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Spatio-temporal patient–individual assessment of synchronization changes for epileptic seizure prediction

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Abstract

Objective: Abnormal synchronization of neurons plays a central role for the generation of epileptic seizures. Therefore, multivariate time series analysis techniques investigating relationships between the dynamics of different neural populations may offer advantages in predicting epileptic seizures.
Methods: We applied a phase and a lag synchronization measure to a selected subset of multicontact intracranial EEG recordings and assessed changes in synchronization with respect to seizure prediction.
Results: Patient individual results, group results, spatial aspects using focal and extra-focal electrode contacts as well as two evaluation schemes analyzing decreases and increases in synchronization were examined. Averaged sensitivity values of 60% are observed for a false prediction rate of 0.15 false predictions per hour, a seizure occurrence period of half an hour, and a prediction horizon of 10 min. For approximately half of all 21 patients, a statistically significant prediction performance is observed for at least one synchronization measure and evaluation scheme.
Conclusions: The results indicate that synchronization changes in the EEG dynamics preceding seizures can be used for seizure prediction. Nevertheless, the underlying pathogenic mechanisms differ and both decreases and increases in synchronization may precede epileptic seizures depending on the structures investigated.
Significance: The prediction method, optimized values of intervention times, as well as preferred brain structures for the EEG recordings have to be determined for each patient individually offering the chance of a better patient–individual prediction performance.

Keywords: Seizure prediction; Seizure anticipation; Phase synchronization; False predictions; Prediction horizon

1. Introduction

Epilepsy is a disorder characterized by intermittent hyper-synchronous activity of local and wide-spread neural networks. So far, the mechanisms underlying this pathophysiological system are incompletely understood. The occurrence of ''seizures'' seems to be unforeseeable for the patients.

Since a significant proportion of epilepsy patients can neither be treated satisfactorily by medication nor by epilepsy surgery, novel treatment methods are required. One new and important device could be based on preventing seizures in advance of their clinical manifestation, a ''brain defibrillator'' in analogy to cardiac defibrillators (Milton and Jung, 2003). The basic idea is to record electric brain activity continuously and to detect preictal changes. If this prediction was early enough, an intervention such as an

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electric stimulation or the delivery of a short-term antiepileptic drug could be triggered to successfully suppress the upcoming seizure (Nicolelis, 2002; Schiff et al., 1994; Gluckman et al., 2001).

Besides the development of proper intervention strategies and their technical realization, a reliable prediction of epileptic seizures is the major challenge. In order to detect preictal changes in the EEG dynamics, concepts originating especially from the theory of linear and non-linear time series analysis have been applied to invasive and scalp electroencephalographic (EEG) recordings (Lehnertz and Elger, 1998; Lehnertz et al., 2001; Lehnertz and Litt, 2005; Mormann et al., 2000, 2003a,b, 2005a; Iasemidis et al., 1990, 2003, 2005; Litt et al., 2001; Litt and Lehnertz, 2002; Esteller et al., 2005; Le van Quyen et al., 1999, 2000, 2001a,b, 2005; Navarro et al., 2002; Osorio et al., 1998; Schindler et al., 2002; Jerger et al., 2001; Chaovalitwongse et al., 2005). These studies have shown that changes in the EEG dynamics prior to seizure onsets are identifiable and that a particular preictal state might exist. However, the reproducibility of studies and the applicability of nonlinear algorithms to EEG data is controversially debated in the recent literature (De Clercq et al., 2003; Lai et al., 2003; Lai et al., 2004; McSharry et al., 2003; Aschenbrenner-Scheibe et al., 2003). Moreover, the existence of a pre-seizure state in some types of epilepsies is also discussed (Lopes da Silva et al., 2003a; Lopes da Silva et al., 2003b).

Since epileptic seizures are generated by an abnormal synchronization of neural populations, bivariate analysis techniques originating from synchronization theory (Pikovsky et al., 2001; Boccaletti et al., 2002) have come into focus of seizure prediction research. The concept of phase synchronization, which requires only a weak interaction and which has been observed even for chaotic oscillatory processes, has attracted particular interest (Rosenblum et al., 1996). We have analyzed the *mean phase coherence* R (Mormann et al., 2000), a measure for phase synchronization, with respect to its seizure prediction performance. A *lag synchronization index* $S_{\min}$ is utilized as a measure for lag synchronization, derived from a function describing the correlation between time series for different time lags (Rosenblum et al., 1997). The latter quantifies amplitude-related synchronization. It is impossible to detect the weak form of synchronization affecting only the phases of the signals using $S_{\min}$. To cover the broad variety of synchronization phenomena which might contribute to changes in the EEG dynamics prior to seizure onsets, we evaluated both quantities.

A decreasing as well as increasing synchronization in the EEG dynamics has been detected in a wide range between several minutes up to a few hours prior to epileptic seizures analyzing long-term intracranial EEG data (Mormann et al., 2000, 2003a,b, 2005a; Le van Quyen et al., 2005). To utilize this observation in order to predict seizures and apply synchronization methods in a therapeutic device to suppress upcoming seizures, the temporal aspects of a prediction have to be considered more closely. In contrast to previous studies (Mormann et al., 2000, 2003a,b, 2005a; Le van Quyen et al., 2005), we have investigated short-term changes of the decreasing and increasing synchronization in the EEG dynamics in pre-seizure periods of 50 min duration, as detecting dynamic changes prior to seizure onsets not too far away from the seizure onset would be preferable for several interventions.

To assess the prediction performance of such short-term synchronization changes, we utilized the concept of the "seizure prediction characteristic" (Winterhalder et al., 2003; Maiwald et al., 2004). It relates sensitivity with specificity as well as two time intervals, the seizure prediction horizon and the seizure occurrence period characterizing the temporal aspects of a prediction. The differentiation between both time intervals is preferable having in mind a clinical application of the seizure prediction algorithm. For an intervention system to be effective against an impending seizure, a minimum time interval between an alarm and the corresponding seizure onset is required, the seizure prediction horizon. This time period can also be referred to as "intervention time". A perfect prediction would indicate the exact point in time when a seizure is going to start. As this cannot be expected for methods analyzing physiological data, quantification of an uncertainty in the prediction time is necessary. The uncertainty in the prediction time, the seizure occurrence period, is the time interval during which the predicted seizure is expected to occur.

Besides calculating sensitivity and specificity as well as the temporal aspects of a prediction, a retrospective analysis of seizure prediction methods has to include a proof of the superiority that a predictor performs better than random (Mormann et al., 2005b; Aschenbrenner-Scheibe et al., 2003; Winterhalder et al., 2003). To decide about the statistical significance of seizure predictability, bootstrap based methods have been proposed (Andrzejak et al., 2003; Kreuz et al., 2004). An alternative and analytic approach is utilized in this study based on comparing seizure prediction characteristic values with critical sensitivity values for a given significance level. The critical sensitivity is calculated on basis of a random prediction following a Poisson process in time and takes into account the number of seizures investigated as well as the number of different features calculated for each patient individually. For example, applying the bivariate and symmetric measure mean phase coherence to EEG time series recorded from six electrode contacts, 15 different time courses of the mean phase coherence are extracted simultaneously. Increasing the number of electrode contacts to a value of 10, for instance, would result in 45 different pairs of electrodes with corresponding time courses of the mean phase coherence. Therefore, the probability of changes in any of these time courses leading to a prediction of seizures by chance strongly increases with the number of electrode contacts investigated.

The paper is organized as follows: Patient characteristics, the EEG database, a description of the phase and

lag synchronization measure, and the methodology to assess the prediction performance are summarized in Section 2. Group results averaged for all 21 patients as well as patient individual results are presented in Section 3. Furthermore, changes in synchronization are analyzed with respect to two evaluation schemes, a decrease and an increase in synchronization. Additionally, the effects of different prediction horizons and spatial effects concerning the brain regions are examined in Section 3. The results are discussed in Section 4 with special emphasis on the spatio-temporal aspects of a prediction.

2. Materials and methods

2.1. Patient characteristics and EEG database

The analyzed database consists of invasive EEG recordings of 21 patients suffering from medically intractable focal epilepsy. The retrospective evaluation of the data received prior approval by the Ethics Committee, Medical Faculty, University of Freiburg. Informed consent was obtained from each patient. The data were recorded during invasive pre-surgical epilepsy monitoring at the Epilepsy Center of the University Hospital of Freiburg, Germany. In 11 patients, the epileptic focus was located in neocortical brain structures, in eight patients in the hippocampus, and in two patients in both. For the 21 patients under investigation, the AEDs and AED levels were not identical as the antiepileptic medication had to be adapted to the individual patient's clinical needs. Patients obtained thus different medications when entering monitoring. Further characteristics of the patients are given in Table 1.

In order to obtain a high signal-to-noise ratio, fewer artifacts, and to record directly from focal areas intracranial grid-, strip-, and depth-electrodes were utilized. The EEG data were acquired using a Neurofile NT digital video EEG system with 128 channels, 256 or 512 Hz sampling rate, and a 16 bit analog-to-digital converter. To eliminate possible line noise and low frequency components, the EEG data sets were preprocessed by a 50 Hz notch filter and a band pass filter between 0.5 and 120 Hz. For analyzes no downsampling was performed.

A subset of electrode contacts was selected prior to the analysis by visual inspection by an experienced electroencephalographer. Three focal electrode contacts, i.e., three recording sites initially involved in ictal activity based on the available electrode coverage of the brain, and three extra-focal electrode contacts, i.e., recording sites not involved at all or – in most cases – latest during spread of ictal activity, were selected for analysis. For the two patients with seizure onset zone in the hippocampus and in the neocortex, two focal contacts were located in the neocortex and one contact in the hippocampus (patient 14) and all three electrode contacts in the neocortex (patient 15). The electrode contacts were referenced to a contact located in a brain structure with lowest epileptic activity. Using a bivariate analysis technique, this selection of electrode contacts leads to three different classes of electrode contact combinations. The focal electrode contacts themselves yield three combinations (foc,foc) as well as the extra-focal contacts themselves (ext,ext). Nine different combinations between focal and extra-focal electrode contacts form the third class (foc,ext).

Details about the EEG data sets analyzed in this study are given in Table 1. In order to determine the specificity of the synchronization measures, interictal, seizure-free EEG data of 24 h for each patient were analyzed. To determine sensitivity, 2–5 seizures (in total 88) were investigated for each patient, including pre-seizure EEG data of at least 50 min duration.

For 13 patients, one complete interictal recording day was available. For the remaining patients, shorter segments with a total duration of 24 h were selected such that comparable times of the day were covered (cf. Table 1). The temporal distance between interictal and pre-seizure recordings was not identical for the patients. The median of the time periods between the last seizure and the interictal data set was 5 h 18 min, the median of the time periods between the interictal data set and the first following seizure was 9 h 36 min.

The seizures analyzed occurred spontaneously; there were no other provoking mechanisms such as hyperventilation or photostimulation used, but medication was reduced in the majority of patients. The seizures analyzed occurred at different times of day.

2.2. Two bivariate synchronization measures

2.2.1. Mean phase coherence R

Weakly coupled self-sustained oscillators are able to synchronize their phases. The phenomenon of phase synchronization has been detected even for coupled, non-identical, chaotic oscillators (Rosenblum et al., 1996). To detect phase synchronization, a definition of the phase $\Phi(t)$ of the real-valued signal $x(t)$ is required. Here, we follow the approach of Gabor's analytic signal (Gabor, 1946)

$$u(t) = x(t) + \mathrm{i}\tilde{x}(t) = A(t)\exp(\mathrm{i}\Phi(t)),$$

where the imaginary part of $u(t)$ is derived using the Hilbert transformation

$$\tilde{x}(s) = \frac{1}{\pi}\ \mathrm{P.V.}\ \int \frac{x(t)}{s-t}\mathrm{d}t.$$

P.V. refers to Cauchy's principle value. Phase synchronization is represented by an almost constant phase difference, i.e., two integer numbers n and m exist with

$$|n\Phi^{(1)}(t) - m\Phi^{(2)}(t)| = |\Phi_{n,m}(t)| < \mathrm{const}$$

for all time points, where $\Phi^{(i)}(t)$ denotes the phase of the signal i at time t. In case of phase synchronization and presence of additional stochastic influence, the distribution of $\Psi_{n,m} = \Phi_{n,m} \bmod 2\pi$ deviates from a uniform distribution (Tass et al., 1998). The deviation from a uniform

Table 1
Patient characteristics and EEG data characteristics

Patient	Sex	Age	Seizure type	H/NC	Electrodes	Preictal EEG data sets				Interictal EEG data sets			
						Total number of seizures	# of seizures between		Seizure frequency (1/day)	Interictal duration (h)	# interictal intervals	Duration of interictal intervals (h)	
							9 am to 9 pm	9 pm to 9am				Between 9 am to 9 pm	Between 9 pm to 9 am
1	f	15	SP,CP	NC	g,s	5	1	4	6.3	24	1	12.00	12.00
2	m	38	SP,CP,GTC	H	d	3	3	0	2.8	24	2	9.00	15.00
3	m	14	SP,CP	NC	g,s	5	0	5	0.6	24	1	12.00	12.00
4	f	26	SP,CP,GTC	H	d,g,s	5	1	4	0.4	24	1	12.00	12.00
5	f	16	SP,CP,GTC	NC	g,s	5	2	3	1.7	24	3	13.50	10.50
6	f	31	CP,GTC	H	d,g,s	3	2	1	0.9	24	1	12.00	12.00
7	f	42	SP,CP,GTC	H	d	3	0	3	0.2	25	1	13.00	12.00
8	f	32	SP,CP	NC	g,s	2	0	2	6.8	24	2	15.75	8.25
9	m	44	CP,GTC	NC	g,s	5	3	2	1.6	24	2	12.25	11.75
10	m	47	SP,CP,GTC	H	d	5	4	1	1.1	24	1	12.00	12.00
11	f	10	SP,CP,GTC	NC	g,s	4	0	4	0.6	24	1	12.00	12.00
12	f	42	SP,CP,GTC	H	d,g,s	4	1	3	1.0	25	1	13.00	12.00
13	f	22	SP,CP,GTC	H	d,s	2	1	1	0.1	24	1	12.00	12.00
14	f	41	CP,GTC	H and NC	d,s	4	1	3	6.3	24	5	11.75	12.25
15	m	31	SP,CP,GTC	H and NC	d,s	4	0	4	0.4	24	1	12.00	12.00
16	f	50	SP,CP,GTC	H	d,s	5	2	3	4.5	24	2	8.75	15.25
17	m	28	SP,CP,GTC	NC	s	5	2	3	1.0	24	1	12.00	12.00
18	f	25	SP, CP	NC	s	5	1	4	6.6	25	1	13.00	12.00
19	f	28	SP,CP,GTC	NC	s	4	3	1	3.6	24	3	6.50	17.50
20	m	33	SP,CP,GTC	NC	d,s	5	3	2	5.1	26	1	14.00	12.00
21	m	13	SP,CP	NC	s	5	1	4	0.2	24	2	6.25	17.75
Total						88	31	57		509		245	264
Mean						4.2			2.5	24.2			

Seizure types: simple partial (SP), complex partial (CP), and generalized tonic–clonic (GTC). Seizure origin: hippocampal (H) and neocortical (NC). Electrodes: grid (g), strip (s), depth (d). Characteristics of the preictal and interictal EEG data segments analyzed. For each patient, either all or five seizures (mean 4.2/total 88) and at least 24 h of interictal EEG recordings (mean 24.2 h/total 509 h) were examined. The seizure frequency varies between 0.1 and 6.8 seizures per day.

distribution can be quantified by Mormann et al. (2000) and Rosenblum et al. (2001)

$$R^2_{n,m} = \langle \cos \Psi_{n,m}(t) \rangle^2 + \langle \sin \Psi_{n,m}(t) \rangle^2,$$

taking values close to zero if there is no deviation and values close to one for preferred values, respectively. When applied to EEG data from epilepsy patients, a decrease in the synchronization index $R := R_{1,1}$, also called mean phase coherence, has been detected in advance of seizure onsets using a sliding window technique (Mormann et al., 2000, 2003a,b). In the present study, the mean phase coherence has been applied to the EEG data for sliding time intervals of 32 s duration, shifted by 1 s for each calculation. The extracted feature, the mean phase coherence, is processed by a median filter of 220 s duration and threshold crossings are used to trigger alarms. Threshold values have been varied between zero and one in steps of 0.01.

2.2.2. Lag synchronization index S_{min}

A different synchronization phenomenon is obtained for an increase in coupling compared to the coupling for phase synchronization between chaotic oscillators. Lag synchronization is characterized by an additional high correlation between the amplitudes with a specific time lag (Rosenblum et al., 1997). The function

$$S^2(\tau) = \frac{\langle (x_2(t+\tau) - x_1(t))^2 \rangle}{\sqrt{\langle x_1^2(t) \rangle \langle x_2^2(t) \rangle}}$$

takes a value close to zero for a time lag $\tau_{\min}$ in case of lag synchronization between two signals x_1 and x_2 (Rosenblum et al., 1997). In the present application to the EEG data, this minimum is calculated for sliding time intervals and for a given range of time lags $\tau \leqslant 1$ s, leading to the lag synchronization index $S_{\min}$. This synchronization measure has been applied to the EEG data for sliding time intervals of 32 s duration, shifted by 1 s for each calculation. The extracted feature, the lag synchronization $S_{\min}$, is processed by a median filter of 220 s duration and threshold crossings are used to trigger an alarm. Threshold values have been varied between zero and one in steps of 0.01.

Both synchronization phenomena may occur for coupled, nonlinear, and even chaotic oscillators and rely on strong physical assumptions, described by the theory of Nonlinear Dynamics. Construction of the phase using the concept of Hilbert transform is based on narrow frequency band signals and narrow frequency bands may have advantages in applications to EEG data (Chavez et al., 2003). However, as we are interested in the seizure prediction performance, we follow earlier studies using wide-band EEG data (Mormann et al., 2000) and analyze changes of the mean phase coherence in advance of seizure onsets.

The theoretical concept of phase synchronization is based on coupled, self-sustained oscillatory processes. It has been shown recently that phase synchronization analysis applied to data sets with unknown dynamics is not capable of detecting the correct class of underlying dynamics (Winterhalder et al., 2006). Thus, in the present application to EEG data, conclusions about the exact type of the underlying dynamics should be avoided. However, the synchronization measures detect interdependencies between signals. In this study, both measures are used to investigate interrelations between the dynamics of different brain structures and are assessed only with respect to their seizure prediction performance. The application of both bivariate measures reflects the intensity of the interaction between two signals, but we do not claim that the measures reflect true synchronization according to the strict physical definition.

2.3. Statistical assessment of seizure prediction performance

In order to illustrate the necessary factors for a proper evaluation of prediction performance, exemplary time courses of the mean phase coherence are shown in Fig. 1 for a preictal and an interictal period, respectively. The seizure onset in Fig. 1a is marked by the vertical line at time point zero. A decrease of the mean phase coherence can be observed approximately 35, 20, and 5 min in advance of the seizure onset. Evaluating this decrease in synchronization, a change in the EEG dynamics is detected as a threshold indicated by the horizontal line is crossed downwards twice.

In contrast to seizure detection and for an intervention system to be effective against an impending seizure, a minimum time interval between an alarm and the corresponding seizure onset is required, the seizure prediction horizon *SPH*. In order to consider an uncertainty in the prediction time, the seizure occurrence period *SOP* is taken into account which is the time interval during which the predicted seizure is expected to occur. The two consecutive time intervals *SPH* and *SOP* follow the first alarm triggered by the downwards threshold crossing of the mean phase coherence (Fig. 1b). In this example, the seizure starts during the seizure occurrence period and is thus predicted correctly.

In Fig. 1c, an exemplary time course of the extracted feature mean phase coherence is shown for an interictal period. The downwards threshold crossing raises an alarm after approximately 10 min, again triggering the two consecutive time intervals *SPH* and *SOP* (Fig. 1d). As no seizure during the interictal period occurs, the prediction has to be classified as a false prediction. Towards the end of the interictal period, a second false alarm is raised. Lowering the value of the threshold would ensure that the false predictions are avoided in the interictal period (Fig. 1c and d), but at the expense of losing the correct prediction (Fig. 1a and b).

This example shows that the choice of the threshold is related not only to the number of correct predictions but also to the amount of false predictions during interictal periods. The observed false prediction rate *FPR* corresponds closely to the specificity of the prediction method. A minimum specificity, i.e., a maximum allowed number

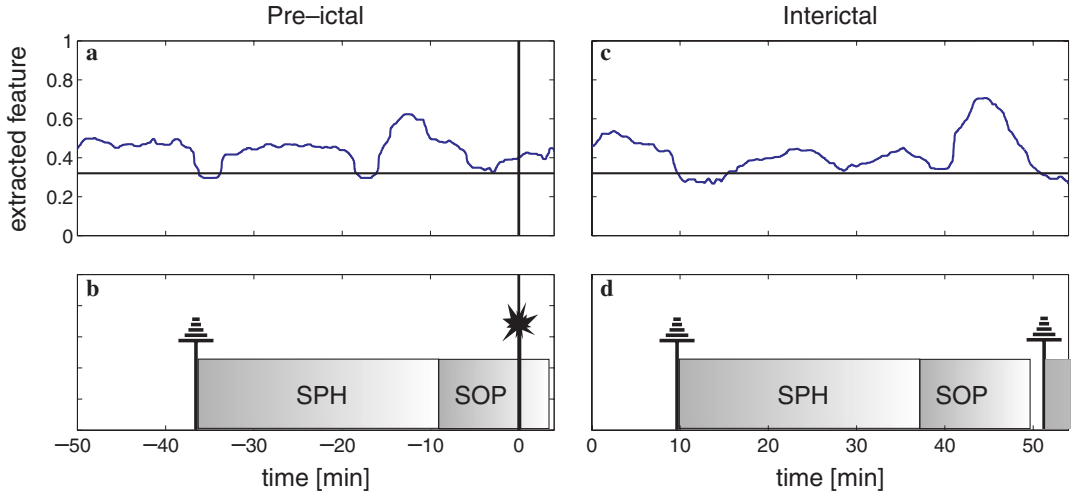

Fig. 1. Operation of a prediction method during a preictal (a, b) and an interictal period (c, d). In (a, b) the seizure onset is marked by the vertical line at time point zero. Exemplary time course of the extracted feature mean phase coherence (a, c). The solid, horizontal lines indicate the threshold. A downwards threshold crossing raises an alarm. Alarm events and the two consecutive time intervals seizure prediction horizon *SPH* and seizure occurrence period *SOP* characterizing a prediction are illustrated in (c, d).

of false predictions per time interval FPR_{max}, can be determined by a suitable choice of the threshold value during interictal epochs. In particular, the maximum false prediction rate is useful in the context of seizure prediction, as the number of false predictions has to be related to the seizure frequency. Considering a prediction method with a sensitivity of 100% and a false prediction rate identical to the seizure frequency, then, every second alarm of the prediction method would be a false one. An average maximum seizure frequency of 3.6 seizures per day (0.15 seizures per hour) of patients during presurgical monitoring has been observed (Haut et al., 2002). Taking this aspect into account, a sensitivity of 100% does not necessarily lead to an appropriate predictor, even for comparably low false prediction rates.

These aspects are incorporated in the concept of the seizure prediction characteristic $S(FPR_{max};SOP;SPH)$ (Winterhalder et al., 2003) which is utilized in the present study. Sensitivity S is calculated as a function of three factors, i.e., the time intervals *SPH* and *SOP* and the maximum false prediction rate FPR_{max}.

A test to decide about the statistical significance of a given value of the seizure prediction characteristic is defined by the "prediction performance" of an unspecific random prediction. For an unspecific random prediction alarms are triggered completely randomly without using any information from the EEG. The probability of predicting at least k of K seizures using d features is

$$P_{\text{binomial},d}\{k;K;P\} = 1 - \left(\sum_{j<k}\binom{K}{j}P^j(1-P)^{K-j}\right)^d$$

based on the probability $P = 1 - e^{-FPR_{max}SOP}$ for one alarm event during *SOP* and a given maximum false prediction rate (Winterhalder et al., 2003). The exponential form of P is valid for $SOP \gg$ sampling interval. As the number of independent features is usually unknown, two critical values are derived. For a significance level α, the lower critical value is given by

$$\sigma_{\text{low}} = \max_k(P_{\text{binomial},1}\{k;K;P\} > \alpha)\cdot 100\%$$

for $d = 1$. For an r-variate, symmetric feature extraction and n electrode contacts investigated, the upper critical value

$$\sigma_{\text{max}} = \max_k(P_{\text{binomial},d_{\text{max}}}\{k;K;P\} > \alpha)\cdot 100\%$$

is obtained for independent features with $d_{\text{max}} = n!/((n-r)!\,r!)$ (Schelter et al., 2006a). In the present study, α is set to 0.05. The upper critical value takes account for the fact that for the prediction technique always the best channel combination is selected. For each prediction method, sensitivity has to exceed at least the lower critical value. A sensitivity of a prediction method exceeding the upper critical value can be interpreted as reliably superior to an unspecific random predictor.

Different values of d lead to different upper critical sensitivity values. For example, comparing sensitivities of the class of focal/focal and of focal/extra-focal combinations would not only yield higher critical values but also higher sensitivities due to the higher number of independent values of d for the class of focal/extra-focal combinations. Thus, it is impossible to compare the sensitivity values between these classes directly. Nevertheless, a test for the performance difference between such different clusters with specific values of d and sensitivities is desired. An exact two-sided paired Wilcoxon signed rank-sum test with respect to each patient for differences in $P_{\text{binomial},d}\{k;K;P\}$-values can be performed, if independence between the clusters of $P_{\text{binomial},d}\{k;K;P\}$-values is assumed.

3. Results

Sections 3.1–3.3 describe an analysis of a decrease in the synchronization of the EEG dynamics with respect to seizure prediction. The prediction performance is investigated as a function of the maximum false prediction rate, the seizure occurrence period, and seizure prediction horizon averaged for all patients and two representative patients. In Section 3.4, the results evaluating a decrease in the synchronization are compared to the results obtained when evaluating an increase in the EEG synchronization. To investigate differences between the prediction performances for individual patients, the sensitivity depending on the seizure prediction horizon is presented for each patient in Section 3.5. Finally, prediction performance with respect to the three classes of electrode combinations is examined. In the following, sensitivities are given as maximum sensitivities for the corresponding electrode combinations, together with the respective critical values.

3.1. Sensitivity as a function of the maximum false prediction rate FPR_{max}

In Fig. 2, sensitivities of the synchronization measures R and $S_{\min}$ are shown as a function of the maximum false prediction rate, for a fixed seizure prediction horizon of 10 min and a seizure occurrence period of 30 min. The investigated values of maximum false prediction rates range between one false prediction within a day and one within one hour. The gray areas mark the corresponding range of the unspecific random prediction, limited by the lower and upper critical values.

In Fig. 2a, the sensitivity values are averaged over all 21 patients. Their averages exceed the averaged lower critical value of the unspecific random prediction for both synchronization measures and all values of FPR_{max}. However, sensitivities are not higher than the averaged upper critical value for several values of the false prediction rate. Values of the maximum false prediction rate exceeding one false prediction per hour are not investigated, as the averaged upper critical value yields a value of 100% and even the averaged lower critical value for the random prediction is higher than 80%.

Patient individual values of sensitivity depending on the false prediction rate are shown for patient 01 and patient 03 exemplarily in Fig. 2b. For patient 01, high sensitivity values between 80% and 100% are obtained for both synchronization measures, even at low false prediction rates. The lower as well as the upper critical value of the unspecific random prediction is exceeded for $FPR_{max} \leqslant 0.7$ false predictions (FP) per hour (approximately 17 false predictions per day) showing a significant prediction.

In contrast, for patient 03, sensitivity values for the synchronization index $S_{\min}$ are not even higher than the lower critical value of the unspecific random prediction. For the mean phase coherence R, sensitivity values are close to the upper critical value of the unspecific random prediction. Therefore, prediction performance by chance cannot be excluded for patient 03, especially for the synchronization measure $S_{\min}$.

3.2. Sensitivity as a function of the seizure occurrence period SOP

For both synchronization measures investigated, dependence of the sensitivity on the seizure occurrence period is shown in Fig. 3. The maximum false prediction rate has been fixed at $FPR_{max} = 0.15$ FP/h, corresponding to 3.6 false predictions within one day, and the seizure prediction horizon at 10 min. The gray areas mark the corresponding range of the unspecific random prediction, limited by the lower and upper critical values.

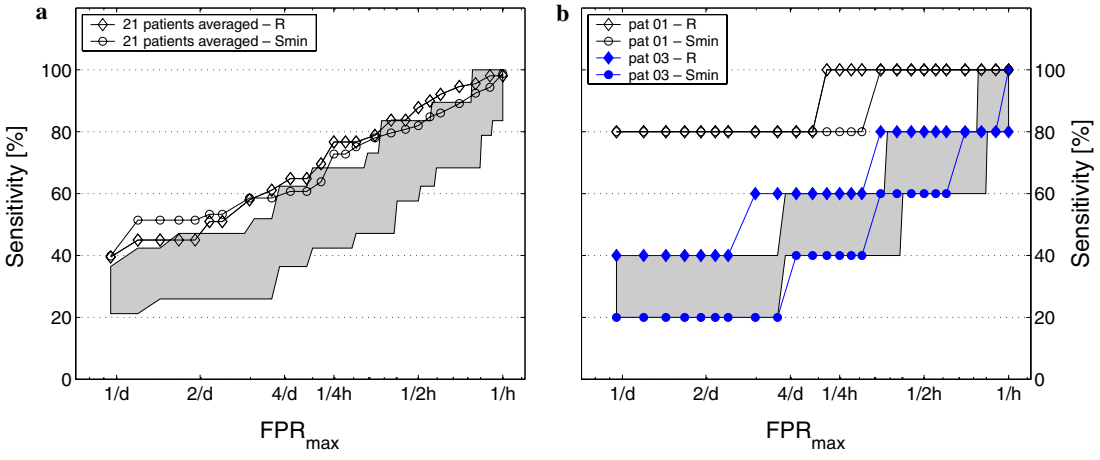

Fig. 2. Sensitivity for the synchronization measures R and $S_{\min}$ depending on the maximum false prediction rate FPR_{max}. The seizure prediction horizon has been set to 10 min and the seizure occurrence period to 30 min. The gray areas mark the corresponding range of the unspecific random prediction, limited by the lower and upper critical values. (a) Sensitivity values and the corresponding critical values are averaged for all 21 patients. (b) Patient individual sensitivity is given for patient 01 and patient 03 exemplarily.

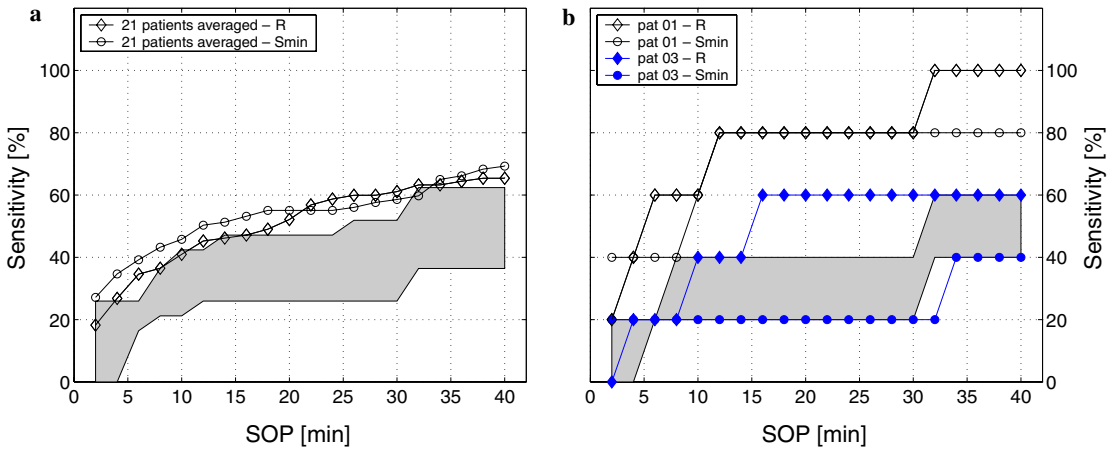

Fig. 3. Sensitivity for the synchronization measures R and $S_{\min}$ depending on the seizure occurrence period. The maximum false prediction rate has been set to $FPR_{max} = 3.6\ \text{FP}/d = 0.15$ FP/h and the seizure prediction horizon to 10 min. The gray areas mark the corresponding range of the unspecific random prediction, limited by the lower and upper critical values. (a) Sensitivity values and the corresponding critical values are averaged for all 21 patients. (b) Patient individual sensitivity is given for patient 01 and patient 03 exemplarily.

In Fig. 3a, sensitivity averaged over all patients yields higher values than the averaged lower critical value of the unspecific random prediction for the entire range of seizure occurrence periods investigated. Furthermore, both synchronization measures yield a similar prediction performance. However, for some values of SOP, sensitivity values of the synchronization index R do not surpass the averaged upper critical value of the unspecific random prediction.

In analogy to the investigation in the previous section, a high and significant seizure prediction performance with respect to the upper critical value of the unspecific random prediction is detected for patient 01 using both synchronization measures (cf. Fig. 3b). On the other hand, for patient 03 significant values of the sensitivity are only obtained for the mean phase coherence R in a range of seizure occurrence periods between 16 and 30 min.

3.3. Sensitivity as a function of the seizure prediction horizon SPH

The dependence of sensitivity on the seizure prediction horizon for both synchronization measures is given in Fig. 4. As SPH reflects the actual prediction time, a high value would offer a long time period to trigger an intervention or prepare the patient for the upcoming seizure. In order not to obscure the impact of SPH on sensitivity, the seizure occurrence period indicating the uncertainty in the prediction time has been chosen to be a quite short time interval of 10 min duration. Again, a maximum false prediction rate of $FPR_{max} = 0.15$ FP/h has been chosen. The gray areas mark the corresponding range of the unspecific random prediction, limited by the lower and upper critical values.

The averaged sensitivity in Fig. 4a is approximately constant for the whole investigated range of prediction

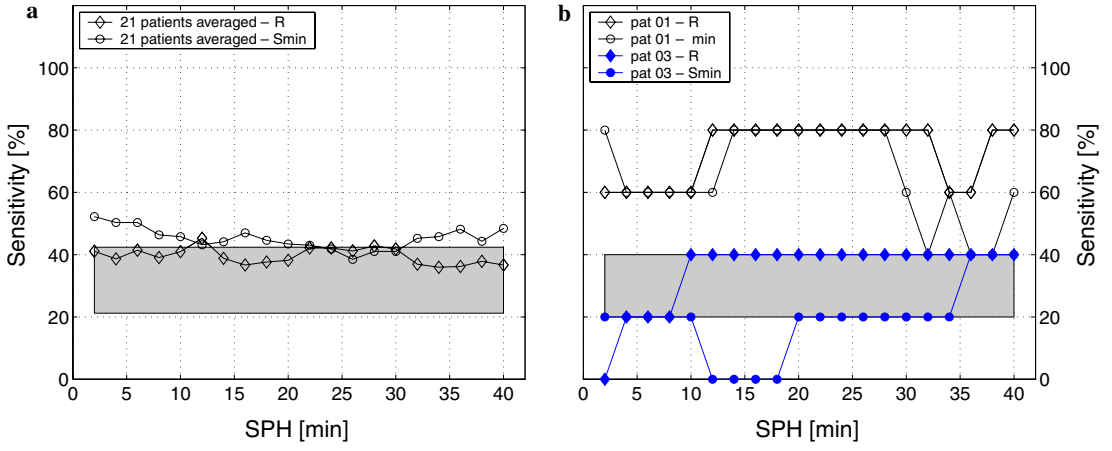

Fig. 4. Sensitivity for the synchronization measures R and $S_{\min}$ depending on the seizure prediction horizon. The seizure occurrence period has been set to 10 min and the maximum false prediction rate to $FPR_{max} = 0.15$ FP/h. The gray areas mark the corresponding range of the unspecific random prediction, limited by the lower and upper critical values. (a) Sensitivity values and the corresponding critical values are averaged for all 21 patients. (b) Patient individual sensitivity is given for patient 01 and patient 03 exemplarily.

horizons and exceeds at least the averaged lower critical value. A slight trend to short prediction horizons is observed for the synchronization measures $S_{\min}$. But there is no common range of prediction horizons which is optimal for all patients.

Individual results for patient 01 and patient 03, respectively, are shown in Fig. 4b. In contrast to the group results, patient 01 has an optimal range of seizure prediction horizons between 10 and 30 min for both seizure prediction methods. The performance of the seizure prediction method is significantly better than the upper critical value for this range. This is not the case for patient 03. But at least for the synchronization index R, the lower critical value is exceeded for several values of the prediction horizon. There is no optimal range of seizure prediction horizons for this patient.

3.4. Comparison between decrease and increase in synchronization

Changes in synchronization preceding an epileptic seizure could consist of either a decrease or of an increase. Though a decrease in synchronization has been observed between signals recorded from several electrode contacts in advance of seizure onsets in the previous sections, it remains to be investigated whether an increase in synchronization can be utilized to predict seizures. Therefore, the prediction performance of the mean phase coherence is analyzed with respect to two evaluation schemes: a decrease and an increase in the mean phase coherence.

Dependency of the sensitivity on the seizure prediction horizon for both evaluation schemes is given in Fig. 5. The seizure occurrence period has again been chosen to be 10 min. A maximum false prediction rate of $FPR_{max} = 0.15$ FP/h has been selected. The gray areas mark the corresponding range of the unspecific random prediction, limited by the lower and upper critical values.

In (a) the averaged sensitivity is shown for all 21 patients. The sensitivity using both evaluation schemes is approximately constant. Analyzing an increase in synchronization leads to a substantially lower averaged sensitivity close to the lower critical value.

In Fig. 5b, sensitivity is shown for patient 10 exemplarily. In contrast to the group result, a high and significant prediction performance is only observed analyzing an increase in synchronization. For prediction horizons between 22 and 30 min, sensitivity values are superior to the upper critical value. A significant prediction performance is not observed for a decrease in synchronization for this patient.

3.5. Sensitivity as a function of SPH for each patient individually

The previous sections have shown that optimal prediction horizons vary considerably between the exemplary patients. Interestingly, changes indicative of an impending seizure may comprise both, a decrease or an increase in synchronization. It appears that changes in synchronization may be utilized to predict seizures, but the evaluation scheme and the performance strongly depends on the individual patient. To emphasize the temporal characteristic of a prediction, sensitivity is calculated as a function of the seizure prediction horizon at a short duration of the seizure occurrence period, for both synchronization measures and for all patients individually with respect to a decrease and an increase in synchronization.

In Figs. 6 and 7, significant sensitivity values with respect to the upper critical values are presented depending on the seizure prediction horizon for each patient individually. The maximum false prediction rate has been set to $FPR_{max} = 0.15$ FP/h and the seizure occurrence period to $SOP = 10$ min. Sensitivity values are shown for both synchronization measures R and $S_{\min}$ and both evaluation

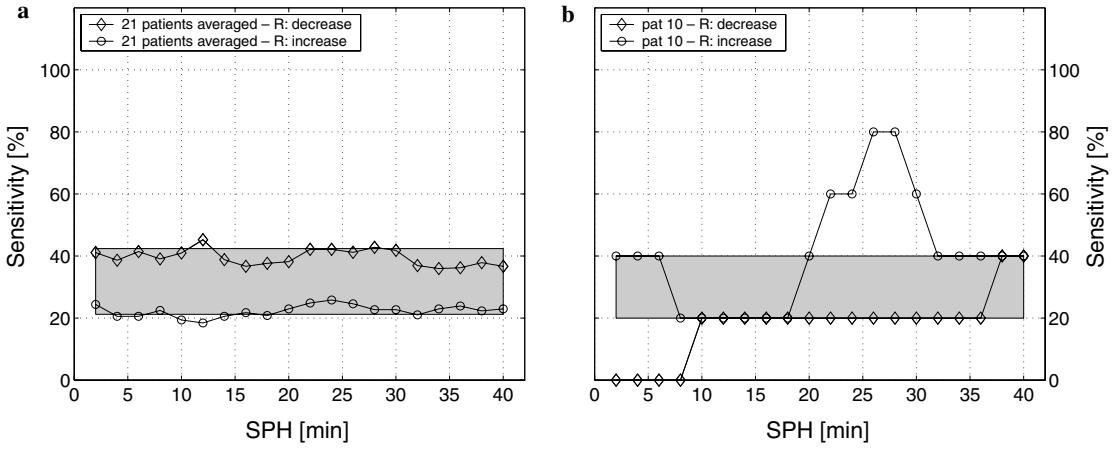

Fig. 5. Sensitivity depending on the seizure prediction horizon for the mean phase coherence R calculated for two different evaluation schemes: decrease and increase in synchronization. The seizure occurrence period has been set to 10 min and the maximum false prediction rate to $FPR_{max} = 0.15$ FP/h. The gray areas mark the corresponding range of the unspecific random prediction, limited by the lower and upper critical values. (a) Sensitivity values and the corresponding critical values are averaged for all 21 patients. (b) Patient individual sensitivity is given for patient 10.

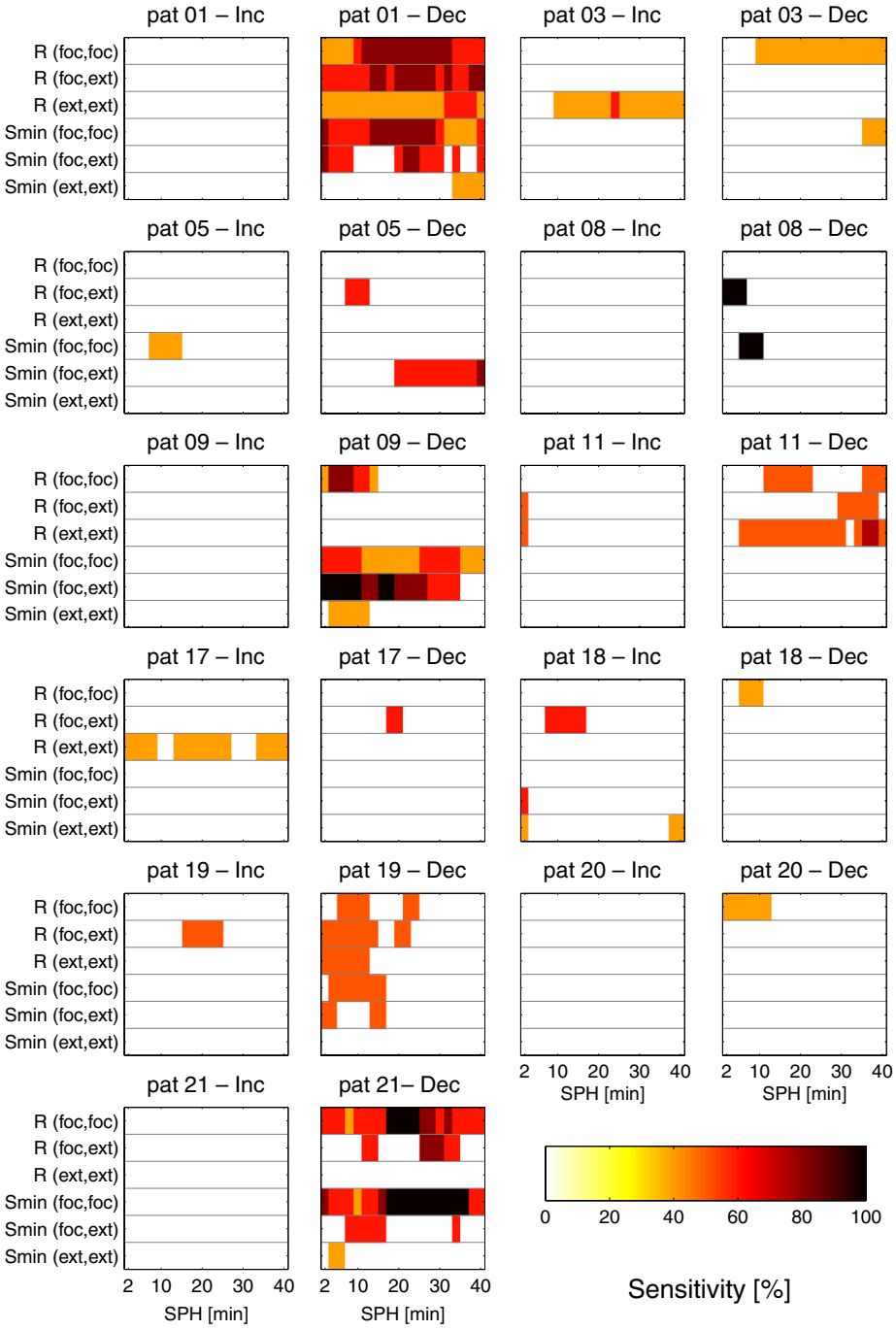

Fig. 6. Sensitivity depending on the seizure prediction horizon for 11 patients with seizure onset zone in neocortical brain structures. The maximum false prediction rate has been set to $FPR_{max} = 0.15$ FP/h and the seizure occurrence period to $SOP = 10$ min. Sensitivities are shown for both synchronization measures R and $S_{\min}$, and for the combinations between focal contacts (foc,foc), between focal and extra-focal (foc,ext), and between extra-focal contacts (ext,ext), respectively. Changes in synchronization are evaluated with respect to an increase (Inc) and a decrease (Dec) in synchronization. Maximum sensitivity values exceeding the upper critical values are shown.

schemes, an increase (Inc) and a decrease (Dec) in synchronization. Furthermore, maximum sensitivity values are estimated for the three different classes of electrode combinations individually, the electrode combinations between pairs of focal contacts (foc,foc), pairs consisting of one focal and one extra-focal contact (foc,ext), and pairs of extra-focal contacts (ext,ext).

For the majority of patients, a decrease in synchronization leads to a high prediction performance for individual optimal ranges of the prediction horizon. For instance for patient 09, high and significant sensitivity values are obtained a few minutes before seizure onsets for both synchronization measures (cf. Fig. 6). Nevertheless, an increase in synchronization also yields a significant predic-

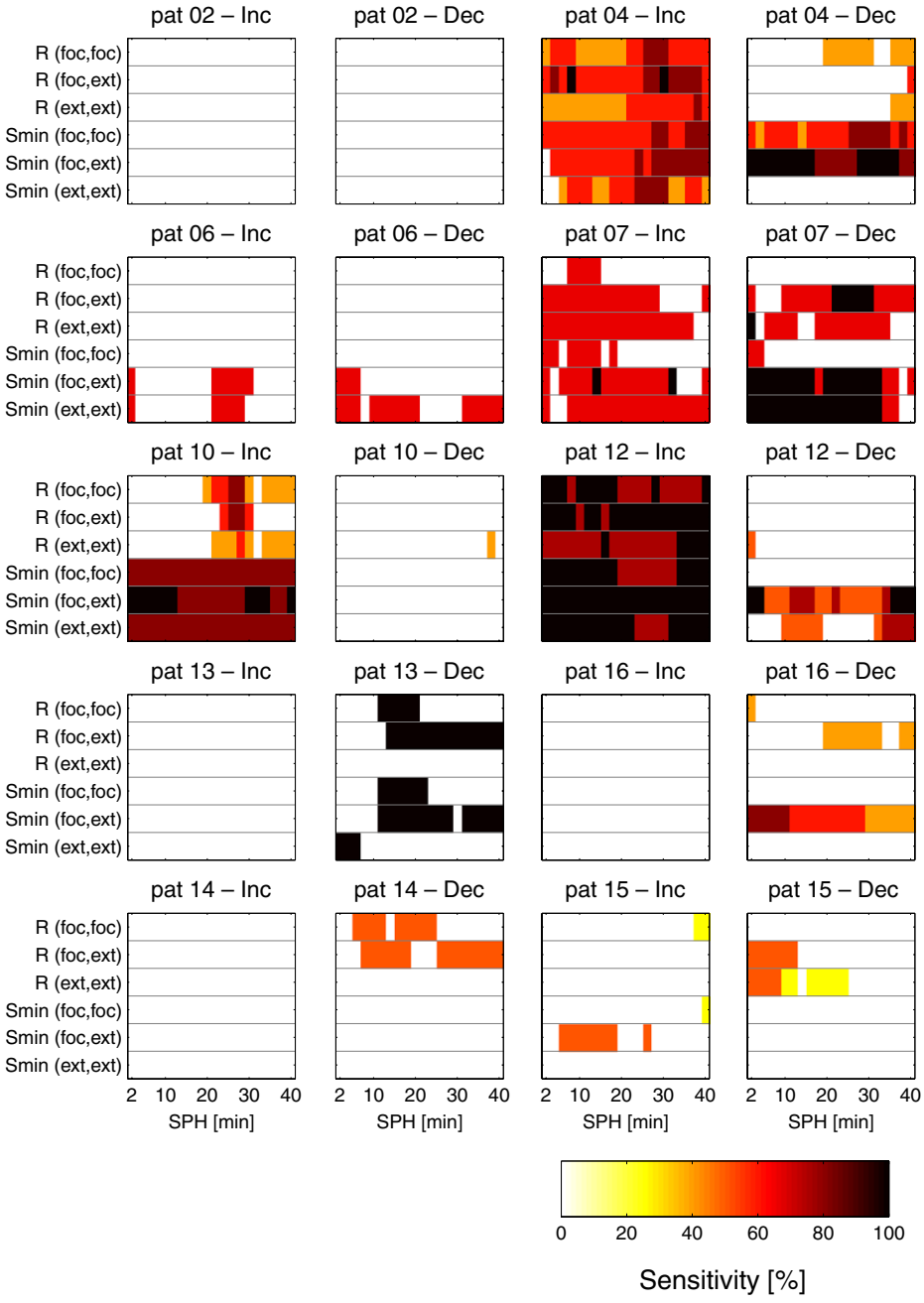

Fig. 7. Sensitivity depending on the seizure prediction horizon for eight patients with seizure onset zone in hippocampal brain structures as well as for two patients with neocortical and hippocampal seizure onset zones (patient 14 and 15). The maximum false prediction rate has been set to $FPR_{max} = 0.15$ FP/h and the seizure occurrence period to $SOP = 10$ min. Sensitivities are shown for both synchronization measures R and $S_{\min}$, and for the combinations between focal contacts (foc, foc), between focal and extra-focal (foc, ext), and between extra-focal contacts (ext, ext), respectively. Changes in synchronization are evaluated with respect to an increase (Inc) and a decrease (Dec) in synchronization. Maximum sensitivity values exceeding the upper critical values are shown.

tion performance for some patients (cf. Fig. 7). Furthermore, not all classes of electrode combinations and both synchronization measures show similar performance. In summary, the prediction performance between all patients differs considerably and no common rules can be proposed neither with respect to optimal prediction horizons, optimal classes of electrode combinations nor with respect to the evaluation scheme, decrease or increase in synchronization.

3.6. Spatial effects of electrode contacts selected for prediction

The previous section presented results for the three different classes of electrode combinations and for the 21 patients individually. This section reports results of a more detailed investigation concerning spatial effects by analyzing different brain structures with the three different classes of electrode contact combinations.

Table 2
Averaged sensitivities (%)

Algorithm	(foc,foc)	(foc,ext)	(ext,ext)
R – increase	25.3	30.3	29.1
$S_{\min}$ – increase	22.0	36.0	23.8
R – decrease	37.3	53.3	34.4
$S_{\min}$ – decrease	37.9	59.8	28.8

For each patient and for each class of electrode combinations, the maximum sensitivity is extracted from a range of seizure prediction horizons between 2 and 40 min for a decrease and an increase in synchronization. Sensitivity values averaged over patients are given.

For each patient and for each class of electrode combinations, the maximum sensitivity is extracted from a range of seizure prediction horizons between 2 and 40 min for a decrease and an increase in synchronization. Values averaged over patients are given in Table 2.

As the number of focal/extra-focal combinations is higher than for the remaining two classes, sensitivities as well as the critical values for these focal/extra-focal combinations are expected to be higher. To decide about the statistical significance of differences in the prediction performance using the three different classes of electrode combinations, $P_{\mathrm{binom},d}\{k;K;P\}$-values of the maximum sensitivity were calculated for each patient and class of combinations (cf. Section 2.3). The corresponding results of exact two-sided paired Wilcoxon signed rank-sum tests with respect to each patient for the differences between the $P_{\mathrm{binom},d}\{k;K;P\}$-values are given in Table 3. A significant difference between two classes of combinations is detected between the focal/extra-focal combinations and the focal/focal as well as the extra-focal/extra-focal combinations for the lag synchronization index $S_{\min}$ and a decrease in synchronization. The results of the tests for an increase in the lag synchronization as well as for the mean phase coherence R are not significant ($p > 0.05$).

Finally, differences in the prediction performance between both synchronization measures were investigated. For each class of electrode combinations exact two-sided paired Wilcoxon signed rank-sum tests were performed for each patient. The results of all six tests are not significant ($p > 0.05$).

4. Discussion

We investigated changes in synchronization in the intracranial EEG dynamics of epilepsy patients with particular emphasis on the temporal aspects of a prediction. The prediction performance was assessed for several values of SPH, SOP, and FPR_{max} by means of the seizure prediction characteristic. The statistical significance was tested on the basis of an analytic approach by comparison with critical sensitivity values for a given significance level; the latter is based on a random predictor following a Poisson process in time. Averaged results for 21 patients as well as individual results for each patient were given with respect to differences in the prediction performance using electrode contacts placed in focal and extra-focal brain structures, respectively. The results show that the preceding changes in synchronization are not uniform and evaluating both decreasing as well as increasing synchronization in the EEG dynamics can yield a significant prediction performance. Averaged sensitivity values of 60% can be observed for a false prediction rate of 0.15 false predictions per hour, an occurrence period of half an hour, and a prediction horizon of 10 min. The result that bivariate synchronization measures can be shown to be superior to a random predictor and both, decreasing and increasing synchrony is observed, is in close agreement with a recent study comparing 30 prediction algorithms (Mormann et al., 2005a).

Analyzing a decrease in synchronization, sensitivities averaged for all 21 patients were close to the averaged upper critical value for dependence on the maximum false prediction rate, on the seizure occurrence period as well as on the seizure prediction horizon for both synchronization

Table 3
Comparison of spatial effects in the prediction performance

decrease / increase	Index R			Index $S_{\min}$		
	(foc,foc)	(foc,ext)	(ext,ext)	(foc,foc)	(foc,ext)	(ext,ext)
(foc,foc)		0.34	0.9		0.01*	0.62
(foc,ext)	0.53		0.19	0.13		0.01*
(ext,ext)	0.45	0.11		0.09	0.57	

Results of an exact two-sided Wilcoxon signed rank-sum tests for the differences between the $P_{\mathrm{binom},d}\{k;K;P\}$-values of the three classes of electrode combinations for both synchronization measures and evaluation schemes. Significant results are marked by asterisks. For the lag synchronization measure $S_{\min}$, the class consisting of pairs of one focal and one extra-focal electrode contact is significantly superior to the class consisting of two focal contacts ($p = 0.01$) as well as to the class consisting of two extra-focal contacts ($p = 0.01$) for a decrease in synchronization.

measures. The relatively low prediction performance was related to a high inter-individual variability in the prediction performance for the different patients. On an individual basis, sensitivity values of both synchronization measures depending on the maximum false prediction rate, seizure occurrence period, and prediction horizon can be considerably higher compared to group results.

Different explanations for the high inter-individual variability in the prediction performance are conceivable. We performed a selection of electrode contacts in this study. This leads to a coarse sampling of the spatio-temporal process which might not be optimal. Analyzing all electrode contacts results in a prediction performance that cannot be shown to be superior to a random predictor, since the random predictor will achieve a spurious sensitivity of 100%. As a trade-off between coverage of the epileptogenic process and the ability to prove superiority to a random predictor, we restricted our analysis to six electrode contacts selected prior to data analysis. Based on the available electrode coverage of the brain, the three recording sites initially involved in ictal activity as well as the three electrode contacts latest involved in seizure spread were analyzed to include focal and extra-focal brain regions. For the patients with non-significant prediction performance, there is a possibility that electrode contacts not matching these selection criteria might lead to a prediction of seizures.

Limitations in the duration of the EEG recordings, different localizations of recording sites and differences in patient characteristics including their antiepileptic medication during the monitoring period may all contribute to the high interindividual variability of the results obtained. In addition, it has been hypothesized recently, that different states of vigilance and circadian changes in the measures might influence the seizure prediction performance (Mormann et al., 2005a). In our study, the seizures analyzed did not occur at similar times of the day, but a relation between seizure prediction performance and time points of seizure onsets is not evident. There is evidence that the distribution of false predictions depends on circadian changes in EEG dynamics (Schelter et al., 2006b).

Up to now, synchronization measures for the detection of changes in the EEG dynamics in long preictal time intervals have been investigated (Mormann et al., 2000, 2003a,b, 2005a; Le van Quyen et al., 2005). Anticipation times between minutes up to several hours were reported. In contrast, our study focused, first, on the temporal assessment under conditions required for a prediction, i.e., short seizure occurrence periods and various seizure predictions horizons that can be considered as intervention times, and, second, on prediction horizons shorter than 1 h. The uncertainty in the exactness of the prediction, the seizure occurrence period, should be as short as possible. The maximum tolerable value of the occurrence period depends on the type of intervention, which is triggered based on a prediction. In the case of a warning of the patient followed by behavioral adaptation, the strain on the patients increases for longer occurrence periods. In the case of an intervention using, for instance, administration of short-acting, anticonvulsive drugs, possible impairment due to side-effects may depend on the duration of an intervention.

The probability of predicting seizures by chance increases with increasing duration of the seizure occurrence period, as the former depends on the product of maximum false prediction rate and seizure occurrence period. For example, accepting five false predictions within one day and a seizure occurrence period of 2 h, the sensitivity of an unspecific random prediction reaches a value of 100%, if up to five seizures and 15 independent features were investigated. Thus, tuning of algorithms to detect long occurrence periods is of limited use for two reasons: the dependence of the random predictor on the seizure occurrence period and the subsequent behavioral or interventional consequences to avoid or suppress the seizures.

Considering the impact of behavioral or interventional consequences would be dispensable if a single treatment could suppress seizures hours in advance of seizure onsets. Whether or not such an intervention is possible is speculative since there is no proof so far. The concept of the seizure prediction horizon allows for long intervention times, as there is no restriction when the intervention has to be placed during the seizure prediction horizon. Thus, we claim that in general long seizure occurrence periods are of limited use, since they quantify the uncertainty of the occurrence of the seizure. For statistical reasons long seizure occurrence periods could be accepted in combination with low false prediction rates, since the product of false prediction rate and seizure occurrence period defines the random predictor.

To assess the seizure prediction performance depending on the duration of the prediction horizon, this time interval has been varied at a short seizure occurrence period of 10 min duration. The group results averaged for all 21 patients have shown that there are no common optimal prediction horizons in the investigated range of 40 min duration. However, analysis on an individual basis has shown that for approximately half the patients optimal values of the prediction horizon exist. These prediction horizons can differ considerably between the patients. The fact that for some patients sensitivity values are non-significant for all investigated prediction horizons does not indicate a non-predictability of seizures for those patients. Changes in the EEG dynamics earlier than the investigated range of 50 min preictal EEG data segments could still be useful for a seizure prediction. But preictal changes in the EEG dynamics of several hours (Mormann et al., 2003b; Le van Quyen et al., 2005) are especially useful for therapeutic or behavioral interventions if the seizure occurrence period is fixed at a short duration. The value of such long preictal changes remains to be investigated in further studies on the basis of longer preictal EEG data sets, by increasing the duration of the seizure prediction horizon for a sufficiently short duration of the seizure occurrence periods.

It has been demonstrated in the present study that there is no common rule for all patients as to whether a decrease or an increase in synchronization precedes seizures. For some patients only a decrease in synchronization yields a significant prediction performance. In contrast, analyzing an increase in synchronization obtains significant prediction performance for some other patients. In recent studies investigating synchronization changes in the EEG dynamics for five patients using long-term EEG recordings, a similar effect has been observed (Le van Quyen et al., 2005; Mormann et al., 2005a). This may point to the fact that various pathogenic mechanisms precede epileptic seizures: a decrease in synchronization between specific brain regions accompanied by an increase in synchronization between other brain regions. Both mechanisms seem to be individually pronounced for the individual patients.

So far, the contribution of inter-focal and extra-focal changes in brain dynamics to the generation of epileptic seizures has remained unclear. Whereas several studies have focused on an investigation of preictal changes in the primary epileptogenic area as indicated by the seizure onset zone (Lehnertz and Elger, 1998; Litt et al., 2001), other results suggest widespread preictal changes (Le van Quyen et al., 2000). The synchronization of focal and extra-focal areas may be of particular importance for the local generation of epileptic activity. Thus, the spatial effects concerning focal and extra-focal brain structures have been investigated by analyzing the three classes of electrode combinations separately.

In the present study, combinations of focal and extra-focal electrodes have a significantly higher prediction performance for the lag synchronization. The statistically significant superiority of the focal/extra-focal electrode combination for the lag synchronization index is achieved by a change in sensitivity of more than 20%. In contrast, for the mean phase coherence R no similar trend is observed. This result indicates that the lag synchronization index captures differences and time delays in the EEG dynamics between focal and extra-focal brain structures in particular. This may point to underlying pathogenic mechanisms, i.e., decoupling of dynamics of focal and extra-focal areas as a contribution to the generation of local, highly hyper-synchronized activity. The result for the mean phase coherence R is in agreement with a previous study (Mormann et al., 2003b), where the spatial distribution of preictal changes in the EEG dynamics was not exclusively restricted to focal brain areas.

In summary, using the seizure prediction characteristic with its critical sensitivity values, we assessed changes in the synchronization of the EEG dynamics with respect to seizure prediction. Examination of dynamics in different brain structures with combinations of focal and extra-focal electrode contacts yields a significantly higher seizure prediction performance than using combinations of exclusively focal or exclusively extra-focal contacts, respectively, for the lag synchronization measure. Our results strongly indicate that the prediction method and its evaluation scheme, optimized values of the prediction horizons, and preferred brain structures for the EEG recordings have to be determined for each patient and prediction method individually.

5. Data availability

The data analyzed in this study are available on request:
Web page: http://www.fdm.uni-freiburg.de/EpilepsyData
Email: epilepsydatabase@fdm.uni-freiburg.de

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References

Andrzejak RG, Mormann F, Kreuz T, Rieke C, Elger CE, Lehnertz K. Testing the null hypothesis of the nonexistence of a preseizure state. Phys Rev E 2003;67:010901.

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.

Boccaletti S, Kurths J, Osipov G, Valladares D, Zhou C. The synchronization of chaotic systems. Phys Rep 2002;366:1–101.

Chaovalitwongse W, Iasemidis LD, Pardalos PM, Carney PR, Shiau DS, Sackellares JC. Performance of a seizure warning algorithm based on the dynamics of intracranial EEG. Epilepsy Res 2005;64:93–113.

Chavez M, Le van Quyen M, Navarro V, Baulac M, Martinerie J. Spatio-temporal dynamics prior to neocortical seizures: Amplitude versus phase couplings. IEEE Trans Biomed Eng 2003;50:571–83.

De Clercq W, Lemmerling P, Van Huffel S, Van Paesschen W. Anticipation of epileptic seizures from standard EEG recordings. Lancet 2003;361:970, author reply 970–1.

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

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.

Iasemidis LD, Shiau DS, Chaovalitwongse W, Sackellares JC, Pardalos PM, Principe JC, et al. Adaptive epileptic seizure prediction system. IEEE Trans Biomed Eng 2003;50:616–27.

Iasemidis LD, Shiau DS, Pardalos PM, Chaovalitwongse W, Narayanan K, Prasad A, et al. Long-term prospective on-line real-time seizure prediction. Clin Neurophysiol 2005;116:532–44.

Gabor D. Theory of communication. J IEE London 1946;93:429–57.

Gluckman BJ, Nguyen H, Weinstein SL, Schiff SJ. Adaptive electric field control of epileptic seizures. J Neurosci 2001;21:590–600.

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

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

Kreuz T, Andrzejak RG, Mormann F, Kraskov A, Stögbauer H, Elger CE, et al. Measure profile surrogates: a method to validate the performance of epileptic seizure prediction algorithms. Phys Rev E 2004;69:061915.

Lai YC, Harrison MAF, Frei MG, Osorio I. Inability of Lyapunov exponents to predict epileptic seizures. Phys Rev Lett 2003;91:068102.

Lai YC, Harrison MAF, Frei MG, Osorio I. Controlled test for predictive power of Lyapunov exponents: their inability to predict epileptic seizures. Chaos 2004;14:630–42.

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

Lehnertz K, Litt B. The First International Collaborative Workshop on Seizure Prediction: summary and data description. Clin Neurophysiol 2005;116:493–505.

Lehnertz K, Andrzejak R, Arnhold J, Kreuz T, Mormann F, Rieke C, et al. Nonlinear EEG analysis in epilepsy: Its possible use for interictal focus localization, seizure anticipation, and prevention. J Clin Neurophysiol 2001;18:209–22.

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

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

Le van Quyen M, Soss J, Navarro V, Robertson R, Chavez M, Baulac M, et al. Preictal state identification by synchronization changes in long-term intracranial EEG recordings. Clin Neurophysiol 2005;116:559–68.

Litt B, Lehnertz K. Seizure prediction and the preseizure period. Curr Opin Neurol 2002;15:173–7.

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.

Lopes da Silva FH, Blanes W, Kalitzin SN, Parra J, Suffczynski P, Velis DN. Dynamical diseases of brain systems: different routes to epileptic seizures. IEEE Trans Biomed Eng 2003a;50:540–8.

Lopes da Silva F, Blanes W, Kalitzin SN, Parra J, Suffczynski P, Velis DN. Epilepsies as dynamical diseases of brain systems: basic models of the transition between normal and epileptic activity. Epilepsia 2003b;44:72–83.

Maiwald T, Winterhalder M, Aschenbrenner-Scheibe R, Voss HU, 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.

McSharry PE, Smith LA, Tarassenko L. Comparison of predictability of epileptic seizures by a linear and a nonlinear method. IEEE Trans Biomed Eng 2003;50:628–33.

Milton J, Jung P. Brain defibrillators: synopsis, problems and future directions. In: Milton J, Jung P, editors. Epilepsy as a dynamic disease. New York: Springer; 2003.

Mormann F, Andrzejak RG, Elger CE, Lehnertz K. Comment on: "Seizure anticipation: do mathematical measures correlate with video-EEG evaluation? Epilepsia 2005b;46:1335–6, author reply 1336–7.

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

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

Mormann F, Kreuz T, Rieke C, Andrzejak RG, Kraskov A, David P, et al. On the predictability of epileptic seizures. Clin Neurophysiol 2005a;116:569–87.

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.

Nicolelis M. Actions from thoughts. Nature 2002;409:403–7.

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.

Pikovsky A, Rosenblum M, Kurths J. Synchronization – a universal concept in nonlinear sciences. Cambridge: Cambridge University Press; 2001.

Rosenblum MG, Pikovsky AS, Kurths J. Phase synchronization of chaotic oscillators. Phys Rev Lett 1996;76:1804–7.

Rosenblum MG, Pikovsky AS, Kurths J. From phase to lag synchronization in coupled chaotic oscillators. Phys Rev Lett 1997;78:4193–6.

Rosenblum M, Pikovsky A, Kurths J, Schäfer C, Tass P. Phase synchronization: from theory to data analysis. In: Moss F, Gielen S, editors. Handbook of Biological Physics. Amsterdam: Elsevier; 2001.

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. Do false predictions of seizures depend on the state of vigilance? A report from two seizure prediction methods and proposed remedies. Epilepsia [in press].

Schiff SJ, Jerger K, Duong DH, Chang T, Spano ML, Ditto WL. Controlling chaos in the brain. Nature 1994;370:615–20.

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.

Tass P, Rosenblum MG, Weule J, Kurths J, Pikovsky A, Volkmann J, et al. Detection of n:m phase locking from noisy data: application to magnetoencephalography. Phys Rev Lett 1998;81:3291–5.

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.

Winterhalder M, Schelter B, Kurths J, Schulze-Bonhage A, Timmer J. Sensitivity and specificity of coherence and phase synchronization analysis. Phys Lett A 2006;356:26–34.