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Application of a multivariate seizure detection and prediction method to non-invasive and intracranial long-term EEG recordings

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Abstract

Objective: Retrospective evaluation and comparison of performances of a multivariate method for seizure detection and prediction on simultaneous long-term EEG recordings from scalp and intracranial electrodes.
Methods: Two multivariate techniques based on simulated leaky integrate-and-fire neurons were investigated in order to detect and predict seizures. Both methods were applied and assessed on 423 h of EEG and 26 seizures in total, recorded simultaneously from the scalp and intracranially continuously over several days from six patients with pharmacorefractory epilepsy.
Results: Features generated from simultaneous scalp and intracranial EEG data showed a similar dynamical behavior. Significant performances with sensitivities of up to 73%/62% for scalp/invasive EEG recordings given an upper limit of 0.15 false detections per hour were obtained. Up to 59%/50% of all seizures could be predicted from scalp/invasive EEG, given a maximum number of 0.15 false predictions per hour. A tendency to better performances for scalp EEG was obtained for the detection algorithm.
Conclusions: The investigated methods originally developed for non-invasive EEG were successfully applied to intracranial EEG. Especially, concerning seizure detection the method shows a promising performance which is appropriate for practical applications in EEG monitoring. Concerning seizure prediction a significant prediction performance is indicated and a modification of the method is suggested.
Significance: This study evaluates simultaneously recorded non-invasive and intracranial continuous long-term EEG data with respect to seizure detection and seizure prediction for the first time.

Keywords: Epilepsy; Long-term EEG analysis; Intracranial EEG; Non-invasive EEG; Seizure detection; Seizure prediction

1. Introduction

Epilepsy patients are afflicted with sudden and recurrent brain dysfunctions, which manifest as seizures. Because most patients cannot anticipate seizure occurrences, life-threatening situations may arise in day-to-day situations (Cockerell et al., 1994). Therefore, treatment strategies are needed to reduce the psychological stress on patients and their social environment to improve their quality of life (Murray, 1993).

Nowadays most epilepsy patients are treated by antiepileptic medications. In the case of pharmacorefractory focal epilepsy, surgical removal of brain tissues early involved in the seizure generation is a possible treatment. Diagnostic evaluations of EEG recordings of patients are necessary to determine the seizure onset zone. Patients undergo a long-term monitoring, i.e. simultaneous EEG and video recordings with scalp, and – if necessary – also with intracranial electrodes. Due to the apparent unpredictability of

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seizures, monitoring takes several days to weeks and is accompanied by the collection and visual inspection of large amounts of EEG and video data. Automatic detection of seizure onsets in EEG can facilitate long-term epilepsy monitoring for diagnostic purposes (Gotman, 1990, 1999), e.g. by on-line detection systems that trigger warning mechanism to alert medical staff (Saab and Gotman, 2005).

Seizure warning devices could also be used for more effective therapeutic treatments. For instance, upcoming seizures could be suppressed by electric stimulation or delivery of short-acting drugs (Stein et al., 2000; Osorio et al., 2005). Alarm systems could also be utilized to warn patients. They also allow behavioral adjustments. Such devices would be of particular interest for epilepsy patients to whom present treatments fail or are ineffective.

In recent years, efforts were undertaken to automatically detect and predict epileptic seizures using EEG data. Numerous univariate, bivariate and multivariate algorithms were published based on EEG analysis of single or multiple electrodes to solve the problem of seizure detection (Osorio et al., 1998; Gotman, 1990, 1999; Schindler et al., 2001; Jerger et al., 2001, 2005; Frei et al., 2002; Saab and Gotman, 2005; Bhavaraju et al., 2006) and prediction (Lehnertz and Elger, 1998; Iasemidis et al., 1990; Le van Quyen et al., 1999, 2000; Mormann et al., 2000, 2003a,b, 2006; Le van Quyen et al., 2001a,b; Jerger et al., 2001; Litt et al., 2001; Navarro et al., 2002; Schindler et al., 2002). Especially multivariate approaches have become a focus of attention recently in EEG analysis as promising tools in epilepsy research (Mueller et al., 2006; Bialonski and Lehnertz, 2006; Schindler et al., 2007).

In general, a detection or a prediction method is designed and evaluated with respect to scalp or invasive EEG data. Whereas in most studies seizure detection or prediction has been performed on either intracranial or non-invasive, surface EEG data, it yet remains an open question whether intracranial or non-invasive, surface EEG should be preferred. This paper is motivated by this question.

If one attempts to compare a prediction or detection method based on univariate or bivariate measures applied to scalp and intracranial EEG recordings, the problem arises how to choose the electrodes in order to obtain a reliable comparison between those positioned on the scalp and for example with those positioned at the seizure onset zone. If the electrode or channel combination is not determined in advance by explicit criteria, using different electrode combinations for the comparison and performance evaluation leads to undesirable multiple testing problems (Schelter et al., 2006a).

Hence, in this paper we examined a multivariate method for automatic seizure detection based on neuronal networks using simulated leaky integrate-and-fire neurons, which was introduced by Schindler et al. (2001). It is based on a simulated neuronal cell model that extracts spatio-temporal information from multi-channel EEG recordings, like spatially synchronous, fast-transient and rhythmic activities, as they often appear in EEG patterns from epileptic activity (Engel, 1987; Dichter and Ayala, 1987). In a subsequent publication, a modification of the detection algorithm was presented to detect pre-seizure changes from EEG in order to achieve a prediction of seizure onsets (Schindler et al., 2002). These two algorithms yield measures for seizure detection and prediction, which are characterized by a few continuously adjustable parameters. By definition they predict or detect using a one dimensional feature even though they can take into account information of all EEG electrodes. The here investigated two methods possess the unique advantage that a preselection of electrodes is not necessary and thus the above-mentioned multiple testing problem between performances from different selections of electrode combinations does not emerge.

While both algorithms mentioned above have been applied to scalp and foramen ovale EEG recordings before (Schindler et al., 2001, 2002; Sazonov et al., 2002) we investigated the questions whether these two methods are also applicable to intracranial EEG, what kind of differences will occur when compared with applications to scalp EEG, and whether they perform better on scalp or intracranial EEG data.

To obtain reliable comparisons, we used continuous long-term EEG data from six patients with simultaneous recordings from scalp and intracranial EEG. This allows comparison of the respective features calculated from scalp and invasive EEG recordings for the detection and the prediction method directly. The data comprise long interictal periods, which are necessary for assessing a high specificity. Sleep and awake phases as well as sub-clinical events were not excluded from the data as they are part of a realistic EEG sample and occur also in prospective settings regarding seizure detection and prediction utilizing EEG.

Seizure detection as well as seizure prediction performance were evaluated and compared retrospectively in a patient-individual manner using both types of EEG data. The seizure prediction performance was assessed with the seizure prediction characteristic in terms of sensitivity, specificity, and intervention times (Winterhalder et al., 2003). A reliable prediction method has to be superior to a prediction by chance, hence the evaluated performances were compared with a random predictor (Mormann et al., 2006; Schelter et al., 2006a). For assessing the performance of the investigated detection method, we adapted the concept of the seizure prediction characteristic with its statistical evaluation for seizure detection.

In the following section, we set out the used data pool and the patients' characteristics and give an outline of the investigated methods. The evaluation procedure of the seizure detection and seizure prediction method is described. In Section 3, the results obtained on scalp and invasive EEG recordings are presented and compared. A discussion of the results follows in Section 4.

2. Methods

2.1. EEG data and patient characteristics

The present study was carried out on continuous long-term EEG recordings from six patients. All patients suffered from pharmacoresistant focal epilepsy and underwent a pre-surgical video-EEG monitoring at the Epilepsy Center of the University Hospital Freiburg, Germany. Scalp and intracranial EEG data were recorded simultaneously and continuously over several days. Invasive recordings were performed via stereotactically implanted depth electrodes, subdural strip and grid electrodes, which had been implanted through burr holes or open skull surgery, respectively. For each patient 30–90 focal and extrafocal invasive electrodes and 21 scalp electrodes, placed according to the international 10–20-system, were analyzed. Focal electrodes are defined as early involved in ictal activity while extra-focal electrodes do not show any ictal activity or are involved late in seizure spread. Focal and extra-focal electrodes were determined by a board-certified epileptologist and confirmed through surgical follow-up. In total, 423 h of EEG data with 26 seizures was investigated.

For the EEG analysis reference electrodes had to be chosen. The choice of reference is a crucial point in EEG analysis as it could influence the results depending on the respective analysis method (Zaveri et al., 2000; Schiff, 2005). Here, for each patient a single intracranial electrode was chosen as reference for scalp and intracranial EEG. Thereby, reference electrodes were selected by common criteria, i.e. their signal had to be free of artifacts, they did not show ictal activity, and the electrode was located far from the epileptic area.

For the evaluation of the seizure prediction performance with the seizure prediction characteristic, interictal periods were distinguished from preictal, ictal, and postictal periods in EEG data. Interictal periods are time intervals without clinically manifested seizure activity. We used EEG periods distanced by two hours from an electroencephalographic end of the preceding seizure and the following seizure onset to represent interictal periods. Preictal periods are the time intervals immediately preceding seizure onsets. For each investigated seizure, one hour preceding the electroencephalographic seizure onset was analyzed to cover the preictal period. Subsequent seizures distanced by less than two hours to a preceding seizure were excluded from the prediction analysis to prevent analysis of possible postictal activity from the preceding seizure. Therefore, one seizure of patient 02 and three seizures of patient 04 were not analyzed. The duration of continuous interictal periods varied between 1.9 and 55.5 h. In total, interictal periods of at least 24 h up to 76.8 h per patient were used.

The EEG data comprise circadian variations and different sleep stages but also sub-clinical seizures as well as short interruptions in the time continuous recording sequence due to diagnostic procedures like MR imaging. Characteristics of patients and corresponding EEG data are shown in detail in Table 1. All patients gave their informed consent to the evaluation of their EEG data. Evaluation of data was approved by the Ethics Committee, Medical Faculty, University of Freiburg.

2.2. EEG data acquisition

The EEG data were obtained using a Neurofile NT (TM) digital video–EEG system with 128 channels at a sampling rate of 256 Hz, and a 16-bit A/D converter. An integrated high and low pass filter of the used amplifier limited the recording bandwidth of the EEG signal to 0.032–97 Hz. EEG recordings of surface and intracranial electrodes were further low-pass filtered using a butterworth filter of 8th order with a cut-off frequency of 20 Hz following Schindler et al. (2002). The data were visually inspected by board-certified epileptologists who marked clinical and electroencephalographic events. These time-points were determined in mutual consent of at least two board-certified epileptologists for each patient.

2.3. The seizure detection and prediction algorithm

The investigated multivariate algorithms are described in detail in Schindler et al. (2001, 2002). Substantially, they

Table 1
Characteristics of patients and EEG data

Patient	Sex	Age	Seizure type	Outcome	Electrode type	No. of intracranial Electrodes	Total interictal period [h]	EEG recording total [h]	No. of seizures	Average seizure duration in EEG [s]
01	m	31	SP, CP, GTC	1b	g, s, d, Sca	56	72.9	93.7	4 (4)	100
02	m	25	SP, CP	1a	g, s, d, Sca	90	52.6	74.7	5 (4)	70
03	m	43	SP, CP, GTC	1a	d, Sca	30	76.9	93.4	4 (4)	210
04	f	42	SP	1d	g, Sca	64	24.0	41.1	6 (3)	50
05	m	47	CP, GTC	no surgery	s, d, Sca	75	50.5	69.6	5 (5)	50
06	m	20	SP, CP, GTC	1a	s, d, Sca	40	38.6	50.5	2 (2)	95
						Sum	315.5	423.0	26 (22)	
						Mean	52.6	70.5	4.3 (3.7)	

Abbreviations: m, male; f, female. Seizure types: simple partial (SP), complex partial (CP), generalized tonic–clonic (GTC). Outcome according to Engel classification. Intracranial electrodes: grid (g), strip (s), depth (d). Scalp electrodes (Sca): 21 scalp electrodes placed according to the 10–20-system. Number of seizures analyzed with the prediction method are given in brackets.

focus on local slopes in EEG signals. Times at which the absolute values of the time-differentiated EEG signal exceed a certain threshold T_1 are marked with unit pulses for each investigated EEG channel. The resulting pulse trains are spatio-temporally integrated by simulated leaky integrate-and-fire neurons. Whenever the accumulation of unit pulses reaches a certain threshold T_2, the simulated neurons create a spike and are reset to zero. The integrate-and-fire neurons act as coincidence detectors for synchronous activity between pulse trains. Frequent coincidences and coincidences between many unit pulse trains increase the spiking rate SR, i.e. the number of spikes per second. The spiking rate is used for seizure detection. The algorithm detects a seizure whenever the spiking rate exceeds a fixed threshold.

In order to predict seizures, the detection method has to be modified. An average spiking rate SR_{av} is calculated from SR using a time-causal sliding window with a window length of 20 min and a sliding step size of one second. From the time course of SR_{av}, the feature $F_{Sz}(t)$ is extracted for seizure prediction by

$$F_{Sz}(t) = \sum_{t'<t} \mathrm{sgn}\left(\frac{\mathrm{dSR_{av}}(t')}{\mathrm{d}t'}\right) \quad (1)$$

where sgn denotes a weighting function given by the sign function

$$\mathrm{sgn}(x) = \begin{cases} -1 & \text{if } x < 0 \\ 0 & \text{if } x = 0 \\ 1 & \text{if } x > 0. \end{cases} \quad (2)$$

Whenever the feature $F_{Sz}(t)$ exceeds a fixed threshold, the algorithm detects pre-seizure changes. The time-points of detection of pre-seizure changes were used for predicting seizures.

The continuously adjustable algorithmic parameters T_1 and T_2 were varied patient-individually resulting in several features of the spiking rate and F_{Sz} for each patient. For scalp and intracranial EEG the parameters ranged between $0.4\frac{\mathrm{mV}}{\mathrm{s}} \leqslant T_1 \leqslant 33.8\frac{\mathrm{mV}}{\mathrm{s}}$ and $0.05 \leqslant T_2 \leqslant 15$ (in arbitrary units).

The originally published algorithm uses a posteriori information about the actual occurrence of seizure onset for the computation of the feature $F_{Sz}(t)$, i.e. $F_{Sz}(t)$ is reset to zero whenever a seizure occurs (Schindler et al., 2002). As we wanted to avoid the usage of a posteriori information for the computation of features, we omitted this step in the presented computations. Furthermore, the originally used weighting function was the asymmetric sgn-function, i.e. there were no zero weightings. This function was replaced by the symmetric sgn-function above, but this has only minor effects on $F_{Sz}(t)$, as zero changes of the spiking rate occur rarely in the computation of the feature. Assuming that SR_{av} reflects some kind of spatio-temporal synchronization of electrical activity in the brain, the symmetric weighting function weights only changes, i.e. an increase and decrease of synchronization.

2.4. Retrospective assessment of the performance

Spiking rates SR(t) and features $F_{Sz}(t)$ were computed for each patient from scalp and invasive EEG recordings separately. Pulse trains were calculated from slopes of all available EEG channels and served as input for the integrate-and-fire neurons for the calculation of SR. Features F_{Sz} were obtained from SR as described above. Thresholds were set retrospectively for SR and F_{Sz} as described in Schindler et al. (2001, 2002).

The performance of the algorithm for seizure detection as well as for seizure prediction was assessed retrospectively. The performance was quantified by sensitivity with respect to the false positive rate, i.e. the false detection rate FDR or the false prediction rate FPR, respectively. The false positive rate depends on the parameters of the corresponding algorithm, i.e. different parameters can lead to the same false positive rate but do not have to result in the same sensitivity. To enable a comparison of performances that can be achieved for different patients, sensitivity was estimated for a range of upper bounds of the false positive rates, here denoted as maximum false detection rate FDR_{max} and maximum false prediction rate FPR_{max}. To obtain a unique result, those parameter values were chosen that corresponded to the best sensitivity and lowest effective false positive rate for a given maximum false positive rate. The maximum false positive rate can be regarded as a measure of specificity in the context of seizure detection or prediction and restricts the number of false positives in a given time interval. Note that sensitivity could always be increased at the expense of specificity.

2.4.1. Assessment of the seizure detection performance

Time-points where SR(t) exceeded the threshold were compared with electroencephalographically marked seizure onsets. After a detection, no further threshold crossings were evaluated within a preset patient specific time interval, the mean seizure duration. These time intervals were chosen in order to prevent multiple detections of single seizures. The relative number of correct detections yields estimates of the sensitivity S, while the number of wrong detections in a given time interval results in the false detection rate FDR, which represents the specificity. Sensitivity was estimated for different upper bounds of the false detection rate, given by FDR_{max}.

2.4.2. Assessment of the seizure prediction performance

For the assessment of the seizure prediction method the seizure prediction characteristic S(IT, SOP, FPR_{max}) was used (Winterhalder et al., 2003). Sensitivity S of the prediction method was evaluated depending on three factors: the intervention time IT, the seizure occurrence period SOP, and the maximum false prediction rate FPR_{max}. The intervention time describes the time required for a successful intervention, e.g. allowing the delivery of drugs to prevent an upcoming seizure. For a correct seizure prediction, it is required that no seizure occurs within this time interval.

The seizure occurrence period reflects a possible temporal variability of the occurrence of a predicted seizure.

For each patient the time courses of the features $F_{Sz}(t)$ from scalp and invasive EEG recordings were separated into interictal and preictal periods. Whenever the feature F_{Sz} crossed the threshold in upward direction a seizure was predicted. The prediction was judged to be correct if an electroencephalographic marked seizure occurred within the seizure occurrence period. Sensitivity was estimated on the preictal data segments from the relative number of correct predictions, while the false prediction rate was determined on interictal segments. Sensitivity was estimated for different values of FPR_{max}, IT, and SOP.

The seizure prediction characteristic was compared with the performance of an unspecific random predictor (Schelter et al., 2006a). The random predictor is based on a Poisson process. Its performance can be derived from a binomial distribution with probability $P = 1 - e^{-SOP \cdot FPR_{max}}$. From the performance of the random predictor, a significance level can be calculated. A critical value $\sigma_{rand,\alpha}$ for the sensitivity of a random prediction can be determined analytically as a function of FPR_{max} and SOP, the total amount K of investigated seizures, and significance level α as

$$\sigma_{rand,\alpha} = \frac{1}{K} \max\{k | P_{binom}\{k; K; P\} > \alpha\} \times 100\% \quad (3)$$

with

$$P_{binom}\{k; K; P\} = 1 - \left(\sum_{j<k} \binom{K}{j} P^j (1-P)^{K-j} \right)^d . \quad (4)$$

The parameter d reflects a correction term for multiple testing, when several independent features are used for a performance assessment. Assuming that the investigated features of each patient are not independent, the parameter d is set to $d = 1$ following Schelter et al. (2006a). With these assumptions, a seizure prediction method is significantly better than a random predictor at significance level α, if its sensitivity is higher than the respective critical value $\sigma_{rand,\alpha}$.

The definition of a critical value $\sigma_{rand,\alpha}$ for the sensitivity of a random prediction was adapted for seizure detection. A critical value for the sensitivity of a random detection was calculated analogously by the equations above, where the maximum false prediction rate and SOP were replaced by the maximum false detection rate and the mean seizure duration.

3. Results

In the following, exemplary features of SR and F_{Sz} are shown. The estimated performances are presented for each patient by means of the sensitivity for the detection and prediction method dependent on the corresponding parameters, FDR_{max} and FPR_{max}, SOP, and IT. Comparisons between the results obtained from scalp EEG data and invasive EEG data are shown.

The ranges of parameters are restricted, i.e. SOP was varied between 2 and 30 min and IT between 5 and 30 min, such that IT + SOP $\leqslant$ 1 h, which is the duration of the analyzed preictal periods. The units of FDR_{max} and FPR_{max} are specified by false positive rates per hour,

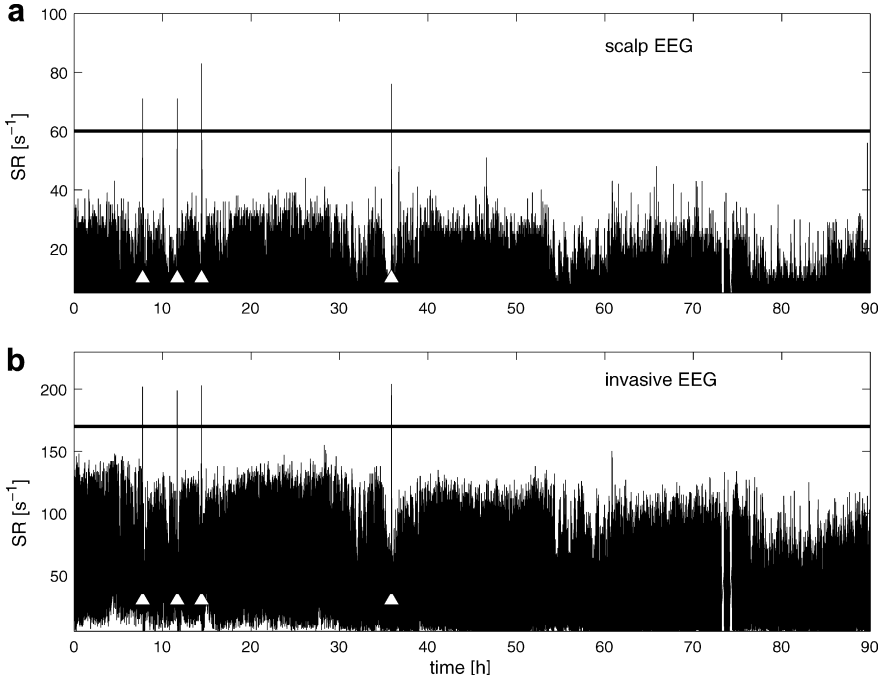

Fig. 1. Detection of seizures: Time course of the spiking rate SR over 90 h calculated on scalp (a) and invasive (b) EEG recordings from patient 01. Electroencephalographic seizure onsets are marked by triangles. An exemplary threshold for SR is given by a horizontal line. At the seizure onsets the spiking rate increases significantly. Threshold crossings coincide with marked seizures in (a) and (b), i.e. all four seizures are detected using scalp as well as invasive EEG data.

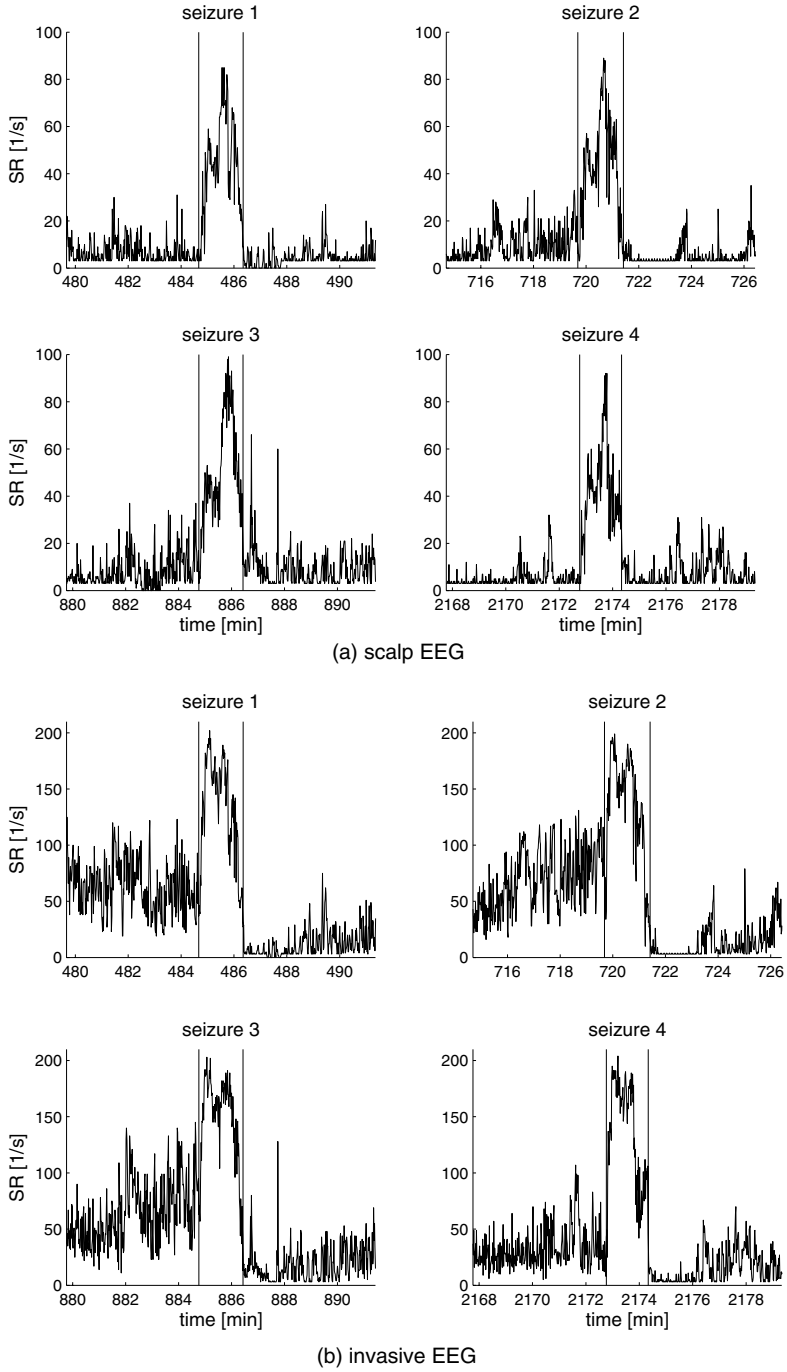

Fig. 2. Extractions of the spiking rate from scalp (a) and invasive (b) EEG data at four seizures of patient 01. The electroencephalographic seizure onsets and seizure ends are marked by vertical lines.

i.e. of number of false detections FD and false predictions FP/h, respectively. The ranges of false positive rates are restricted by the length of the analyzed EEG data. The lower bound for FPR_{max} depends on the length of the interictal periods. The duration of interictal periods in our data pool differs between patients (Table 1). As the minimal length of an investigated interictal period is 24 h, sensitivities for less than one false alarm per day, i.e. 0.042 FP/h, are not available for patient 04. Altogether, FPR_{max} was varied between 0.015 and 0.5 FP/h. Analogously, there are restrictions to FDR_{max} for the seizure detection. For FDR_{max}, we set a lower bound to the minimal length of the EEG recording, i.e. in our case 0.024 FD/h. As an upper reference point for FPR_{max} and FDR_{max} the mean seizure frequency can be used (Maiwald et al., 2004). During presurgical monitoring, an average seizure frequency of 0.15 seizures per hour was reported for pharmacorefractory epilepsy (Haut et al., 2002).

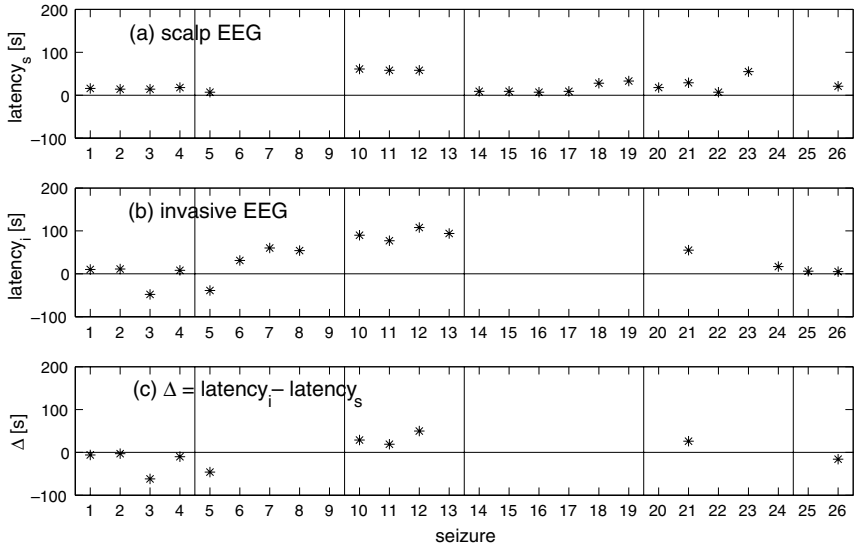

Fig. 3. Latencies of threshold crossing times of the spiking rate from scalp EEG (a) and invasive EEG (b) with respect to the electrographic seizure onset for all investigated seizures of all patients. Negative values represent detection before electrographic seizure onset. The difference $\Delta = \text{latency}_i - \text{latency}_s$, between latencies from invasive and scalp EEG, is shown in (c). Negative values of Δ represent an earlier detection from invasive EEG data and positive values an earlier detection from scalp EEG data, respectively. Vertical lines separate seizures of different patients.

3.1. Results for seizure detection

In Fig. 1, an exemplary time course of a spiking rate is shown. It was calculated from scalp (a) and invasive (b) EEG recordings of patient 01. Electroencephalographic seizure onsets are marked by triangles. The horizontal line represents a threshold for the spiking rate. At each seizure onset the spiking rate increases and crosses the threshold which yields detection times of seizures. For this patient all four seizures were detected from scalp as well as invasive EEG data without false positives.

There is a characteristic dynamic pattern of the spiking rate with a rapid increase and decrease right within the electroencephalographic marked seizure onset and end, which is similar for all four seizures. This is illustrated for this patient in more detail in Fig. 2. For a better visual representation the spiking rate is shown only at regions of several minutes around the seizures. Vertical lines mark the electroencephalographic seizure onsets and seizure ends, respectively. This behavior is observed in features from invasive EEG as well as from scalp EEG, whereas there is a steeper increase of the feature from invasive EEG than from scalp EEG.

Due to this observed different patterns of the spiking rates from scalp and invasive EEG during the seizures, detection latencies and differences in the threshold crossing times between seizures detected from scalp and intracranial EEG data were investigated. In order to compare the threshold crossing times between different features obtained from scalp and invasive EEG, we chose for each feature the smallest possible threshold for a given maximum false detection rate of 0.15 FD/h. The latencies were determined by comparing the detection time-points obtained from scalp and invasive EEG data of respective seizures with their electroencephalographic seizure onsets, i.e. the latency is the difference between the time-point of detection and the time-point of the electroencephalographic onset.

In Fig. 3 the latencies of threshold crossing times of the spiking rate from scalp EEG and invasive EEG with respect to the electroencephalographic seizure onset are shown for all investigated 26 seizures of the six patients. The latencies are in general positive, i.e. most of the seizures are detected after the occurrence of the electroencephalographic seizure onset. The latencies are also compared between scalp and invasive EEG. As not all seizures are detectable from invasive as well as scalp EEG recording, the latencies are only comparable for in total ten seizures of the patients 01, 02, 03, 05 and 06. For patient 01 and patient 02, as well as for patient 06, the differences $\Delta = \text{latency}_i - \text{latency}_s$ between the latencies from invasive and scalp EEG are negative, i.e. an earlier detection was possible using invasive EEG recordings. For patient 03 and patient 05, latency differences Δ are positive and therefore the seizures of these patients were detected earlier using scalp EEG recordings than invasive EEG recordings.

Patient individual results of the detection performances from invasive and non-invasive EEG recordings are presented in Fig. 4. The performances are given in dependence on $\text{FDR}_{\max}$, which was varied between 0.025 and 1 FD/h. For patient 01 a sensitivity of 100% is obtained for all values of $\text{FDR}_{\max}$ with either type of data acquisition. For patient 02, sensitivity increases from 0% to 80% with increasing $\text{FDR}_{\max}$. For this patient there is no clear superiority over performances either from scalp or from invasive EEG recordings. For $\text{FDR}_{\max} < 0.1$ FD/h sensitivity obtained from scalp EEG is higher than sensitivity from

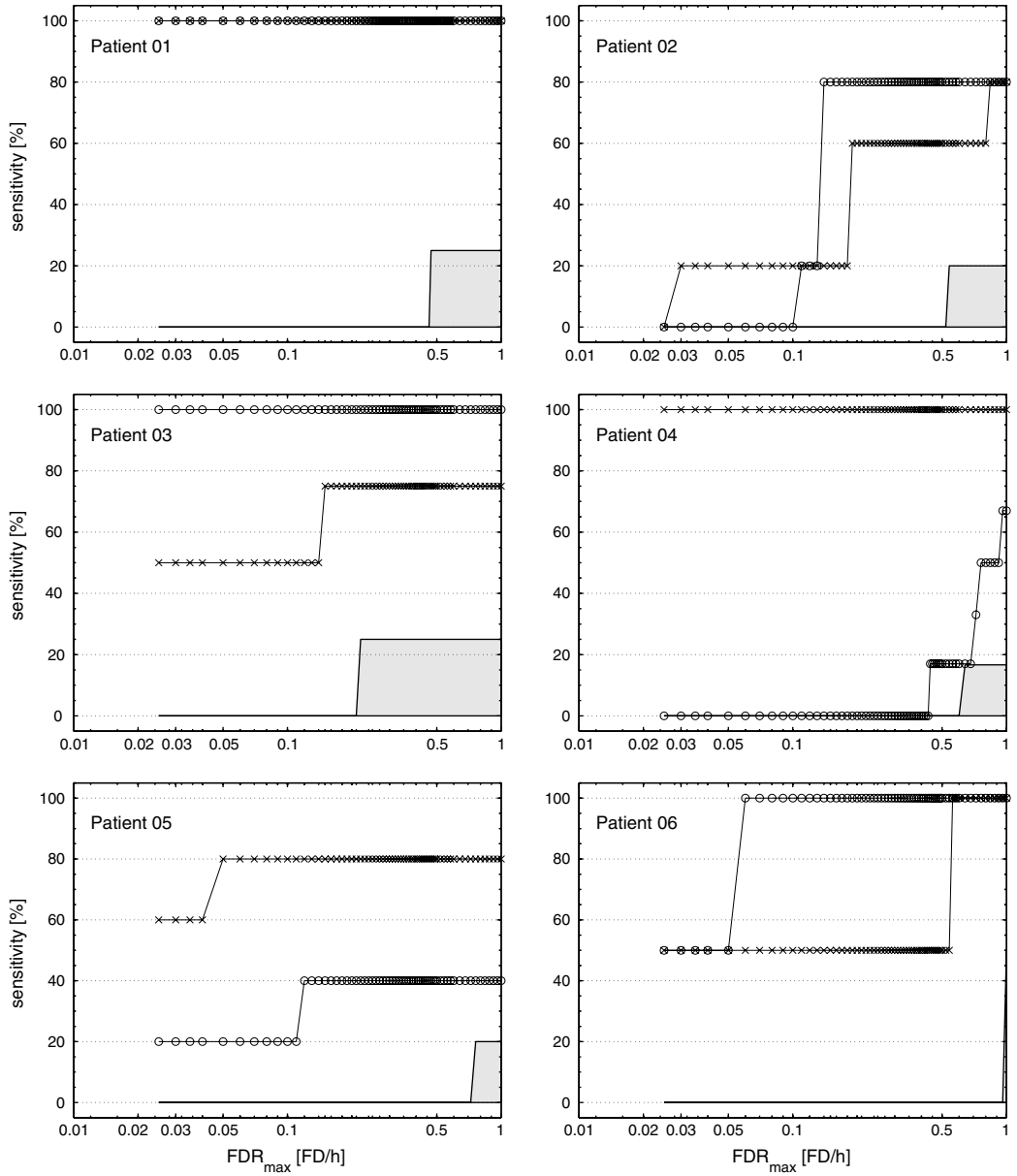

Fig. 4. Sensitivity of the investigated detection method in dependence on the maximum false detection rate for each patient. Different graphs result from the scalp EEG (×) and from invasive EEG (○) recordings. Gray shaded areas mark non-significant regions $\sigma_{\mathrm{rand},0.05}$ of sensitivity.

invasive EEG. For $\mathrm{FDR}_{\max} > 0.1$ FD/h there is a reverse behavior. For patient 03 sensitivity from invasive EEG is 100% and always higher than sensitivity from scalp EEG. However for patient 04 and patient 05 sensitivity determined from scalp EEG recordings is higher than from invasive EEG. In particular for patient 04, we obtained a difference in sensitivity between the recording sites of up to 100% for $\mathrm{FDR}_{\max}$ less than 0.5 FD/h. In this case, the sensitivity from invasive EEG is in accordance with the critical value of a random detector at 5% significance level. For patient 06 sensitivity from invasive EEG data is higher than or equal to the sensitivity obtained from scalp EEG data. Although the recordings of the investigated intracranial electrodes of patient 06 did not result in an exact determination of the seizure onset zone, all seizures could be detected from the spiking rate calculated from invasive EEG recordings. Sensitivities from scalp and invasive EEG of all patients are almost always above respective critical values of a random predictor and indicate that significant detection performances could be obtained for all six patients.

The estimated averaged performance of the detection method, evaluated from 26 analyzed seizures from invasive and non-invasive EEG recordings, is shown in Fig. 5. Regions below the averaged critical values $\sigma_{\mathrm{rand},0.05}$ of a 5% significance level of a random detector are shown by gray areas. The sensitivity from scalp EEG data varies between 61% and 88%. Sensitivities from scalp EEG recordings are always higher than sensitivities from invasive EEG recordings, which range between 38% and 77%.

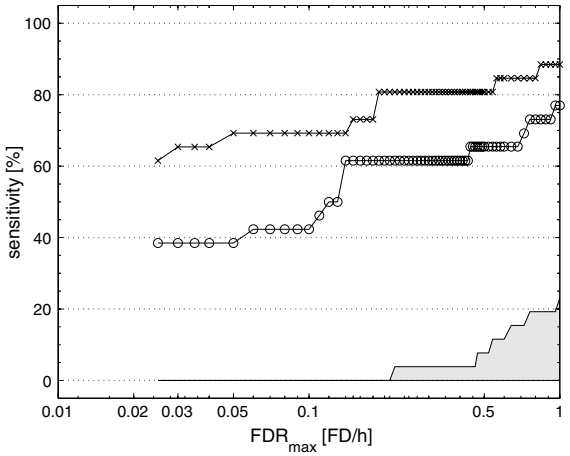

Fig. 5. Performance of the seizure detection method with respect to FDR_{max} obtained from scalp EEG (×) and from invasive EEG (○) recordings. Gray shaded areas mark regions below averaged critical values $\sigma_{rand,0.05}$ of a 5% significance level of a random detector.

The differences in the performances correspond to a difference of two up to eight seizures of all investigated seizures that were detected from the spiking rate from scalp EEG recordings but not from the spiking rate from invasive EEG recordings. The obtained sensitivities are clearly above critical values of a random detector and thus strongly indicate significant detection performances from scalp and invasive EEG data.

3.2. Results for seizure prediction

Exemplary time courses of the features $F_{Sz}(t)$ are shown in Fig. 6, which are calculated from invasive EEG and scalp EEG recordings for patient 01 over nearly four days. Electroencephalographic seizure onsets are marked by vertical lines. There are four seizures occurring. Both features show a characteristic pattern around the seizure onsets. Especially for this patient, a drop in the feature can be observed around the seizure onsets, which is more distinct in the feature from invasive EEG data. Note that such a drop was not observed for the other patients.

For some patients, generated features F_{Sz} reflect circadian changes in EEG dynamics. For example in Fig. 7, features calculated from scalp and invasive EEG data are shown for patient 06 over two days. Both features show a similar dynamical behavior with time. During night when the patient was sleeping, the features are fluctuating strongly with increased values. Changes in the features due to seizure onsets are not as obvious as for patient 01.

For an intervention time of 5 min and a seizure occurrence period of 30 min, estimates of sensitivity are shown for each patient in dependence on the maximum false prediction rate in Fig. 8. Different graphs result from calculations from scalp EEG and from invasive EEG recordings. Critical values of a 5% significance level of sensitivity $\sigma_{rand,0.05}$ are also shown.

With increasing FPR_{max}, sensitivity and critical values increase, too. Only for patient 02 and patient 06 sensitivity evaluated from invasive EEG data remains constant at 50%. For patient 03, patient 04, and patient 06, sensitivities obtained from scalp EEG recordings are always higher than or equal to those from invasive EEG recordings. For patient 03 sensitivities from invasive EEG correspond to the critical values $\sigma_{rand,0.05}$ for all investigated values of FPR_{max} and are therefore non-significant.

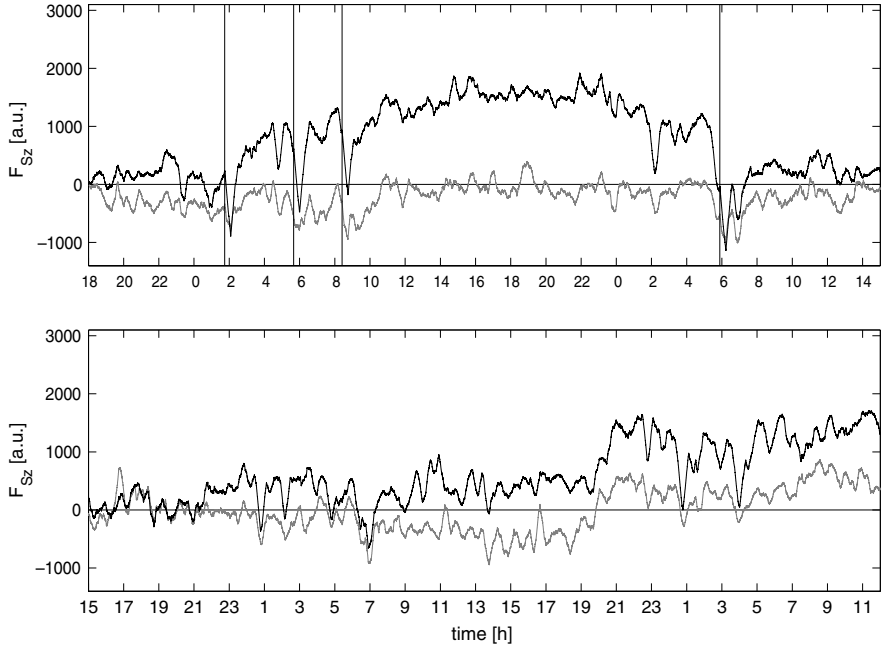

Fig. 6. Time continuous course of feature $F_{Sz}(t)$ over 90 h calculated on invasive (black) and scalp (gray) EEG recordings of patient 01. Electroencephalographic seizure onsets are marked by vertical lines.

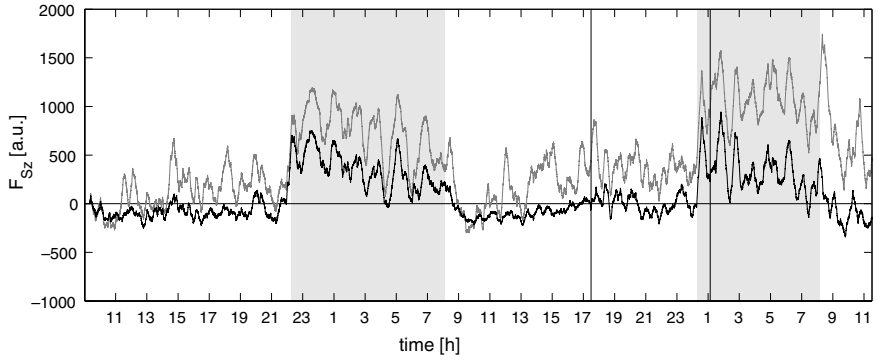

Fig. 7. Features $F_{Sz}(t)$ of patient 06 calculated from invasive EEG (black) and scalp EEG (gray) data showing a circadian rhythm. Electroencephalographic seizure onsets are marked by vertical lines. Shaded regions mark times at which the patient was sleeping.

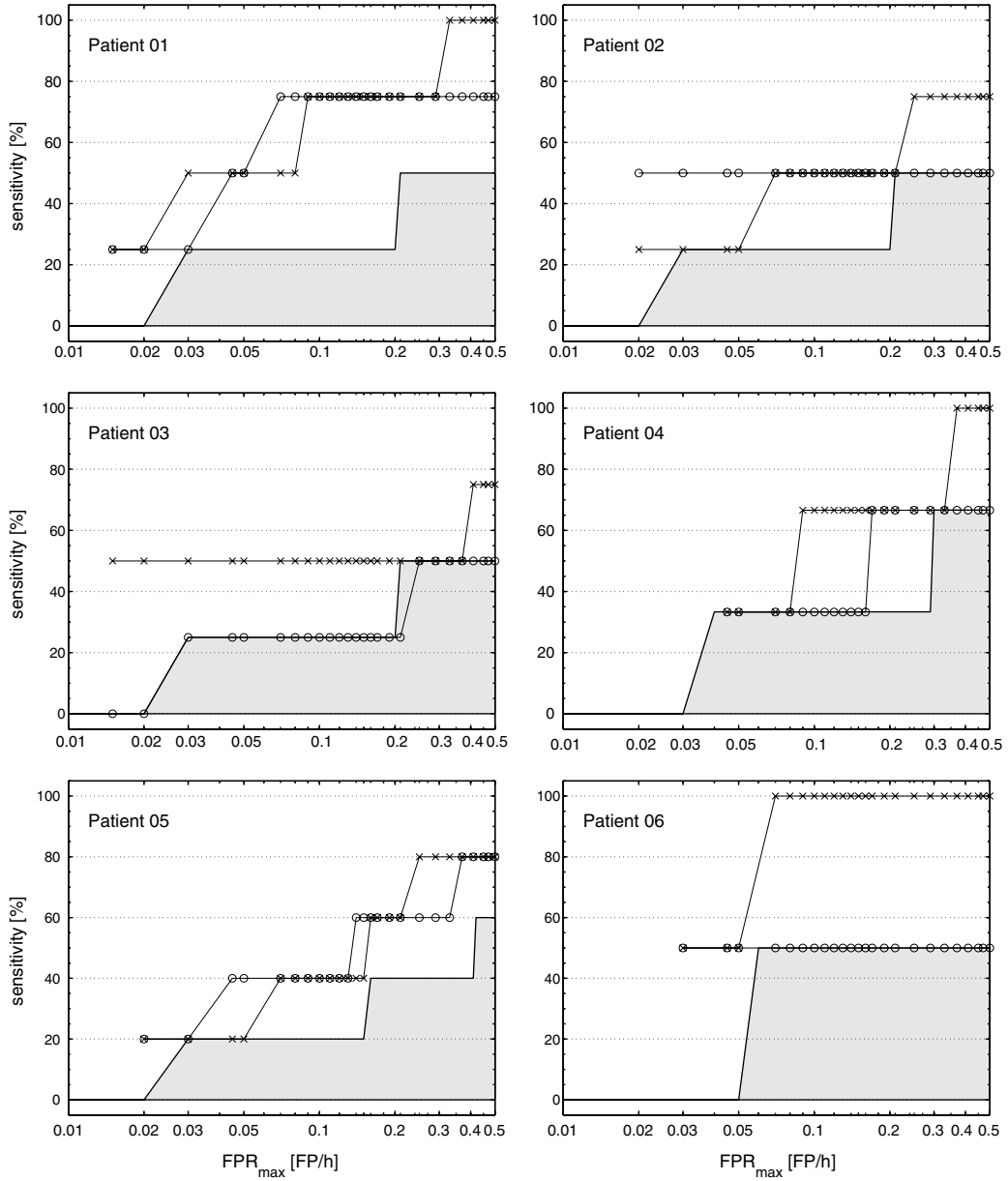

Fig. 8. Sensitivity of the investigated seizure prediction method in dependence on maximum false prediction rate for each patient. IT and SOP are fixed at 5 and 30 min, respectively. Different graphs result from scalp EEG (×) and from invasive EEG (○) recordings. Gray shaded areas mark regions below critical values $\sigma_{\mathrm{rand},0.05}$ of a 5% significance level of a random predictor.

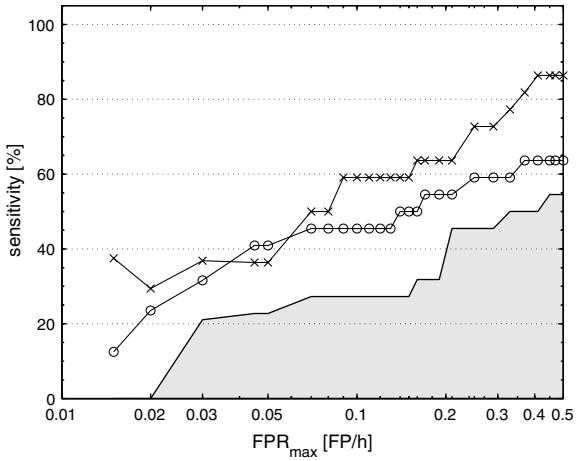

Fig. 9. Comparison between averaged performances of the seizure prediction method obtained from scalp (×) and invasive (○) EEG recordings and averaged critical values of a random predictor (gray area) in dependence on the false prediction rate FPR_{max}. The parameter IT is set to 5 min and SOP to 30 min.

The averaged sensitivity of the prediction performances is shown in Fig. 9 for both recording sites. The averages are obtained by equally weighting all investigated seizures of all patients. Sensitivities from scalp and invasive EEG data are always above the averaged critical values $\sigma_{rand,0.05}$ of a random predictor, indicating significantly better performances than a random predictor. On average a sensitivity of about 59% was obtained from scalp recordings, which is about 9% larger than from invasive recordings. This difference corresponds to the prediction of two additional seizures.

In Fig. 10 sensitivity is shown in dependence on the intervention time IT for each patient and recording site. Seizure occurrence period and maximum false prediction rate are fixed to SOP = 30 min and $FPR_{max} = 0.15$ FP/h. The sensitivities vary only slightly with respect to IT and recording site for all patients, i.e. differences correspond to the prediction of one seizure. Compared to the critical values $\sigma_{rand,0.05}$, we find for most of the patients ranges of IT where the sensitivity is larger than $\sigma_{rand,0.05}$, i.e. for those ranges of IT the prediction performance may be significantly better than a random predictor. For patient 03 and patient 06 performances obtained from invasive EEG recordings are in accordance with the critical value of the used random predictor for all investigated values of IT and therefore non-significant.

4. Discussion

In this study, we investigated long-term EEG data of non-invasive and intracranial EEG electrodes in order to compare them with respect to seizure detection and seizure prediction. The usage of simultaneously recorded non-invasive and intracranial EEG recordings allowed a direct comparison of generated features and estimated performances. We assessed a seizure detection and a seizure prediction method based on integrate-and-fire neurons which is able to incorporate EEG information without restrictions to the number of electrodes (Schindler et al., 2001, 2002). Two multivariate measures were utilized, the spiking rate SR and the feature F_{Sz}, while the original computation proposed for F_{Sz} was modified in order to avoid usage of a posteriori knowledge. The idea behind these two measures is based on physiological and pathophysiological properties of brain activity with respect to synchronization and desynchronization in advance of seizure generation. Therefore, the spiking rate can be interpreted as a measure that represents the level of spatio-temporal synchronized bioelectrical activity in the brain. In that sense, the feature F_{Sz} represents a measure for the gradually increase and decrease of spatio-temporal synchronization, respectively. We note that the performance evaluation carried out here was based on a retrospective analysis of the features, as parameters are set retrospectively.

4.1. Seizure detection

Detection of seizures corresponded to a rapid change of the spiking rate SR at seizure onset towards higher spiking rates, indicating an increase of synchronous activity in multichannel EEG. At a seizure end, SR dropped rapidly to low spiking rates. This is in agreement with Schindler et al. (2001). The same dynamical behavior was observed at spiking rates calculated from invasive EEG recordings.

The rapid increase and decrease of the spiking rate may be used for the identification of the electroencephalographic seizure onset and seizure end and provides a useful tool, for example to mark seizure onsets and seizure ends in EEG recordings or to confirm seizure times obtained from visual inspection of EEG at monitoring.

For some patients we observed, that if detection is possible from the spiking rate computed from invasive and non-invasive EEG data, seizures can be detected earlier from invasive EEG. The earlier detection using intracranial EEG recordings may reflect the coverage of the seizure onset zone whereas surface EEG is dependent on the latency of propagation of epileptic activity to areas of the convexity with involvement of extended pyramidal neuronal networks. Otherwise, the high sensitivity of seizure detection based on surface EEG may depend on the degree of propagation for clinically manifested seizures investigated here and may not be transferable to its performance on subclinical electrographic ictal events. Note that we also observed a tendency of the detection method to detect seizures after their electroencephalographic detection timepoint. Anyway, for the interpretation of this observation one has to consider that the detection of seizures by the human observer uses a posteriori information. That means, seizure onsets are identified retrospectively using clearcut seizure patterns determined during the course of the seizures to identify the earliest detectable signs of

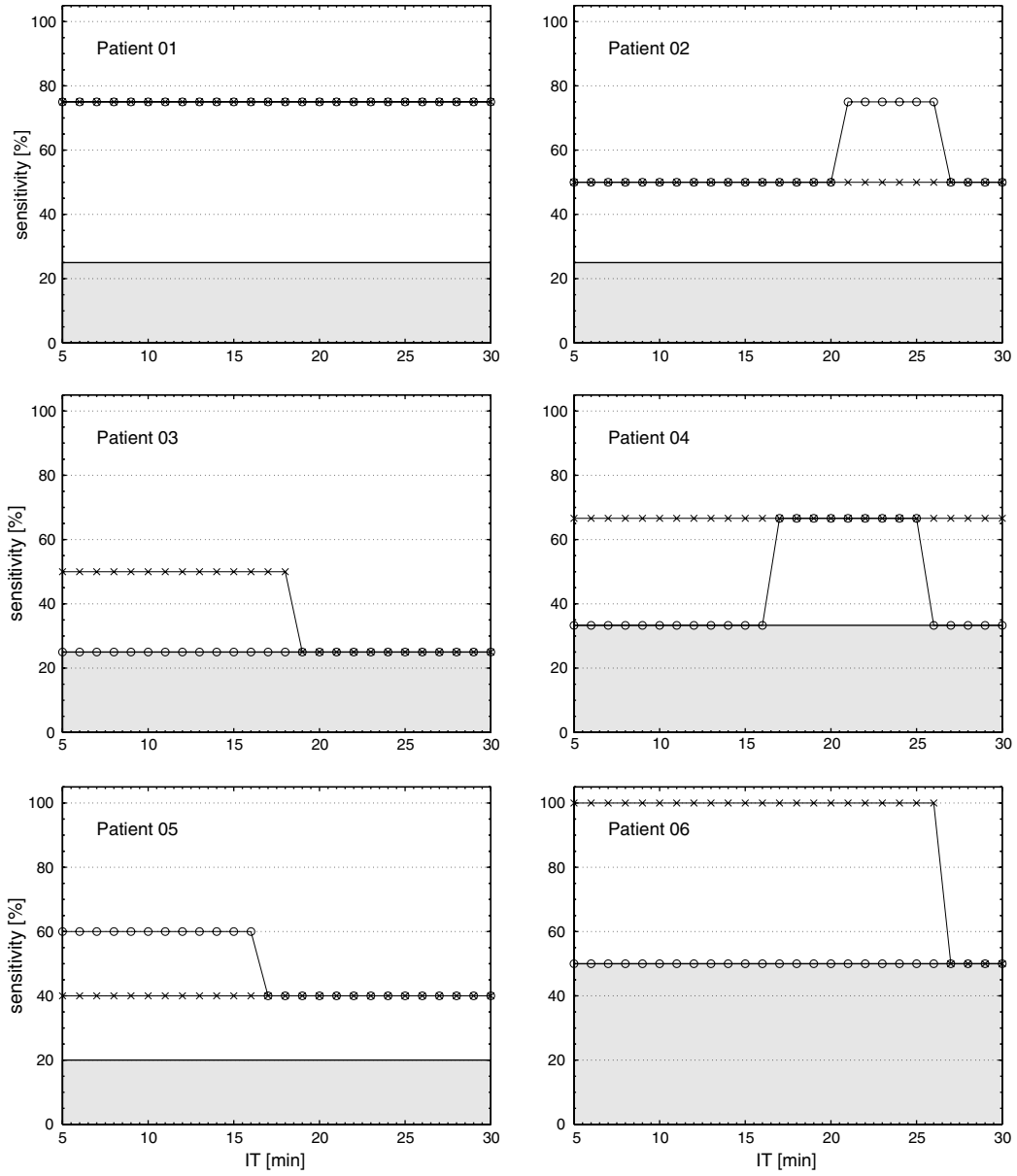

Fig. 10. Dependency of sensitivity on the intervention time IT with fixed SOP = 30 min and $FPR_{max} = 0.15$ FP/h. Different graphs result from scalp EEG (×) and from invasive EEG (○) recordings. Gray shaded areas mark non-significant regions of a 5% significance level of a random predictor.

these patterns. In contrast to this, the detection algorithm here uses only information included in the EEG sections preceding the seizure. Thus, the time-causal processing of EEG data but also the choice of parameter settings for the detection algorithm may contribute to a latency between the visual determination of the first presence of the seizure pattern and the detection of ictal activity by the algorithm.

For the investigated data the performances of seizure detection differed with respect to recording site and patient, especially for one patient a performance difference of up to 100% was obtained. The result of this single patient may have mainly influenced the observation of a tendency to a better average performance utilizing scalp EEG than invasive EEG. Possible explanations may be the effect of the variable locations of invasive EEG electrodes for measuring the spatio-temporal synchronization with the spiking rate. The scalp EEG electrodes cover a large area of the brain and collect smoothed superpositions of brain signals, whereas intracranial electrodes record signals of small brain areas. Thus, measuring spatio-temporal synchronization might be dependent on the location of electrodes. Moreover, the spiking rate is based on rather specific assumptions on the evolution of seizures, i.e. a seizure has to cause an increase of the spiking rate due to an increase of the spatio-temporal synchronization of bioelectrical activity. These assumptions might not be fulfilled for the evolution of seizures for all patients and thus cause variations in the performance between patients (Shoeb et al., 2004; Schindler et al., 2007).

For the evaluation of the investigated multivariate detection method, we made no preselection of electrodes either for scalp or invasive EEG. For the here used multivariate algorithms it is not necessary to select certain single electrodes to measure spatial synchronous activity in the brain. The simulated integrate and fire neurons of the algorithms can be regarded as coincidence detectors that extract electrodes that comprise this type of activity via the spatio-temporal integration. This is in contrast to former evaluations of published bivariate prediction measures where it was necessary to compare electrodes pairwise, which led to multiple testing problems (Schelter et al., 2006a). This problem can be avoided using multivariate algorithms like the here investigated ones.

In an earlier evaluation of the detection method which was used in this study applied to about 11 h scalp EEG recordings of 15 patients by Sazonov et al. (2002), a sensitivity of 87% and a false detection rate of about $\leqslant$1.18 FD/h were found. This result agrees with ours, though we investigated false detection rates $\leqslant$1 FD/h. Compared to other published detection methods like, for instance, Wilson et al. (2004) or Saab and Gotman (2005), our results show similar detection ability, when choosing comparable false detection rates.

4.2. Seizure prediction

For a successful seizure prediction with regard to clinical applications, required values of sensitivity, specificity, and prediction times strongly depend on the mechanism of an intervention system and its effect on patient (Winterhalder et al., 2003). Although we obtained an average sensitivity of 59% from scalp EEG and 50% from invasive EEG on our data pool, for clinical applications sensitivity should be increased to obtain a sufficient seizure prediction with small $\mathrm{FPR}_{\max}$ ($\mathrm{FPR}_{\max} < 0.15$ FP/h) (Aschenbrenner-Scheibe et al., 2003; Maiwald et al., 2004). This is based on considerations, that e.g. for pharmacorefractory patients with a typical mean seizure frequency of three seizures per month (Bauer and Burr, 2001), for an intervention system with a false prediction rate of 0.15 FP/h, up to 97% of all alarms would be false alarms, even for a sensitivity of 100%. If we apply these considerations to our results obtained from 420 h EEG and 22 seizures, a sensitivity of 50% would cause 85% false alarms.

An important standard for the assessment of the performance of a prediction method is the comparison with the performance of a random predictor (Mormann et al., 2006). A critical value $\sigma_{\mathrm{rand},\alpha}$ for a significance level α of such a random predictor was presented for estimations of sensitivity of prediction methods from EEG signals in an earlier study (Schelter et al., 2006a). The comparison of the performances of the prediction method investigated with $\sigma_{\mathrm{rand},\alpha}$ for $\alpha = 0.05$ indicates that on average the prediction method may perform better than an unspecific random predictor regardless of the recording site of the investigated EEG, but for single patients also non-significant sensitivities were obtained. Further, a reliable prediction method should provide a patient specific value for the intervention time. In our study, for most patients sensitivity is nearly independent of the investigated duration of the chosen intervention time IT.

A possible explanation of this insufficient performance may be found by regarding the features itself. Characteristically for the seizure prediction pattern of the investigated method, the feature F_{Sz} increases before seizure onset. But this pattern also appears within interictal segments, during which F_{Sz} oscillates irregularly with comparable amplitude to preictal segments. For one patient we also found a characteristic sudden drop in F_{Sz} which interrupts the increase of F_{Sz} some minutes in advance of the seizure onset. For other patients, features obtained from scalp as well as from invasive EEG recordings actually showed circadian variations. This indicates that the feature F_{Sz} is also sensitive to non-seizure related brain activities.

For patient 06, an extensive coverage of brain areas mostly secondarily involved in epileptic activity shows particularly clearly a circadian rhythmicity which corresponds well to changes in vigilance derived from sleep staging of surface EEG. Thus, there is a major increase in the baseline of the feature F_{Sz} when this patient fell asleep and a decrease to a lower level of F_{Sz} when the patient awoke again over several cycles. Altogether these observations confirm well the results of a previous study based on non-intracranial EEG (Schindler et al., 2002), where the features also oscillated with increased amplitude during night, indicating sleep induced changes of the measure.

Such circadian changes may markedly affect the performance of seizure prediction algorithms when a single threshold crossing is used as a criterion for the identification of the preictal period (Schelter et al., 2006b). For example increases of the feature F_{Sz} during sleep may cause increased false predictions at night, due to the application of a fixed threshold in the presented retrospective analysis. The usage of a continuously adapted threshold compensating for increases of mean and variance of the feature may obviate such false predictions during sleep and thus improve the performance (Mormann et al., 2003a; Esteller et al., 2005; Schelter et al., 2006b). Moreover, an analysis of false predictions, for example by visual inspection of features and respective EEG data in a retrospective analysis, may help to provide insights into underlying mechanisms causing false predictions (Navarro et al., 2005). But note that false predictions during periods of sleep may not have the same therapeutic implications for patients (Schelter et al., 2006b).

Thus, the measure used here certainly does not only reflect synchronous behavior of pathological activity as expected in the seizure onset zone but also physiological changes. Such not epilepsy-related variability may limit the specificity of the measure for seizure prediction but otherwise it may offer additional fields of implementations. Interestingly the features obtained from simultaneous scalp

and intracranial EEG recordings comprise a very similar dynamic behavior and showed similar influences of seizure and non-seizure related influences from EEG.

4.3. Conclusions and outlook

Features of the prediction method obtained from scalp and corresponding invasive EEG recordings showed a similar dynamical behavior. Conspicuous differences between the respective performances were not observed. An adaptation of the investigated multivariate prediction method originally developed for non-invasive EEG to intracranial EEG data is possible. The prediction performances achieved on the investigated data pool were not sufficient regarding a clinical valid seizure prediction with large sensitivities and specificities, but alterations of the prediction algorithm, e.g. utilizing dynamical thresholds, in order to improve the performance are conceivable.

Further we observed that seizure detection is also possible on intracranial EEG recordings. Depending on the patient, detection performances may be superior utilizing scalp or intracranial EEG. Due to the obtained detection performances, possible supporting applications of the detection method are conceivable, for instance an automatic detection of epileptic seizures during clinical monitoring with large sensitivities and reasonable false detection rates.

We observed influences of sleep on the spiking rate and F_{Sz}. Future investigations will examine the effects of sleep as well as changes of vigilance, and subclinical seizures on the performance of the considered detection and prediction method. In this study and previous applications of the investigated detection and prediction method, fixed thresholds were used for seizure detection and prediction. A further current point of interest is the application of dynamical thresholds in order to improve performances (Schelter et al., 2006b).

In particular, the usage of time-continuous, simultaneous EEG recordings of scalp and invasive electrodes enables new possibilities in analyzing multivariate seizure detection and prediction algorithms. It may provide new insights into underlying mechanisms of generation and propagation of seizures as well as physiological synchronization mechanisms. Thus, further collection of such data is an important objective and will improve future efforts in statistical validations in this field.

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References

Aschenbrenner-Scheibe R, Maiwald T, Winterhalder M, Voss HU, Timmer J, Schulze-Bonhage A. How well can epileptic seizures be predicted? An evaluation of a nonlinear method. Brain 2003;126:2616–26.

Bauer J, Burr W. Course of chronic focal epilepsy resistant to anticonvulsant treatment. Seizure 2001;10:239–46.

Bhavaraju NC, Frei MG, Osorio I. Analog seizure detection and performance evaluation. IEEE Trans Biomed Eng 2006;53:238–45.

Bialonski S, Lehnertz K. Identifying phase synchronization clusters in spatially extended dynamical systems. Phys Rev E 2006;74:051909.

Cockerell O, Johnson A, Sander J, Hart Y, Goodridge D, Shorvon S. Mortality from epilepsy: results from a prospective population-based study. Lancet 1994:918–21.

Dichter MA, Ayala GF. Cellular mechanisms of epilepsy: a status report. Science 1987;237:157–64.

Engel Jr J. Outcome with respect to epileptic seizures. In: Engel Jr J, editor. Surgical treatment of the epilepsies. New York: Raven Press; 1987. p. 553–71.

Esteller R, Echauz J, D'Alessandro M, Worrell G, Cranstoun S, Vachtsevanos G, et al. Continuous energy variation during the seizure cycle: towards an on-line accumulated energy. Clin Neurophysiol 2005;116:517–26.

Frei MG, Haas SM, Osorio I. Adaptation of a real-time seizure detection algorithm. Stochastic Theory and Control: Proceedings of a Workshop held in Lawrence, Kansas. Berlin/Heidelberg: Springer; 2002. p. 131–6.

Gotman J. Automatic seizure detection: improvements and evaluation. Electroencephalogr Clin Neurophysiol 1990;76:317–24.

Gotman J. Automatic detection of seizures and spikes. J Clin Neurophysiol 1999;116:130–40.

Haut SR, Swick C, Freeman K, Spencer S. Seizure clustering during epilepsy monitoring. Epilepsia 2002;43:711–5.

Iasemidis L, Sackellares J, Zaveri H, Williams W. Phase space topography and the Lyapunov exponent of electrocorticograms in partial seizures. Brain Topogr 1990;2:187–201.

Jerger KK, Netoff TI, Francis JT, Sauer T, Pecora L, Weinstein SL, et al. Early seizure detection. J Clin Neurophysiol 2001;18:259–68.

Jerger KK, Weinstein SL, Sauer T, Schiff SJ. Multivariate linear discrimination of seizures. Clin Neurophysiol 2005;116:545–51.

Le van Quyen M, Martinerie J, Baulac M, Varela F. Anticipating epileptic seizures in real time by a non-linear analysis of similarity between EEG recordings. Neuroreport 1999;10:2149–55.

Le van Quyen M, Adam C, Martinerie J, Baulac M, Clemenceau S, Varela F. Spatio-temporal characterizations of non-linear changes in intracranial activities prior to human temporal lobe seizures. Eur J Neurosci 2000;12:2124–34.

Le van Quyen M, Martinerie J, Navarro V, Baulac M, Varela F. Characterizing neurodynamic changes before seizures. J Clin Neurophysiol 2001a;18:191–208.

Le van Quyen M, Martinerie J, Navarro V, Boon P, D'Have M, Adam C, et al. Anticipation of epileptic seizures from standard EEG recordings. Lancet 2001b;357:183–8.

Lehnertz K, Elger C. Can epileptic seizures be predicted? Evidence from nonlinear time series analysis of brain electrical activity. Phys Rev Lett 1998;80:5019–22.

Litt B, Esteller R, Echauz J, D'Alessandro M, Shor R, Henry T, et al. Epileptic seizures may begin hours in advance of clinical onset: a report of five patients. Neuron 2001;30:51–64.

Maiwald T, Winterhalder M, Aschenbrenner-Scheibe R, Voss H, Schulze-Bonhage A, Timmer J. Comparison of three nonlinear seizure prediction methods by means of the seizure prediction characteristic. Physica D 2004;194:357–68.

Mormann F, Lehnertz K, David P, Elger C. Mean phase coherence as a measure for phase synchronization and its application to the EEG of epilepsy patients. Physica D 2000;144:358–69.

Mormann F, Andrzejak R, Kreuz T, Rieke C, David P, Elger C, et al. Automated detection of a pre-seizure state based on a decrease in synchronization in intracranial EEG recordings from epilepsy patient. Phys Rev E 2003a;67:021912.

Mormann F, Kreuz T, Andrzejak R, David P, Lehnertz K, Elger C. Epileptic seizures are preceded by a decrease in synchronization. Epilepsy Res 2003b;53:173–85.

Mormann F, Elger CE, Lehnertz K. Seizure anticipation: from algorithms to clinical practice. Curr Opin Neurol 2006;19:187–93.

Mueller M, Jiménez YL, Rummel C, Baier G. Localized short-range correlations in the spectrum of the equal-time correlation matrix. Phys Rev E 2006;74:041119.

Murray J. Coping with the uncertainty of uncontrolled epilepsy. Seizure 1993;2:167–78.

Navarro V, Martinerie J, Le Van Quyen M, Clemenceau S, Adam C, Baulac M, et al. Seizure anticipation in human neocortical partial epilepsy. Brain 2002;125:640–55.

Navarro V, Martinerie J, Quyen MLV, Baulac M. Seizure anticipation: Do mathematical measures correlate with video–EEG evaluation? Epilepsia 2005;46:385–96.

Osorio I, Frei M, Wilkinson S. Real-time automated detection and quantitative analysis of seizures and short-term prediction of clinical onset. Epilepsia 1998;39:615–27.

Osorio I, Frei MG, Bhavaraju NC, Sunderam S, Giftakis J, Bhavaraju NC, et al. Automated seizure abatement in humans using electrical stimulation. Ann Neurol 2005;57:258–68.

Saab ME, Gotman J. A system to detect the onset of epileptic seizures in scalp EEG. Clin Neurophysiol 2005;116:427–42.

Sazonov A, Schindler K, Duempelmann M, Loher T, Donati F, Mathis J, et al. Evaluation of a method for automatic detection of epileptic seizures from electroencephalogram (EEG). Epilepsia 2002;43(Suppl 7):50.

Schelter B, Winterhalder M, Maiwald T, Brandt A, Schad A, Schulze-Bonhage A, et al. Testing statistical significance of multivariate time series analysis techniques for epileptic seizure prediction. Chaos 2006a;16:013108.

Schelter B, Winterhalder M, Maiwald T, Brandt A, Schad A, Timmer J, et al. Do false predictions of seizures depend on the state of vigilance? A report from two seizure-prediction methods and proposed remedies. Epilepsia 2006b;47:2058–70.

Schiff SJ. Dangerous phase. Neuroinformatics 2005;3:315–8.

Schindler K, Wiest R, Kollar M, Donati F. Using simulated neuronal cell models for detection of epileptic seizures in foramen ovale and scalp EEG. Clin Neurophysiol 2001;112:1006–17.

Schindler K, Wiest R, Kollar M, Donati F. EEG analysis with simulated neuronal cell models helps to detect pre-seizure changes. Clin Neurophysiol 2002;113:604–14.

Schindler K, Leung H, Elger CE, Lehnertz K. Assessing seizure dynamics by analysing the correlation structure of multichannel intracranial EEG. Brain 2007;130:65–77.

Shoeb A, Edwards H, Connolly J, Bourgeois B, Treves ST, Guttag J. Patient-specific seizure onset detection. Epilepsy Behav 2004;5:483–98.

Stein AG, Eder HG, Blum DE, Drachev A, Fisher RS. An automated drug delivery system for focal epilepsy. Epilepsy Res 2000;39:103–14.

Wilson SB, Scheuer ML, Emerson RG, Gabor AJ. Seizure detection: evaluation of the Reveal algorithm. Clin Neurophysiol 2004;115:2280–91.

Winterhalder M, Maiwald T, Voss HU, Aschenbrenner-Scheibe R, Timmer J, Schulze-Bonhage A. The seizure prediction characteristic: a general framework to assess and compare seizure prediction methods. Epilepsy Behav 2003;4:318–25.

Zaveri HP, Duckrow RB, Spencer SS. The effect of a scalp reference signal on coherence measurements of intracranial electroencephalograms. Clin Neurophysiol 2000;111:1293–9.