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The seizure prediction characteristic: a general framework to assess and compare seizure prediction methods

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Abstract

The unpredictability of seizures is a central problem for all patients suffering from uncontrolled epilepsy. Recently, numerous methods have been suggested that claim to predict from the EEG the onset of epileptic seizures. In parallel, new therapeutic devices are in development that could control upcoming seizures provided that their onset is known in advance. A reliable clinical application controlling seizures, consisting of a seizure prediction method and an intervention system, would improve patient quality of life. The question therefore arises as to whether the performance of the seizure prediction methods is already sufficient for clinical applications. The answer requires assessment criteria to judge and compare these methods, but recognized criteria still do not exist. Based on clinical, behavioral, and statistical considerations, we suggest the "seizure prediction characteristic" to evaluate seizure prediction methods. Results of this approach are exemplified by its application to the "dynamical similarity index" seizure prediction method using 582 hours of intracranial EEG data, including 88 seizures.

Keywords: Epilepsy; Seizure prediction; Intracranial EEG recordings; EEG analysis; Dynamical similarity index; Statistical analysis

1. Introduction

The recurrent and sudden incidence of seizures can lead to dangerous and possibly life-threatening situations [1]. Since disturbance of consciousness and sudden loss of motor control often occur without any warning, the ability to predict epileptic seizures would reduce patients' anxiety, thus improving quality of life and safety considerably [2]. Constraints in everyday life would be alleviated, and secondary behavioral disturbances might be avoided. Knowing in advance that a seizure will occur could widen therapeutic options dramatically. For example, long-term treatment with antiepileptic drugs, which may cause cognitive or other neurological side effects, could be reduced to a targeted and short-acting intervention [3].

During the last decade, several methods have been suggested for prediction of epileptic seizures, based on intracranial or scalp EEG recordings, that use concepts of linear and nonlinear time series analysis [4–16]. It has been claimed that seizures can be predicted at least 20 minutes beforehand, maybe up to 1.5 hours prior to onset for temporal lobe epilepsy. However, there has been so far no evaluation of the performance of seizure prediction methods based on long-term high-quality data [17]. Furthermore, recognized performance standards for assessing and comparing seizure prediction methods are lacking [18]. Up to now, most seizure prediction methods have been evaluated by analyzing few and brief preseizure data sets to obtain their sensitivity. Moreover, no or insufficient interictal data have been investigated to determine their specificity.

In 1998, Osorio et al. proposed that both seizure detection and prediction methods should be evaluated with respect to sensitivity *and* false prediction rate

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[19,20]. We have extended this approach and suggest the "seizure prediction characteristic" to evaluate and compare the performance of seizure prediction methods. This assessment criterion is based on clinical and statistical considerations.

In the following, we focus on the properties and basic requirements of a clinically applicable seizure prediction method, which determine its assessment criterion in a straightforward way. Our approach is illustrated by its application to the "dynamical similarity index," a seizure prediction method introduced by Le van Quyen et al. [7]. For this purpose, we have used intracranial EEG data from 21 patients with pharmacorefractory focal epilepsy. The examined data pool comprises 582 hours of EEG data and 88 seizures.

2. Seizure prediction methods and intervention systems

A clinical application controlling seizures consists of a seizure prediction method that raises an alarm in case of an upcoming seizure and an intervention system that is able to control a seizure (Fig. 1). For a successful application the properties and interdependencies of these two components have to be considered.

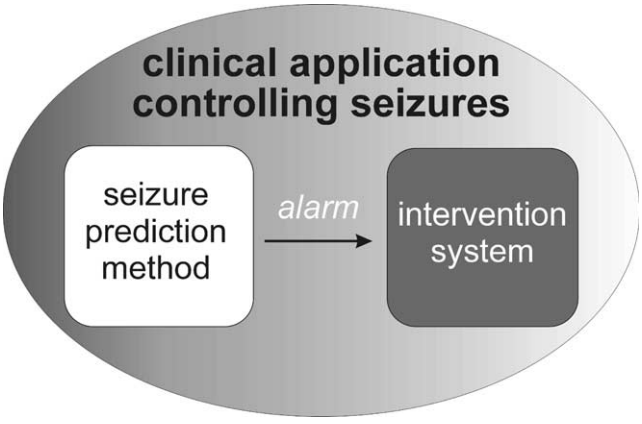

Fig. 1. A clinical application controlling seizures consists of two components: a seizure prediction method raising an alarm in case of an upcoming seizure and an intervention system that is able to control the seizure.

A seizure prediction method has to forecast an upcoming epileptic seizure by raising an alarm in advance of seizure onset. A perfect seizure prediction method would indicate the exact point in time when a seizure is to occur. This ideal behavior is not expected of current prediction methods analyzing EEG data. We suggest considering this uncertainty by use of the seizure occurrence period (*SOP*), which is defined as the period during which the seizure is to be expected. In addition, to render a therapeutic intervention or a behavioral adjustment possible, a minimum window of time between the alarm raised by the prediction method and the beginning of *SOP* is essential. This window of time is denoted as the seizure prediction horizon (*SPH*) (Fig. 2).

These two periods have to be taken into account to judge a correct prediction. For a correct prediction, a seizure must not occur during the seizure prediction horizon, but during the seizure occurrence period. The exact time of seizure onset may vary within *SOP*, thereby reflecting the uncertainty of the prediction. It is preceded by the seizure prediction horizon *SPH*, which mirrors the capability of the method to give an alarm early enough for a proper reaction.

If the seizure prediction horizon were long enough, a simple warning would enable a patient to prepare herself or himself for an arising seizure. He or she could avoid a dangerous situation, for example, a swimming pool or a busy street. Instead of warning the patient, an intervention by an implanted "brain pacemaker" is also imaginable. This device could activate a minipump to deliver anticonvulsive drugs into the epileptic focus or trigger electrical stimulations, controlling the seizure [21].

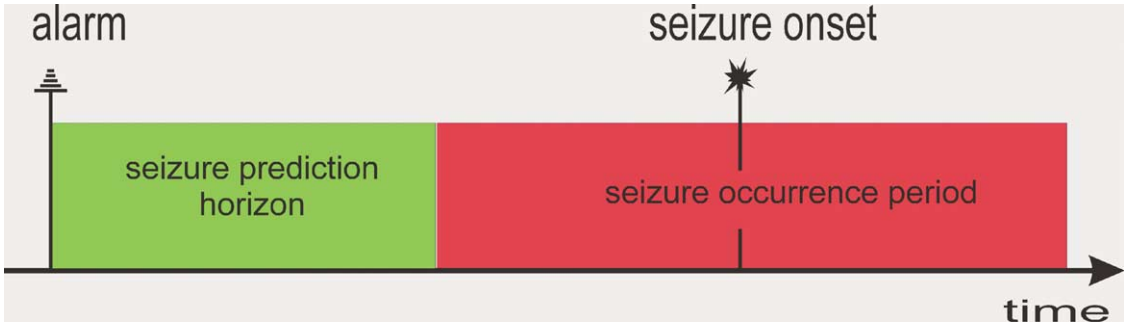

Fig. 2. A seizure prediction method has to forecast an upcoming epileptic seizure by raising an alarm in advance of seizure onset. As a perfect prediction, indicating the exact time of seizure onset, is not expected, consideration of an uncertainty is required. We suggest the seizure occurrence period (*SOP*) to be defined as the period during which the seizure is supposed to occur. In addition, a minimum window of time between an alarm and the beginning of the *SOP* is essential for therapeutic devices. This time window is denoted as the seizure prediction horizon (*SPH*).

3. Sensitivity and false prediction rate

A seizure prediction method should forecast a high percentage of seizures. This "sensitivity" is calculated as the fraction of correct predictions to all seizures. In a realistic setting, false predictions cannot be prevented and have to be permitted if they appear scarcely. They are quantified by the number of false predictions in a given time interval, the false prediction rate (*FPR*), which is the appropriate measure for specificity in the present context.

To increase sensitivity, the parameters of a seizure prediction method may be adjusted for each patient. Unfortunately, this also influences the false prediction rate, as shown by the following example. Let us assume a seizure prediction method based on a feature extracted from the EEG data, which has significantly higher values during preictal than during interictal states. Crossing a threshold triggers an alarm. As illustrated in Fig. 3, lowering the threshold increases the number of crossings and therefore increases sensitivity. After lowering the threshold parameter, the seizure prediction method is not only more sensitive in preictal but also in interictal epochs, leading to more false predictions. In the extreme case of a very low threshold every seizure will be predicted, increasing sensitivity up to 100%. This is achieved at the expense of a large number of false alarms during interictal phases. Because of this interdependency, sensitivity always has to be evaluated together with the false prediction rate.

4. The maximum false prediction rate FPR_{max}

It may not be possible to circumvent false alarms completely, but their negative impact leads to the question of how many of them can be tolerated per time unit. The negative effects of false predictions depend on the chosen intervention system. In the case of a simple warning, the patient prepares himself or herself during the seizure prediction horizon and expects a seizure at any moment during the seizure occurrence period. Since in the case of a false prediction, the seizure will not arise during this time, the patient is unnecessarily scared. Too many false alarms may result in the effect that patients will not take further alarms seriously and will be un-

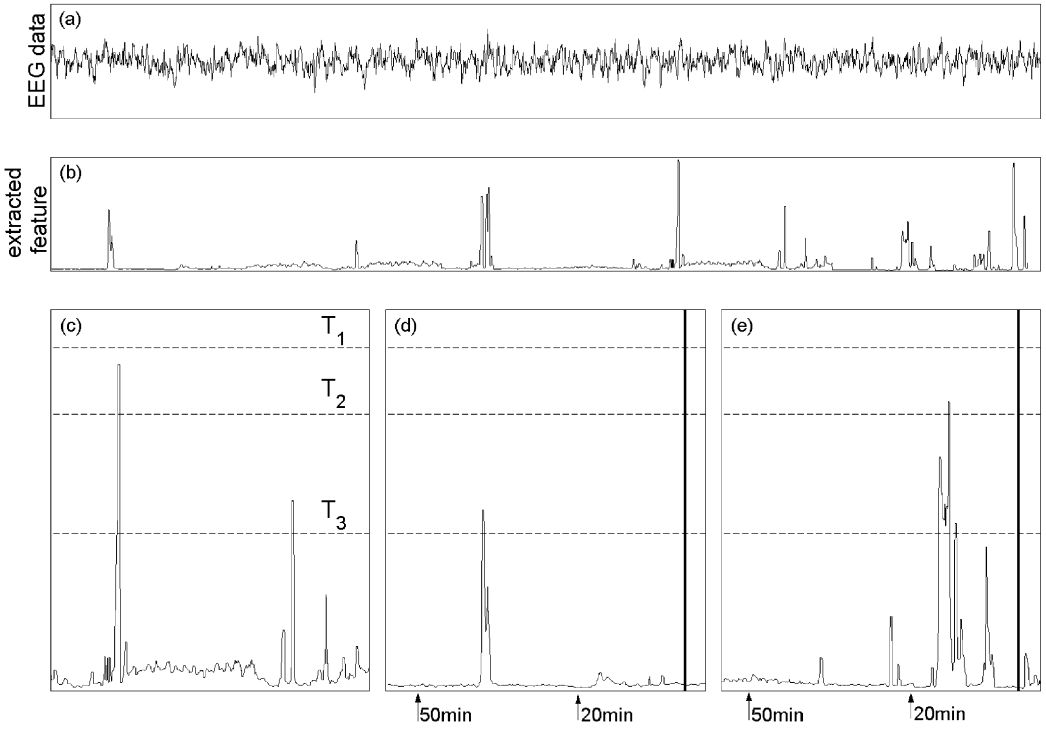

Fig. 3. (a,b) Examples of EEG data (a) and an extracted feature (b) used by a seizure prediction method. (c–e) One-hour interictal (c) and two-hour preictal (d,e) epochs. Bold vertical lines mark seizure onsets. Upward crossing of a threshold triggers an alarm. Three different thresholds (dashed lines) illustrate the dependency between sensitivity and false prediction rate: For T_1 no alarm occurs either during the preictal or interictal phases, meaning zero sensitivity and zero false predictions. Threshold T_2 leads to the correct prediction of the second seizure in (e) in a time interval 20 minutes before seizure onset, at the expense of one false prediction during the interictal epoch in (c). Decreasing the threshold to T_3 to predict the first seizure in (d) produces another false alarm. Hence, ignoring the false prediction rate may yield a high sensitivity when adapting the seizure prediction method's parameters. For evaluation of a prediction method the simultaneous calculation of sensitivity and false prediction rate is required.

prepared for seizures. On the other hand, patients taking all alarms seriously will potentially suffer from a huge psychological stress.

Interventions like the administration of anticonvulsive drugs and triggering an electrical stimulation are accompanied by possible side effects which may add up to relevant neuropsychological impairment, if too many interventions based on false predictions are carried out. Hence, depending on the patient and chosen intervention system, a maximum false prediction rate ($FPR_{\max}$) has to be defined that is still acceptable from a clinical point of view.

The average seizure incidence may indicate a reasonable range for $FPR_{\max}$. In the setting of presurgical monitoring there is an artificially high seizure frequency due to the reduction of anticonvulsive medication. Here, a maximum averaged number of 0.15 seizure per hour, or 3.6 seizures per day, was reported [22]. Under normal conditions, patients with pharmacorefractory focal epilepsy have a mean seizure frequency of about three seizures per month, meaning 0.0042 seizure per hour [23]. Values of $FPR_{\max}$ higher than the mean seizure frequency of 0.15 seizure per hour during monitoring are questionable with respect to possible clinical applications. Even if all seizures can be predicted correctly, at least 50% of all alarms would be false alarms for patients during monitoring. This percentage increases to 97% in the case of epileptic patients under normal conditions.

5. Minimum seizure prediction horizon ($SPH_{\min}$) and maximum seizure occurrence period ($SOP_{\max}$)

All intervention systems require a certain period to become effective. Whereas implanted devices may need only a few seconds to control an upcoming seizure, a warning system has to predict the seizure at least tens of seconds before onset, providing enough time to prevent dangerous situations. This intervention period determines the minimum seizure prediction horizon ($SPH_{\min}$) for a successful clinical application.

Similarly, the chosen intervention system determines the maximum seizure occurrence period ($SOP_{\max}$). Because the exact point of time for seizure onset is unknown, interventions like electrical stimulation and delivery of anticonvulsive drugs should have effects lasting the whole seizure occurrence period. Longer occurrence periods may increase the risk of additional side effects of such a prolonged intervention. This determines an upper limit for the seizure occurrence period.

In case of a warning system, the patient's psychological stress increases with longer seizure occurrence periods, because a seizure is expected at any moment during this interval. Seizure occurrence periods that are too long contribute to the patient's anxiety. Clinical considerations have to determine a maximum stress level leading to an upper bound for the seizure occurrence period.

Apart from clinical aspects, comparison with unspecific prediction methods gives insight into a reasonable scale for the seizure occurrence period, based on statistical relations.

6. Unspecific seizure prediction methods

Seizure prediction methods should have a significantly higher sensitivity than unspecific ones like the random and periodical prediction methods.

6.1. Random prediction method

One unspecific prediction method is random prediction, in which alarms are triggered completely randomly without using any information from the EEG. The relation of the random prediction method to any other method is as follows: In general, the parameters of a seizure prediction method are adjusted to increase sensitivity until the false prediction rate equals the upper bound $FPR_{\max}$. Then, during a small interictal time interval I the probability of an alarm is $p = FPR_{\max} \cdot I$. Observing a longer time interval W, the probability P of at least one alarm can be calculated as

$$P = 1 - (1 - FPR_{\max} \cdot I)^{W/I} \approx 1 - e^{-FPR_{\max} W} \quad \text{for } I \ll W.$$

For $W = SOP$, this is exactly the sensitivity of a random prediction method, because it is the probability of at least one alarm during the seizure occurrence period.

6.2. Periodical prediction method

The periodical prediction method is another unspecific prediction method in which no information from the EEG is used. Here, alarms are raised periodically. If during interictal phases the false prediction rate equals $FPR_{\max}$, the probability P of an alarm during the seizure occurrence period SOP is

$$P = \min\{FPR_{\max} \cdot SOP,\ 100\%\}.$$

This is the sensitivity of a periodical prediction method.

In the case of high values of SOP or $FPR_{\max}$, both unspecific prediction methods achieve high sensitivity approaching 100%. For example, if we consider a maximum false prediction rate of one false prediction per hour (FP/h) and a seizure occurrence period of 50 minutes, the random prediction method yields a sensitivity of 57%, and the periodical prediction method, a sensitivity of 83%. Hence, for maximum false prediction rates, which are too high, or seizure occurrence periods, which are too long, the performance of any specific seizure prediction method cannot be distinguished from the results of these unspecific prediction methods.

7. Assessing seizure prediction methods

The parameter set of a seizure prediction method is adjusted until the method is most sensitive without producing false predictions exceeding the upper bound $FPR_{\max}$. Therefore, interictal data of at least $1/FPR_{\max}$ duration are required to verify the condition for the false prediction rate. For example, to verify $FPR_{\max}$ corresponding to one false alarm per day, at least 24 hours of interictal data are necessary. During this time interval only one false prediction is permitted. Even more EEG data are needed to examine the prediction method's performance with a maximum false prediction rate of the same magnitude as the mean seizure frequency of three per month, typically for patients with pharmacorefractory focal epilepsy.

The values for the maximum false prediction rate $FPR_{\max}$, the minimum seizure prediction horizon $SPH_{\min}$, and the maximum seizure occurrence period $SOP_{\max}$ depend on a particular intervention system, which is generally unknown at the time of the development of a particular seizure prediction method. Therefore, the prediction method should be evaluated for a reasonable range of $FPR_{\max}$, SPH, and SOP. Consequently, a seizure prediction method cannot be assessed by a single parameter, but its performance is mirrored by the dependence of sensitivity S on the maximum false prediction rate, the seizure prediction horizon, and the seizure occurrence period for a given seizure prediction method, leading to the seizure prediction characteristic

$$S = S(FPR_{\max}, SPH, SOP).$$

This approach enables the assessment and comparison of various seizure prediction methods independently of any particular clinical application. As a minimum requirement, a seizure prediction method should be superior to unspecific seizure prediction methods, such as the random or periodical prediction methods, by achieving a significantly higher seizure prediction characteristic.

8. An application: the dynamical similarity index method

Le van Quyen et al. introduced a seizure prediction method called "dynamical similarity index" [7]. In several studies, they applied their method to EEG data from patients suffering from temporal lobe epilepsy [8,9] and neocortical epilepsy [15]. We implemented the dynamical similarity index as introduced in [7]; a brief description of the method is given in Appendix A.

The dynamical similarity index was applied to a large data pool of intracranial EEG data from 21 patients suffering from pharmacorefractory focal epilepsy. The data were recorded during presurgical epilepsy monitoring with invasive electrodes. Preictal period was defined as the period preceding the first unambiguous electrographic ictal EEG pattern in clinically manifest seizures, as judged by certified epileptologists. For every patient, 2–5 seizures (mean 4.2) with preictal periods of 50 minutes and 24 hours of interictal data sets were analyzed. Altogether 582 hours of EEG data, including 88 seizures, were investigated.

For the dynamical similarity index, the average seizure prediction characteristic $S(FPR_{\max}, SPH, SOP)$ for all patients was calculated in the aforementioned manner. Figs. 4 and 5 display the seizure prediction characteristic with fixed values for $SOP = 30$ minutes and $FPR_{\max} = 0.15$ FP/hour, respectively. In both figures, SPH is fixed to 5 seconds, corresponding to the minimum seizure prediction horizon of very fast intervention systems. The dotted lines display the performance of the periodical prediction method; the dashed lines, the random prediction method.

The logarithmically scaled maximum false prediction rate $FPR_{\max}$ covers three regions (Fig. 4): values around $FPR_{\max} = 0.004$ FP/hour correspond to the mean seizure frequency of pharmacorefractory focal epilepsy patients with three seizures per month. Here, contiguous EEG data of several days are required to evaluate the corresponding sensitivity. Our data pool, comprising 24 hours of interictal data for every patient, enables the evaluation of at least one false alarm per day, i.e., 0.042 false prediction per hour.

In the middle region, ranging from one false prediction per day up to the averaged maximum seizure frequency during monitoring, 3.6 per day, sensitivity amounts to 21–42%. However, the false prediction rate is at least 10 times higher than the mean seizure frequency under normal conditions.

For higher maximum false prediction rates up to $FPR_{\max} = 1$ FP/hour, sensitivity strongly increases and reaches values close to 100%. The reason for this is evident: After an alarm, the seizure prediction method is inactivated and produces no further alarms during the seizure prediction horizon and the seizure occurrence period. Suppose a maximum false prediction rate of one per hour and a refractory period $SPH + SOP$ of half an hour after every alarm. In this case only half the amount of EEG data is used to test for false predictions. Now, more sensitive parameter settings can be chosen yielding a higher sensitivity. This relation is illustrated by an unspecific periodical prediction method (dotted line): it "predicts" correctly about 50% of the seizures for $FPR_{\max} = 1.0$ FP/hour.

Relating a maximum false prediction rate of $FPR_{\max} = 0.2$ FP/hour to the spontaneous seizure rate of 0.15 seizure per hour in the monitoring setting, 57% of the alarm events would be false predictions. In the general case with three seizures per month, the fraction of false alarms increases up to 98%. Hence, only maximum false prediction rates at least below 0.15 FP/hour are reasonable.

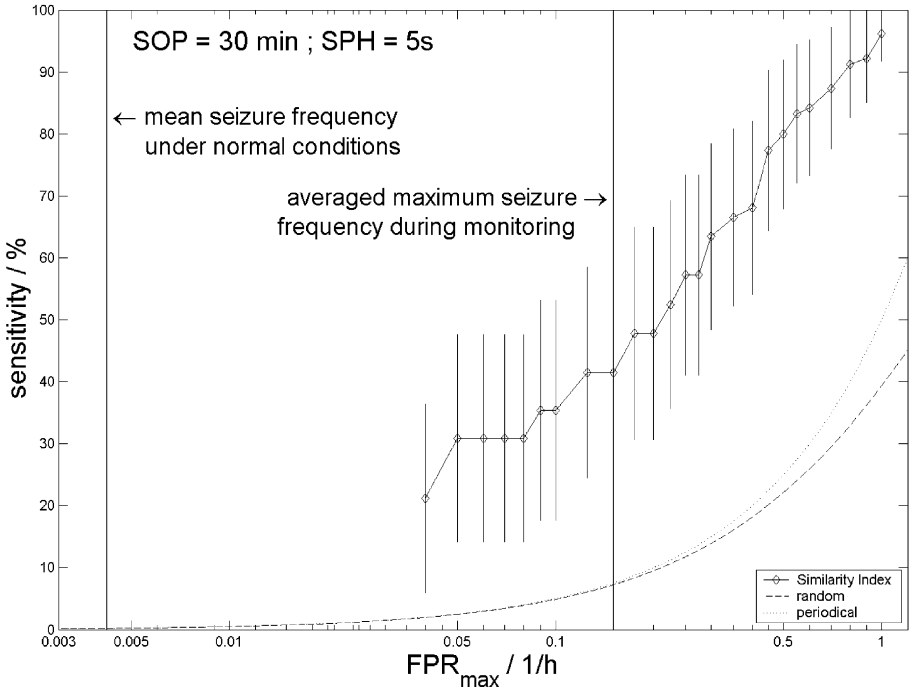

Fig. 4. Seizure prediction characteristic $S(FPR_{\max}, SPH = 5$ seconds, $SOP = 30$ minutes) for the dynamical similarity index with twice its standard deviation calculated from all patients. The dashed line displays the performance of the random prediction method; the dotted line, the periodical prediction method. Vertical lines mark averaged maximum seizure frequencies during epilepsy monitoring and for patients with pharmacorefractory focal epilepsy under normal conditions.

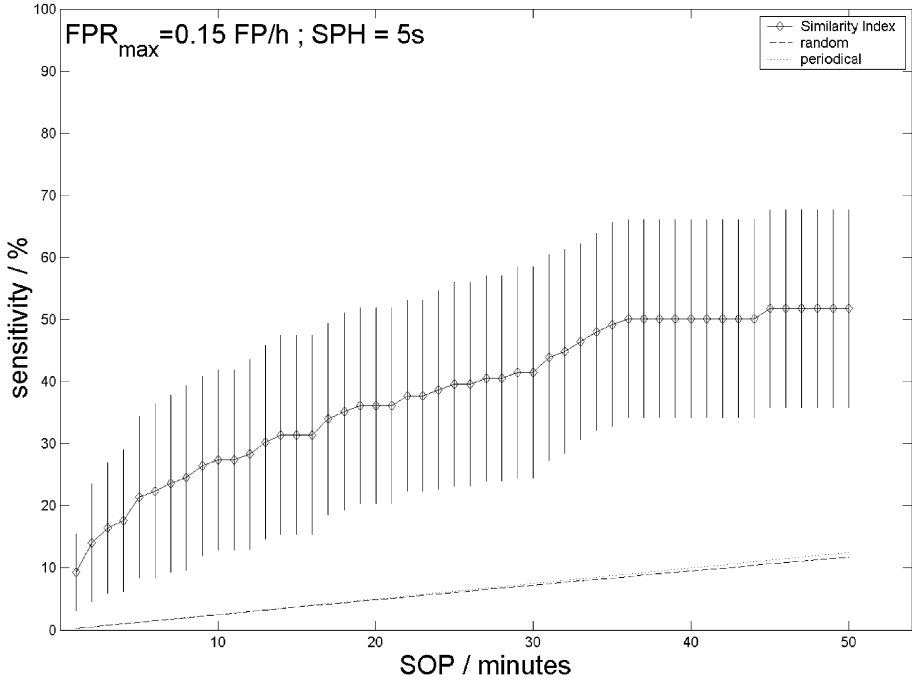

Fig. 5. Seizure prediction characteristic $S(FPR_{\max} = 0.15$ FP/hour, $SPH = 5$ seconds, $SOP)$ for the dynamical similarity index with twice its standard deviation calculated from all patients. The dashed line displays the performance of the random prediction method; the dotted line, the periodical prediction method.

Fig. 5 displays the dependency of the seizure prediction characteristic on the seizure occurrence period (SOP) for a given maximum false prediction rate of 0.15 FP/hour, which corresponds to the averaged maximum seizure frequency during monitoring. For short seizure occurrence periods of a few minutes, sensitivity amounts

to 10–20%. Up to $SOP = 36$ minutes, sensitivity increases faster than for the unspecific prediction methods. For longer seizure occurrence periods, sensitivity plateaus at about 50%. The slight increase in sensitivity for this range cannot be distinguished from the increase in the random and periodical prediction methods, and is therefore not a performance feature of the method.

In summary, the values of the seizure prediction characteristic of the dynamical similarity index are significantly higher than those of the unspecific prediction methods. For a reasonable range of false predictions per hour below the averaged maximum seizure frequency during monitoring, seizure occurrence periods up to 30 minutes, and a small seizure prediction horizon of 5 seconds, its sensitivity ranges from 21 to 42%.

9. Conclusion

The unpredictability of upcoming seizures is a central problem for patients with uncontrolled epilepsy and for their relatives [24]. The level of uncertainty and the associated stress of a patient will be reduced dramatically if a correct prediction of seizures is possible [25], leading to a higher degree of perceived self-control [26]. To contribute to a reduction in uncertainty about the imminent occurrence of a seizure, it is necessary to consider both false and correct predictions.

The above considerations, however, demonstrate that adjusting the parameters of a prediction method to achieve higher sensitivity also increases the false prediction rate. Therefore, to assess seizure prediction methods, the simultaneous calculation of false prediction rate and sensitivity is essential.

Too many false alarms may cause patients to ignore a warning system or lead to possible side effects of unnecessary interventions, causing physiological impairment. A clinical application achieving a high sensitivity at the expense of a high false prediction rate is questionable with respect to the quality of life of patients. Frequent false predictions might even immobilize the patients' coping processes [25] and contribute to the patients' helplessness and depression [27]. Therefore, depending on a chosen intervention system, a maximum false prediction rate has to be determined based on these considerations.

Not only the maximum false prediction rate, but also the values for the minimum seizure prediction horizon and maximum seizure occurrence period have to be based on these considerations. In the case of a warning system, the patient's psychological stress would likely increase with longer seizure occurrence periods. In contrast, a seizure prediction horizon that is too short would not provide enough time to avoid situations that could endanger the patient in the event of a seizure. Hence, for a particular intervention system and depending on clinical and behavioral considerations, a maximum false prediction rate, a maximum seizure occurrence period, and a minimum seizure prediction horizon have to be determined.

As in general an intervention system is unknown during the development of a seizure prediction method, sensitivity has to be calculated for a range of values for the maximum false prediction rate, the seizure prediction horizon, and the seizure occurrence period. This relation is described by the seizure prediction characteristic. It can be determined for any particular seizure prediction method and thus constitutes an objective measure of their performance. It allows not only for an assessment but also for a comparison of different seizure prediction methods. This is a prerequisite for the further development of seizure prediction methods with the aim of improving patients' quality of life.

Appendix A. The "dynamical similarity index"

The "dynamical similarity index" introduced by Le van Quyen et al. [7] compares the dynamic of the EEG data in a sliding window S_t with the data in a fixed reference window S_{ref} of an interictal period. This reference is chosen far from any seizure and lasts 300 seconds.

For the calculation, new time series I_n are computed as time intervals between two positive zero crossings of the EEG data. A delay embedding with dimension $m = 16$ and delay $\tau = 1$ leads to $A_n = (I_n, I_n - \tau, \ldots, I_{n-(m-1)\tau})$. To reduce noise, the trajectory matrices $\boldsymbol{A}(S_t)$ of the sliding window and $\boldsymbol{A}(S_{\mathrm{ref}})$ of the reference window are projected on the principal axes of the reference window, yielding $\boldsymbol{X}(S_t)$ and $\boldsymbol{X}(S_{\mathrm{ref}})$, respectively. The principal axes are calculated by means of a singular value decomposition of the reference window. A random selection $\boldsymbol{Y}(S_{\mathrm{ref}})$ of $\boldsymbol{X}(S_{\mathrm{ref}})$ in the phase space is compared with $\boldsymbol{X}(S_t)$ using the cross-correlation integral

$$C(S_{\mathrm{ref}}, S_t) = \frac{1}{N_{\mathrm{ref}} N_t} \sum_{i=1}^{N_{\mathrm{ref}}} \sum_{j=1}^{N_t} \Theta\left(r - \left\| \vec{\boldsymbol{Y}}_i(S_{\mathrm{ref}}) - \vec{\boldsymbol{X}}_j(S_t) \right\|\right).$$

Here, $\|\cdot\|$ denotes the euclidian norm, Θ the Heaviside step function, and N_{ref} and N_t the number of points in the phase space of the reference and sliding windows, respectively. The distance r is defined as the 30% quantile of the cumulative neighborhood distribution of the reference window.

Finally, the dynamical similarity index $\gamma(S_t)$ is given by

$$\gamma(S_t) = \frac{C(S_{\mathrm{ref}}, S_t)}{\sqrt{C(S_{\mathrm{ref}}, S_{\mathrm{ref}}) C(S_t, S_t)}}.$$

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