibe *et al.* [29]	2003	Correlation dimension	21	88	588	509	Algorithmic	Yes	Yes	No	50[e]	34	0.10	NS	No
Van Drongelen *et al.* [30]	2003	Kolmogorov entropy	5	5	5	0	Algorithmic	Yes	No	No	60	60	NA	21	No
Li *et al.* [31]	2003	Marginal predictability	8	24	37	13.3	Statistical	No	No	No	60	NS	NS	NS	No
Drury *et al.* [32]	2003	Marginal predictability	14	44	59	14.7	Statistical	No	No	No	60	NS	NS	30	No
Maiwald *et al.* [33•]	2004	Accumulated energy	21	88	588	509	Algorithmic	Yes	Yes	No	32[e]	30	0.15	NS	No
Gigola *et al.* [34]	2004	Accumulated energy	4	13	26	10.5	Statistical	Yes	NS	No	70	92	0	NS	No
D'Alessandro *et al.* [35••]	2005	Feature selection	2	19[b]	177	140	Algorithmic	No	No	Yes	10	100/13[g]	1.10/0.71[g]	2/NS[g]	No
Esteller *et al.* [36]	2005	Accumulated energy	4	42	294	> 168	Algorithmic	Yes	Yes	No[d]	180[e]	71	0.11[f]	85	No
Harrison *et al.* [37]	2005	Accumulated energy	5	51	311	< 92	Statistical	No	No	No	60	0	–	–	No
Iasemidis *et al.* [38]	2005	Dynamical entrainment	2	11[b]	41	> 8	Algorithmic	No	No	yes	120	82	0.15[f]	78	No
Jerger *et al.* [39]	2005	Synchronization/correlation	1	9	18	9	Statistical	No	No	No	60	22	–	–	Yes
Jouny *et al.* [40]	2005	Complexity/synchrony	2	25	177	NS	Statistical	No	No	No	60	0	–	–	No
Le Van Quyen *et al.* [41•]	2005	Phase synchronization	5	52	305	25−120	Algorithmic	Yes	No	No[d]	Variable	69	n.s	187	No
Mormann *et al.* [42••]	2005	30 different measures	5	51	311	> 107	Statistical	Yes	Yes	No	5−240[e]	NS	NS		Yes
Kalitzin *et al.* [43•]	2005	Phase clustering	3	20	> 75	NS	Statistical	Yes	Yes	No		NS	NS		No
Navarro *et al.* [44•]	2005	Similarity index	13	129	227	0	Algorithmic	No	Yes	No	120	64	NA	> 13	No
Chaovalitwongse *et al.* [45••]	2005	Dynamical entrainment	10	64[b]	597	> 404	Algorithmic	No	No	Yes	180	69	0.15[f]	72	Yes[i]
Harrison *et al.* [46]	2005	Correlation dimension	20	960	2347	NS	Statistical	Yes	No	No	90/15[e]	0	–	–	No

Adapted, extended, and updated from Maiwald *et al.* [33•]. NS, not specified; NA, not analyzed.
[a]Selected out of a group of 10 patients.
[b]Results listed are those obtained for out-of-sample testing data after in-sample optimization on training data.
[c]Only from five selected patients.
[d]Algorithm designed to run prospectively, but results are reported for training and testing data together.
[e]Various predefined prediction horizons were analyzed.
[f]Uncorrected false positive rate including preictal periods.
[g]Separate results reported for two different patients.
[h]Separate results reported for two different measures.
[i]Inconclusive validation: surrogate seizure times are not treated in the same way as original seizure times.

phenomena using characterizing measures such as the largest Lyapunov exponent [48], the correlation density [5] or a dynamical similarity index [6,7,11]. The common feature of these studies was that their focus of interest was entirely limited to the preictal period and that they did not include an evaluation of control recordings from the seizure-free interval, so the specificity of the applied techniques was not assessed.

Another group of studies tackled the issue of specificity by comparing preictal changes in dynamics to interictal control recordings, although the findings reported in these studies remained on an exemplary level. One of these proof of principle studies showed that for selected examples from a subgroup of the analyzed patients, the changes in dynamical similarity occurred more frequently before seizures than during the interictal EEG [18]. Another study reported first indications of changes in synchronization between different brain areas before seizures that were not found in exemplary seizure-free recordings [8]. In a review of their own work, Le Van Quyen and coworkers [14] referred to a submitted study including patients with neocortical epilepsy that seemed to confirm these findings. Unfortunately, this study was never published. Some years later, this group published exemplary results using phase synchronization analysis after bandpass filtering of the EEG and reported preictal changes in synchronization to occur predominantly in the beta band [24].

In the first controlled studies comprising defined groups of patients with preictal and interictal control recordings, measures like the correlation dimension [3,4], dynamical entrainment [12] (defined by the authors as the convergence of largest Lyapunov exponents in certain selected channels), accumulated signal energy [13,34], simulated neuronal cell models [19], or phase synchronization [20,21] were shown to be capable of distinguishing interictal from preictal data. These were followed by a number of studies (mostly carried out on more extensive databases) that found a substantially poorer predictive performance than indicated in earlier reports for the correlation dimension [29], the similarity index [28], and accumulated energy [33•]. Around this time a controversy evolved regarding both the reproducibility of earlier studies [22] and the problems and pitfalls associated with nonlinear measures used to characterize EEG time series [49–51].

Around the turn of the millennium when mass data storage capacity became available, epilepsy centers were able to store the complete data acquired during presurgical monitoring without the necessity of selecting sample recordings. In 2005 a series of studies from different groups was published that was carried out on a set of five continuous multi-day recordings provided by different epilepsy centers for the First International Collaborative Workshop on Seizure Prediction held in Bonn in April 2002 [52•]. The aim of this workshop was to have different groups test and compare their methods on a joint data basis. Results from the different groups for the most part showed a poor performance of univariate measures, while a slightly superior performance was found for bivariate measures (cf. next section for definition). One of these studies found a discriminative power for interictal and preictal amplitude distributions for certain measures of synchronization that was shown to be significant using a rigorous statistical validation [42••].

The first attempts to test seizure prediction algorithms in a prospective study design [27,35••,38] yielded sensitivities and specificity rates that most epileptologists would consider unacceptable for clinical implementation. Whether the performance of the algorithms was at all better than random was not investigated. A recent study [45••] attempted such a validation based on a method proposed 2 years earlier [53], but the validation concept was not applied correctly so the results must be regarded as inconclusive.

Assessing the performance of a prediction algorithm

In order to judge the relative merit of the different studies on seizure prediction published to date, it is necessary to realize how the performance of a seizure prediction technique is assessed. Most of the prediction techniques published up to now have certain common features. They use a moving window analysis in which a linear or nonlinear characterizing measure is calculated from a window of EEG data with a predefined length, then the subsequent window of EEG is analyzed, etc. The duration of these analysis windows usually ranges between 10 and 40 s. Depending on whether the employed measure is used to characterize a single channel or relations between two or more EEG channels, it is referred to as a univariate, bivariate or multivariate measure, respectively. The moving window analysis thus renders time profiles of a characterizing measure for different channels or channel combinations.

The study design used to evaluate these time profiles in a next step can be either statistical or algorithmic. A statistical design is retrospective by nature and usually compares the amplitude distributions of the characterizing measures from the interictal with those from the preictal period in one way or another. The temporal structure of the time profiles is typically not preserved in this type of analysis. Such a design can be useful to investigate and compare the potential predictive performance of different characterizing measures under different conditions.

An algorithmic analysis, in contrast, uses a design that produces a time-resolved output, that is, an output for every point of a time profile. For, practical applications, the algorithm should ideally be prospective, that is, its output at a given time should be a function of the information available at this time. Prediction algorithms usually employ certain thresholds. If the time profile of a characterizing measure crosses the threshold, the algorithm produces an alarm. This alarm can be either true or false, depending on whether it is actually followed by a seizure or not. For this distinction, it is necessary to define a prediction horizon – the period after an alarm within which a seizure is expected. If an alarm is followed by a seizure within the prediction horizon, it is classified as a true alarm (true positive), otherwise it is regarded as a false alarm (false positive). In addition, it may be useful to require a minimum time interval between an alarm and a seizure occurrence for this alarm to count as a successful prediction if the algorithm is to be used for seizure prevention. This minimum intervention time can be introduced as an additional constraint. (Note that in the literature, different definitions are used for these quantities, e.g. one group has used the term 'seizure occurrence period' instead of prediction horizon and 'seizure prediction horizon' for the minimum intervention time [28,29,33•].) In studies that employ a statistical instead of an algorithmic design, the prediction horizon corresponds to the assumed preictal period.

If a seizure is not preceded by an alarm within the prediction horizon, this will be counted as a false negative. The sensitivity of a prediction algorithm is usually quantified as the number of seizures with at least one alarm within the preceding prediction horizon divided by the total number of seizures. In order to statistically quantify the specificity of a prediction algorithm, most studies have reported specificity rates measured in false predictions per hour. Note, however, that different definitions for false positive rates are in use. Several groups have determined false prediction rates by counting all false positives and dividing this number by the total duration of the analyzed recording [23,27,36,38,45••], thereby ignoring that for each seizure contained in the recording, there is a preictal period (i.e. the prediction horizon) during which every alarm is counted as a true prediction and false predictions cannot occur by definition. Other groups have therefore used corrected false prediction rates that were calculated only for the interictal period (i.e. the inter-seizure interval without the preictal period) [20,21,28,29,33•].

In this context it is important to realize that a reported false prediction rate cannot be judged independent from the prediction horizon since in a prospective prediction algorithm a false alarm will leave the patient mistakably awaiting a seizure for the duration of the prediction horizon. It is only after this duration that the patient will know if the alarm was a false warning or not.

Consider as an example an algorithm with a 2 h prediction horizon that yields a sensitivity of $9/11 = 82\%$ of seizures and an uncorrected false prediction rate of $6/41\ \mathrm{h} = 0.15/\mathrm{h}$ [38]. Such a performance means that a patient will on average (assuming that seizures and false prediction rates are uniformly distributed over time) spend $6 \times 2/(41 - 11 \times 2) = 63\%$ of the interictal period waiting for a seizure that will not occur while still failing to anticipate every fifth seizure. An algorithm yielding the same results for a prediction horizon of 10 min would instead leave the patient in futile expectation of a seizure only in 3% of his seizure-free time. This example shows that a prediction rate should be judged in view of the prediction horizon used by the algorithm and that it is the product of these two quantities that should be compared across studies.

A better way to assess the specificity of a prediction algorithm would be to report the portion of time from the interictal period during which a patient is not in the state of falsely awaiting a seizure.

Another important issue in the evaluation of a prediction algorithm is the use of a-posteriori information. For a prospective prediction algorithm, this type of information is not available. Two typical cases of using a-posteriori information are found in the literature: in-sample optimization of parameters of the algorithm, and a-posteriori selection of one or more channels with optimum performance.

In-sample optimization or training of parameters is present whenever parameters used for the calculation of the characterizing measure of the EEG or of the prediction algorithm itself are adjusted to produce optimal performance of the algorithm for a given set of data. Such an optimization is likely to result in an overestimated performance that will not be reproducible when applying the algorithm to other, out-of-sample testing data that were not used in the optimization process. In order to assess the true performance of a prediction algorithm, it is therefore inevitable to test it on out-of-sample on independent data.

Another way of using a-posteriori information relates to the selection of channels that are able to discriminate an interictal from a preictal state. The large majority of studies have shown that out of the available number of recording channels, only a limited number carry information that can actually be used for the detection of a preseizure state, while the remaining channels are likely to increase the number of false detections without contributing to the detection sensitivity of an algorithm. The task at hand is to decide in advance which channels are best suited for the purpose. While many early studies reported preictal changes in channels within or close to the seizure onset zone [3–7], more recent ones have found channels in more remote, in some cases even contralateral, areas to carry the relevant information [21,26,35••,36,41•,42••].

Several studies have attempted to tackle this problem by using the first few seizures to select the appropriate channels for the algorithm before trying to detect precursors of the seizures that follow [26,35••,36,41•]. Such a procedure implies that the spatio-temporal dynamics preceding a seizure do not change from seizure to seizure. Iasemidis *et al.* [27,38] designed an algorithm using a selection of channels that is re-adjusted after every seizure such that it would have been optimal for the seizure that has just occurred. Such a procedure is based on the implicit assumption that preictal dynamics change to a certain degree from seizure to seizure, but that the preictal dynamics of a seizure still depend on the dynamics of the previous one. If these algorithms proved to be better than random prediction, they could provide valuable clues for new theories on the mechanisms involved in ictogenesis, as well as being beneficial to patients.

If an algorithm is designed to run prospectively, its quasi-prospective out-of-sample performance can be tested retrospectively on continuous long-term recordings that were not previously used for parameter optimization or channel selection. Once this quasi-prospective performance (in terms of correct alarms and false alarms for the given prediction horizon) has been assessed, it remains to be tested whether it is indeed superior to that of an algorithm working with random prediction. For this aim, Winterhalder *et al.* [38,54] have designed a framework to assess the performance of such a random predictor.

In retrospective statistical studies on predictability, however, it may be desirable to investigate and compare the potential predictive performance of different characterizing measures allowing different thresholds and parameters. In this case the use of a random predictor for statistical validation would require corrections for multiple testing that can be difficult to perform. Here the concept of seizure time surrogates, as introduced by Andrzejak *et al.* [53], can provide a means for statistical validation. In this process, artificial seizure onset times are generated by randomly shuffling of the original inter-seizure intervals. Using these surrogate seizure onset times instead of the original onset times, the EEG data are then subjected to the same algorithms or prediction statistics that were used for the original onset times. Only if the performance of the algorithm for the original seizure times is better than the performance for a number of independent realizations of the surrogate seizure times can the null hypothesis, namely that a given algorithm cannot detect a preseizure state with a performance above chance level, be rejected. The advantage of this type of statistical validation is that it can be applied to any type of analysis, algorithmic or statistical. A modification of this surrogate test has recently been proposed based on a constrained randomization of the time profile of the characterizing measure [55].

Conclusion

The more rigorous methodological design in recent seizure prediction studies has shown that measures previously considered suitable for prediction perform no better than a random predictor [37,42••]. Evidence has accumulated, however, that certain measures, particularly measures quantifying relations between recording sites, appear to perform significantly better than random prediction [38,41•,42••], even if rigorous statistical validation is applied [42••].

The few studies that have used prediction algorithms in a quasi-prospective manner (i.e. without the use of a-posteriori information) either did not include a statistical validation [27,35••,38] or do not allow conclusions on statistical validity, as the exact same analysis procedure was not applied to the seizure time surrogates as to the original onset times [45••].

The current literature does not allow a definite conclusion as to whether seizures are predictable using prospective algorithms. In order for this question to be answered by future studies, the use of a sound and strict methodology including a rigorous statistical validation is inevitable.

The next necessary step in the field of seizure prediction will be to test retrospectively on long-term recordings whether the prediction algorithms devised to date are able to perform better than a random predictor in a quasi-prospective setting on out-of-sample data. This step is an indispensable prerequisite to justify prospective clinical trials involving invasive seizure intervention techniques such as electrical stimulation.

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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

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 211).

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