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Seizure Prediction in Epilepsy: From Circadian Concepts via Probabilistic Forecasting to Statistical Evaluation

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Abstract— **Seizure prediction performance is hampered by high numbers of false predictions. Here we present an approach to reduce the number of false predictions based on circadian concepts. Based on eight representative patients we demonstrate that this approach increases the performance considerably. The fraction of patients for whom we found a significant seizure prediction performance was increased from 25% to 38% by accounting for circadian dependencies.**

I. INTRODUCTION

Epilepsy is among the most common chronic diseases of the central nervous system. Roughly 0.5% - 1% of the world's population are effected by epilepsy [1]. Approximately one third of the epilepsy patients cannot be treated by common treatment strategies. Surgical resection of the epileptogenic nervous tissue is an option only for a subgroup of these patients. Novel options for treating those patients are urgently needed. A prediction of the time when epileptic seizures occur would not only allow warnings to the patients, such that they could avoid potentially endangering situations, but also enabling closed-loop therapeutic strategies. Short term intervention techniques could be used including EEG-controlled local application of anticonvulsant drugs [2], or closed-loop electrical brain stimulation [3].

During recent years, a number of prediction methods have been developed [4], [5], [6], [7], [8]. Based on linear and nonlinear analysis techniques, pre-seizure changes in the dynamics of intracranial and scalp EEG recordings have been examined and employed for seizure prediction. Evidence for the existence of a pre-seizure state has been given in several studies. So far in studies that involved statistical validation and correction for in-sample optimization, significant seizure prediction performances could only be found in a subset of patients [9], [10].

One of the main challenges is that current seizure prediction studies show high false positive rates. This motivated an investigation towards potential causes for false predictions. It was found that commonly used seizure prediction methods raise a considerable number of false alarms during night time [11]. Since seizures occurring while the patient is sleeping could be considered as less dangerous, a missed seizure during night time can be accepted. In other words, the sensitivity of raising alarms during night time can be reduced. This will eventually avoid false positives. Additionally, allowing more flexibility in the adaptation of thresholds will also likely result in higher sensitivities. Based on these hypotheses, we here designed a seizure prediction study that accounts for night- and day-time. As we base our study on thresholding of certain feature time series derived from the analysis techniques, we use different thresholds for night- and daytime. We emphasize that other techniques than thresholding have been employed for seizure prediction. For this new paradigm, the corresponding assessment and evaluation strategies have been adjusted.

The manuscript is structured as follows. First the database that is used for this study is described. In Sec. III the methods are introduced followed by discussing the assessment and evaluation strategies in Sec. IV. The approach for including circadian characteristics is presented in Sec. V together with the explanation of the necessary changes to the evaluation strategies of Sec. IV. Results will be presented in Sec. VI. The possibility to use probabilistic forecasting for circadian seizure prediction approaches will be suggested in Sec. VII.

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II. DATABASE

The databased used in this study consists of 8 representative patients suffering from focal epilepsy (Tab. 1). Seizures were located in different brain areas which are the hippocampus (H) or neocortex (NC) and were of different types, i.e. simple partial (SP), complex partial (CP) or secondarily generalized (SG). Data were recorded during presurgical monitoring. Electroencephalography (EEG) electrodes, either depth (D), grid (G) or strip (S), were implanted and used for recording. The total recording duration was approximately 1400 h. During this period in total 172 seizures occurred. The outcome after surgery was in 4 out of 8 patients excellent, Engel classification [12] Ia, while in one patient it was IIb and in three patients there was so far no outcome, i.e. no surgery (no). Details can be found in Tab. 1.

III. METHODS

Seizure prediction algorithms and studies all function in a similar way (Fig. 1). The raw data, i.e. in our case electroencephalography (EEG) data, are processed by a seizure prediction method (Fig 1a). This is typically an algorithms originating from the field of linear and nonlinear time series analysis. Many algorithms have actually been suggested and tested so far, for a review see [7]. One of the most promising algorithms investigated in previous seizure prediction studies is the so-called mean phase coherence. The mean phase

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Patient	1	2	3	4	5	6	7	8
Gender	f	m	f	m	f	m	f	f
Age	29	11	11	34	37	35	50	63
Localization	H	NC	H	H	H	H,NC	NC	H
Electrodes	d	g	s,d	s,d,g d	s,d	s,g	s,d	
Seizure types	SP,CP	SP,CP	SP,CP	SP,CP	SP,SG,CP	SP,SG,CP	SP,CP	CP
Outcome	Ia	Ia	no	Ia	Ia	no	llb	no
Seizures	9	54	14	26	7	26	15	21
Recording duration (h)	183.1	141.4	155.0	225.3	260.1	180.0	124.4	118.9

TABLE I

PATIENT CHARACTERISTICS, INCLUDING GENDER, AGE, LOCALIZATION: HIPPOCAMPAL (H), NEOCORTICAL (NC), ELECTRODE TYPES: DEPTH (D), GRID (G), STRIP (S), SEIZURE TYPES: SIMPLE PARTIAL (SP), COMPLEX PARTIAL (CP), SECONDARILY GENERALIZED (SG), ENGEL OUTCOME AFTER SURGERY AS WELL AS THE NUMBER OF SEIZURES AND THE RECORDING TIME.

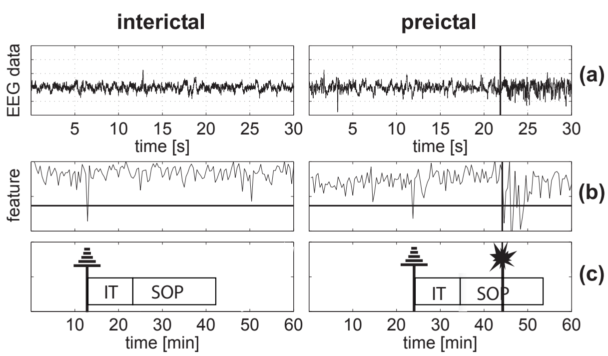

Fig. 1. Basic functioning of seizure prediction algorithms for interictal and preictal epochs; interictal is the time interval between seizures, while preictal is the time span right before a seizure. Raw data, here electroencephalography (EEG) data (a), are analyzed by linear and nonlinear time series analysis techniques leading to features (b) – note the different temporal resolution. Threshold crossings of the feature are considered to be alarms of the device and the two time intervals intervention time (IT)and seizure occurrence period (SOP) start. If there is a seizure in (SOP), the alarm is a true positive.

coherence is a measure for the interaction between pairs of signals, in our case pairs of EEG signals.

The output of this algorithm is referred to as a feature. This feature is used for seizure prediction rather than the raw EEG data. Whenever the feature crosses a certain threshold an alarm is raised (Fig. 1b and c). After the alarm, there is a specific time interval which is the sum of two time windows. These two time windows are the intervention time (IT), allowing the patient to prepare for the upcoming seizure or an automatic intervention to become effective, and the seizure occurrence period (SOP), limiting the time for which the seizure is predicted to occur (Fig. 1c). If a seizure does not start in the time window SOP, the corresponding alarm has to be considered to be a false alarm. Thus, the sensitivity, i.e. the fraction of correctly predicted seizure, as well as the specificity, quantified by the false prediction rate, are determined by the threshold. So far only one fixed but optimized threshold was used.

IV. SEIZURE PREDICTION CHARACTERISTICS AND STATISTICS

To assess the seizure prediction performance we use the so-called seizure prediction characteristics (SPC). It quantifies the sensitivity of a seizure prediction algorithm as a function of three parameters. These three parameters are, first, the specificity assessed by the false prediction rate, second, the intervention time (IT), third, the seizure occurrence period (SOP) (Fig. 1c). The two time windows IT and SOP depend on the desired intervention, which could be a warning of the patient or an automatic application of a drug.

To evaluate whether or not the obtained seizure prediction performance is above chancel level, statistical evaluation is inevitable. Various approaches are conceivable, several have been suggested that utilize Monte-Carlo based approaches, while others are based on analytical considerations. We here follow the analytical evaluation technique [13].

For the analytical approach, critical sensitivity values are derived based on a false prediction rate FPR and the SOP [14], [10]. An uninformative process is utilized which raises alarms with fixed and constant probability at any sampling point. This leads to the probability $P_h = \mathrm{FPR} \cdot h$, where h is the sampling interval. The probability to randomly "predict" a seizure correctly, i.e. the probability to trigger at least one alarm such that the seizure falls in the following seizure occurrence period SOP, can be approximated by $P \approx \mathrm{FPR} \cdot \mathrm{SOP}$ for $\mathrm{FPR} \cdot \mathrm{SOP}$ considerably smaller than one [14].

The random predictor can be corrected for multiple testing which occurs due to the retrospective optimization of the prediction method. For d independent optimizations, the probability to predict at least k of K seizures follows [10]

$$P_d(k,K,P) = 1 - \left[1 - \sum_{j \geq k} \begin{pmatrix} K \\ j \end{pmatrix} P^j (1-P)^{K-j} \right]^d . \quad (1)$$

The critical sensitivity which is achieved by the random predictor based on a significance level α is thus given by

$$\sigma_{\text{analytical}} = \mathrm{argmax}_k \left\{ P_d(k,K,P) > \alpha \right\} / K \cdot 100\,\%. \quad (2)$$

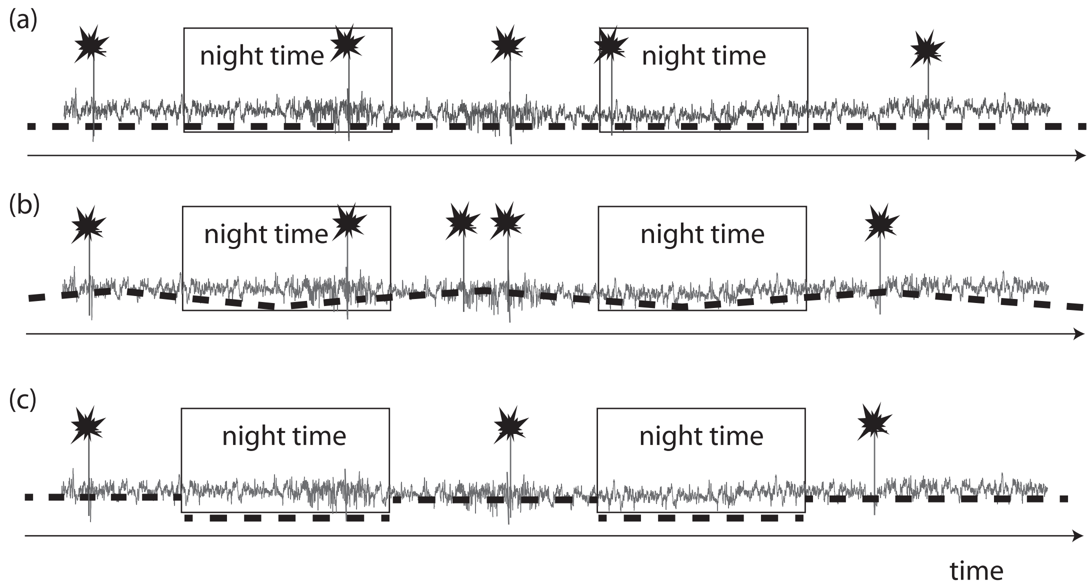

Fig. 2. Schematic drawing of different thresholding (dashed line) strategies, (a) constant threshold, (b) arbitrary threshold function, (c) different but picewise constant thresholds.

If the observed sensitivity of the actual prediction method is larger than the critical sensitivity of the random predictor, it can be regarded statistically significant. In the following we will use $d = 1$ as the lower critical value and the maximum d for the upper critical value.

V. CIRCADIAN RHYTHMS

As mentioned in the Introduction it has been observed that false predictions follow a circadian dependency for several seizure prediction algorithms [11]. This is of particular importance when taking into consideration that usually also more seizures occur during night time. In other words, the fraction of seizures predicted by pure chance is expected to be increased during night as there are simply more seizures. Thus, it is necessary to develop seizure prediction algorithms that take into account the time of the day. This can be achieved by adjusting the threshold of raising alarms for night and daytime separately (Fig. 2).

In Fig. 2a the current approach is depicted. It is based on one threshold that is optimized independently of day- and night-time. Figure 2b presents a long term goal where an arbitrary functional form of the threshold is conceivable. This is approximated here by constant thresholds that might, however, be different during day- and night-time (Fig. 2c). This new flexibility has consequences for the statistical evaluation. A straightforward approach to tackle this statistically is to increase the number of degrees of freedom d by a factor of two accounting for the two different thresholds.

VI. RESULTS

In Fig. 3 the results for the 8 patients are presented. The sensitivity is shown as a bar plot for the standard approach of one threshold (normal – Fig. 2a) and the circadian approach (circadian – Fig. 2c). The false prediction rate was limited to 3.6 false predictions per day. The intervention time was varied between 10 min and 60 min and the seizure occurrence period to 30 min. These are reasonable parameters for issuing warnings. The circadian performance is always higher than the sensitivity of the standard approach. The asterisk denotes statistical significance. The performance of the standard approach is significant in 50% of the patients, while it is significant in 100% of the eight patients for the circadian approach for the lower critical value. For the more important upper critical value we still see an increase from 20% to 30%. Thus, not only the (average) sensitivity increases but also the number of significant cases. We emphasize that both 25% and 38% of the cases are highly significant.

VII. PROBABILISTIC FORECASTING

Using adaptive thresholds is also a step towards probabilistic seizure prediction. In probabilistic seizure prediction the yes/no decisions about upcoming seizures are replaced by probabilistic quantifications of the likelihood for a seizure to come. During night time, the average probability for a seizure would be decreased compared to day time. The arbitrary functional form as presented in Fig. 2b, is closest to the probabilistic concept. The threshold crossing would then be replaced by the probability that can be identified with the current value of the threshold. So the threshold changes its interpretation towards a probability.

The assessment and evaluation for probabilistic seizure prediction is also already developed and can be used to quantify the corresponding seizure prediction performance. This will be investigated in a forthcoming study.

VIII. CONCLUSIONS

A reliable prediction of epileptic seizure would enable novel option for those patients that cannot be treated by

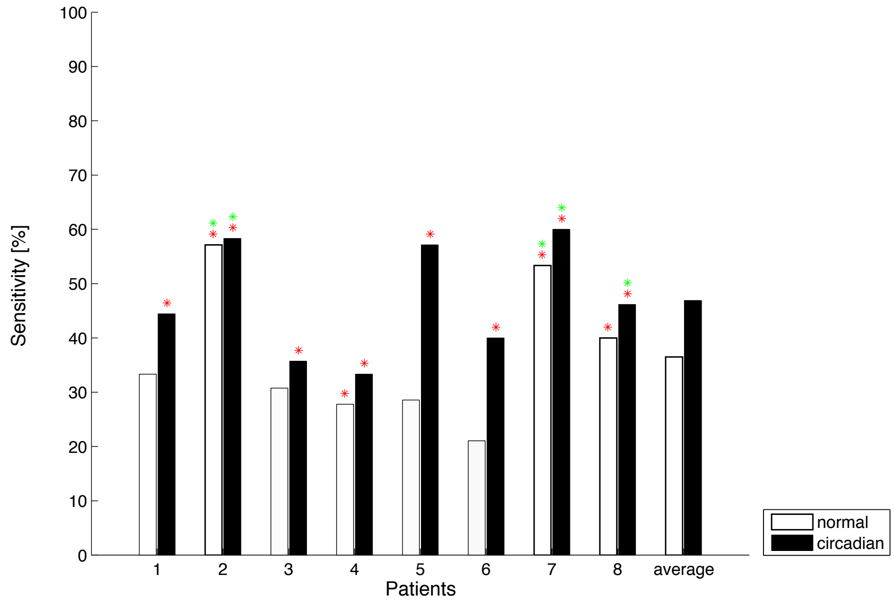

Fig. 3. Results of the performance investigation for the 8 patients for standard thresholding (Fig. 2a) (normal) as well as circadian thresholding (Fig. 2c) (circadian). One asterisk denotes significance to the lower critical value, while two asterisk denotes significance to the upper critical value.

common therapeutic strategies so far. Many published seizure prediction algorithms are, although statistically significant, not yet showing a clinically relevant seizure prediction performance. This is mainly due to the fact that the number of false positives is rather high. Avoiding false positives for fixed sensitivities is thus of utmost importance.

In this manuscript we have presented a strategy to avoid false positive alarms using circadian concepts. We have not used information whether or not a patient is sleeping such that an online implementation of this algorithm is conceivable.

We could obtain a significant seizure prediction performance in approximately 40% of the patients. Additionally the sensitivity could be increased. It is still below a clinically relevant performance but we only used two different thresholds. Allowing for more different threshold values up to an arbitrary functional form will eventually increase the performance further. It might also lead to probabilistic forecasting concepts in the future.

IX. ACKNOWLEDGMENTS

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