How well can epileptic seizures be predicted? 
An evaluation of a nonlinear method

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Summary
The unpredictability of the occurrence of epileptic seizures contributes to the burden of the disease to a major degree. Thus, various methods have been proposed to predict the onset of seizures based on EEG recordings. A nonlinear feature motivated by the correlation dimension is a seemingly promising approach. In a previous study this method was reported to identify ‘preictal dimension drops’ up to 19 min before seizure onset, exceeding the variability of interictal data sets of 30–50 min duration. Here we have investigated the sensitivity and specificity of this method based on invasive long-term recordings from 21 patients with medically intractable partial epilepsies, who underwent invasive pre-surgical monitoring. The evaluation of interictal 24-h recordings comprising the sleep–wake cycle showed that only one out of 88 seizures was preceded by a significant preictal dimension drop. In a second analysis, the relation between dimension drops within time windows of up to 50 min before seizure onset and interictal periods was investigated. For false-prediction rates below 0.1/h, the sensitivity ranged from 8.3 to 38.3% depending on the prediction window length. Overall, the mean length and amplitude of dimension drops showed no significant differences between interictal and preictal data sets.

Keywords: epilepsy; false-prediction rate; intracranial EEG; nonlinear analysis; seizure prediction

Abbreviations: FPR = false-prediction rate

Introduction
Epilepsy is characterized by sudden recurrent and transient disturbances of perception or behaviour resulting from excessive synchronization of cortical neuronal networks. Owing to the sudden and unforeseeable occurrence of epileptic seizures, everyday activities are impaired and can become dangerous for patients (Cockerell et al., 1994). The unpredictability of seizure onset is one of the most important causes of morbidity and stress in patients with epilepsy (Murray, 1993; Buck et al., 1997). Being able to predict the onset of seizures would render the implementation of alarm systems and novel therapeutic approaches possible; e.g. automated interventional measures like the application of anticonvulsant drugs or electrical brain stimulation (Stein et al., 2000). In addition, the identification of a pre-seizure state could contribute to the investigation of the pathophysiological mechanisms causing seizures.

Recently, there has been growing interest in whether methods from nonlinear dynamics are able to identify preictal states from EEG recordings (Iasemidis et al., 1990, 1997; Pijn et al., 1991, 1997; Pritchard and Duke, 1992; Lehnertz and Elger, 1995, 1998; Pritchard et al., 1995; Martiner et al., 1998; Osorio et al., 1998; Schiff, 1998; Moser et al., 1999; Jerger et al., 2001; Le Van Quyen et al., 2001b; Lai et al., 2002; Navarro et al., 2002; Osorio et al., 2002; Winterhalder et al., 2003; for recent reviews see Lehnertz et al., 2001; Le Van Quyen et al., 2001a; Litt and Lehnertz, 2002; Litt and Echauz, 2002). Seizure prediction times from minutes to hours have been reported.

In a pioneering work, the group of Lehnertz and Elger applied a nonlinear feature motivated by the correlation dimension to intracranial EEG data recorded from the seizure focus (Lehnertz and Elger 1995, 1998; Lehnertz et al., 2001). They observed reductions in the dimensional complexity of brain activity immediately preceding seizures. ‘Dimension drops’ of sufficient amplitude and duration were regarded as a specific feature defining seizure preceding states. Such seizure-preceding states
were found to last up to 25 min. In a study with data from patients with mesial temporal lobe epilepsy of hippocampal origin and neocortical lesional epilepsy, 67% of the seizures from the hippocampal group and 29% of the seizures in the neocortical group were preceded by predictive dimension drops (Lehnertz et al., 2001).

These studies were based only on low numbers of seizures per patient and short interictal data segments. The acceptance of seizure-preceding dimension drops as predictive, however, depends critically on the variability of the dimension during the interictal periods evaluated. As Litt and Lehnertz (2002) pointed out, seizure prediction methods should be assessed based on long-term EEG recordings. We have thus used contiguous data segments over 24 h, including circadian variations, to validate the potential of the correlation dimension method to predict seizures.

As the sensitivity of preictal dimension drops directly preceding seizures turned out to be low when evaluated based on long-term interictal data, we extended our analysis by accepting false predictions and analysing longer time windows preceding seizure onset. This allowed for a combined evaluation of specificity and sensitivity based on clinical requirements and the comparison of the method with an unspecific random alert system.

### Material and methods

#### Patients

Invasive EEG recordings from 21 patients with medically intractable focal epilepsy of temporal and extratemporal origin were used for this study. Their clinical characteristics are summarized in Table 1. All patients underwent a complete presurgical evaluation comprising high resolution MRI, functional imaging, neuropsychological evaluation, and video telemetry with interictal and ictal surface and invasive EEG recordings. Patients with intracranial electrodes were chosen in order to study EEG data within the epileptogenic zone at high signal-to-noise ratio. Intracranial recordings were performed via stereotactically implanted depth electrodes, and via subdural strip and grid electrodes implanted through burr holes or open skull surgery, respectively. The positions of intracranially implanted electrodes were identified on reconstructed 3D MRI data sets (Schulze-Bonhage et al., 2002). All patients gave their informed consent to the evaluation of their EEG data. Retrospective evaluation of data was approved by the Ethics Committee, Medical Faculty, University of Freiburg.

### EEG data acquisition

EEG data acquisition was performed with a Neurofile NT digital video EEG system (it-med, Usingen, Germany), with

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<th>Origin</th>
<th>Electrodes</th>
<th>Resection/ outcome</th>
<th>No. seizures analysed</th>
<th>Interictal true period/h</th>
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Resection outcome according to Engel classification. M = male; F = female. Seizure types: SP = simple partial; CP = complex partial; GTC = generalized tonic-clonic. Origin: H = hippocampal; NC = neocortical. Electrodes: g = grid; s = strip; d = depth.
128 channels, 256 or 512 Hz sampling rate, and a 16 bit analogue-to-digital converter. Data were bandpass filtered between 0.53 and 80 Hz. Filtering at 0.53 Hz was necessary to improve the stationarity of the data and to remove trends (van der Heyden et al., 1999). A 50 Hz notch filter was applied to remove line noise. The data were continuously recorded from implantation to explantation of the electrodes. All EEG and video data were visually inspected by board-certified epileptologists. Major events, both clinical and electroencephalographic, were marked in the EEG data files. Preictal data sets from 88 clinically manifest seizures (30 seizures with hippocampal origin, mean of 3.8 seizures per patient; 58 seizures with neocortical origin, mean of 4.5 seizures per patient) were analysed. For a given patient, either all available or five consecutive seizures were used. Each preictal data set contained at least 50 min of preictal data. At least 24 h of interictal data per patient (total 509 h) was used, comprising circadian rhythms including a complete sleep–wake cycle. The median of the time periods between the last seizure preceding 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. For each patient, three intracranial electrodes located in or in close proximity to the seizure onset zone were evaluated (Fig. 1). These electrodes were referenced to an electrode displaying only a minimal amount of epileptic activity.

**Calculation of the correlation dimension**

The effective correlation dimension $D_{2\text{eff}}$ is a nonlinear feature that is motivated by the correlation dimension $D_2$ (Grassberger and Procaccia, 1983a, b). $D_2$ is a measure for the fractality of the attractor of a low-dimensional, deterministic, stationary, dynamical system. The correlation dimension is obtained by first calculating a correlation sum $C_m(r)$ for a collection of $K$ points embedded in a reconstructed $m$-dimensional phase space (Takens, 1981). This sum counts the fraction of all pairs of points $y_i, y_j$ that are closer than a given distance $r$ (Theiler, 1986; Kantz and Schreiber, 1997)

$$C_m(r) = \frac{1}{N_p} \sum_{i=1}^{K-W} \sum_{j=i+w}^{K} \theta(r - \|y_i - y_j\|),$$

where $\theta$ is the Heaviside step function ($\theta(x) = 0$ if $x \leq 0$, $\theta(x) = 1$ if $x > 0$) and $N_p = (K - W + 1)(K - W)/2$ is a normalization factor (with a Theiler correction of $W$ points). In the limit of an infinite amount of data and for large enough $m$ and for small $r$, $C_m(r)$ is expected to scale with a power law, $C_m(r) \propto r^{D_2}$, and the correlation dimension $D_2$ is defined by:

$$D_2 = \lim_{r \rightarrow 0} \frac{\frac{d\log C_m(r)}{d\log r}}{r}.$$

If applied to measured data, existence of a proper scaling is not necessarily given. To establish a scaling behaviour, local slopes $C_m'(r) = \frac{d\log C_m(r)}{d\log r}$ of the correlation sum should be calculated (Kantz and Schreiber, 1997).

We followed the operational method of Lehnerz and Elger (1998) to obtain an effective scaling region from the local slopes $C_m'(r)$ of the correlation sums. An average $D^*$ over the number of points $N_r$ of $r$ values in the interval $[r_l, r_u]$ of $C_m'(r)$ between a lower bound of the hypersphere radius $r_l$ and an upper bound $r_u$ defines the effective correlation dimension

$$D^*_m = \frac{1}{N_r} \sum_{r_{r_l}}^{r_u} C_m'(r).$$

The upper bound $r_u$ is attributed to the largest $r$ where $C_m'(r_{ru}, m = 1) > 0.975$. The lower bound $r_l$ is defined as:
\[ r_i = \min \{ r < r_u | |C'_m_{\text{max}}(r_u) - C'_m_{\text{max}}(r)| \leq \delta \}, \]
\[ \text{with } \delta = 0.05 \quad C'_m_{\text{max}}(r_u), \quad m_{\text{max}} = 25. \]

Finally, \( D_{2}^{\text{eff}} \) is given as:
\[
D_{2}^{\text{eff}} = \begin{cases} 
D' & \text{if } N_r \geq 5 \\
10 & \text{else}
\end{cases}
\]

If no scaling region could be determined, \( D_{2}^{\text{eff}} \) was set to the default value of 10. \( D_{2}^{\text{eff}} \) was calculated for the interictal and the preictal data sets of patient data. For each electrode, channel sample correlation integrals according to Equation 1 were calculated for moving data window epochs of 4096 data points. These epochs were shifted along the EEG sequence with 2048 points overlap. The time series was embedded into \( m \)-dimensional phase space (\( m = 25 \)) with a delay \( \tau = 2 \) sampling points, and \( W = 8 \) sampling points. To smoothen the output curve of the \( D_{2}^{\text{eff}} \) data, a median filter over three data points was applied.

**Definition of predictive dimension drops**

According to Lehnertz et al. (2001), a preictal dimension drop is considered predictive: (i) if it is confined to the epileptogenic area; (ii) if it directly precedes a seizure; and (iii) if preictal dimension drop parameters, duration and amplitude, exceed the maximum values of interictal dimension drops (determined per electrode). Figure 2 depicts the definition of the parameters of an interictal and of a preictal dimension drop, the latter of which directly precedes a seizure. For each recording site from all interictal data sets for each patient, the mean interictal level \( D_{\text{avg}} \) is determined. For interictal data sets, \( t_i \) is defined as the longest time interval with \( D_{2}^{\text{eff}} \) below \( D_{\text{avg}} \). For preictal data, \( t_p \) is the time interval between seizure onset and the previous downward crossing of \( D_{2}^{\text{eff}} \) with \( D_{\text{avg}} \). The maximum deflections \( d_i \) and \( d_p \) are defined as the difference between the minimum of \( D_{2}^{\text{eff}} \) and \( D_{\text{avg}} \) during \( t_i \) and \( t_p \), respectively. As there is no natural order relation in the 2D parameter space, we first determined \( t_i \) for each interictal data set and then measured \( d_i \) within this drop.

**Evaluation**

To evaluate the dimension drops obtained from the effective correlation dimension method, two kinds of analyses were performed. First, it was investigated for each electrode whether dimension drops were predictive according to the three requirements of the above definition. Preictal dimension drops which directly precede a seizure were identified and the parameters \( t_p \) and \( d_p \) were compared with the maximal parameters from the interictal data sets. Secondly, in order to evaluate specificity and sensitivity of the method in consideration of clinical demands, the drops were analysed under less strict requirements. Instead of requirement (ii), that predictive preictal dimension drops had to precede seizures, they were evaluated within a predefined time window before seizure onset. This conforms to analogous analyses done by other groups (Martinerie et al., 1998; Le Van Quyen et al., 1999; Litt et al., 2001). The mean values \( t_{p, \text{avg}}, d_{p, \text{avg}}, t_{i, \text{avg}} \) and \( d_{i, \text{avg}} \), and the medians \( t_{p, \text{med}}, d_{p, \text{med}}, t_{i, \text{med}} \) and \( d_{i, \text{med}} \) of the parameters of the dimension drops, and of all drops with \( t_p, t_i \geq 80 \text{ s} \), corresponding to 10 data points of \( D_{2}^{\text{eff}} \), were
calculated for the preictal and the interictal period, respectively. Requirement (iii) was loosened, in that dimension drop parameters regarded as predictive did not have to exceed maximum values of interictal parameters. This led to an optimization method for an alarm system suitable for online analysis as explained below.

The prediction of a seizure corresponds to the classification of all possible observations into the two disjoint subsets: (i) ‘a seizure will occur’ or (ii) ‘no seizure will occur’, which leads to the classification of each data set into ‘preictal’ or ‘not preictal’, respectively. To quantify prediction performance, we use the notion of sensitivity and false-prediction rate (FPR). The sensitivity is the number of correct predictions in relation to the total number of predictions. Specificity is quantified by the FPR, given as the number of falsely predicted seizures per hour of interictal data. For a given FPR, the associated threshold values for the parameters specifying the dimension drops are calculated. Minimal durations of dimension drops were evaluated for up to half the prediction window length in increments of 1 min. Sensitivity is derived by applying these thresholds to the preictal dimension drops. The results are displayed as sensitivity/FPR curves. Lower threshold values give a higher probability of correct predictions at the expense of higher FPR. By proper adjustment of the threshold, one can trade off sensitivity for FPR. The calculation of sensitivity was based on three prediction windows of 10, 20 and 50 min duration, ending 5 s before the electrographic seizure onset. After a false prediction in the
The alarm mechanism was deactivated for the duration of the respective alarm window for the preictal analysis.

Figure 3 gives an example with interictal (Fig. 3a and b) and preictal (Fig. 3c and d) data sets of one patient. A dimension drop directly precedes a seizure in Fig. 3d. However, the dimension drop parameters do not exceed the maximal interictal values in Fig. 3b. Hence, the drop is not predictive according to the above definition. The evaluation with allowed false alarms in the 10, 20 and 50 min alarm window depends on the derived thresholds $T$ and the minimal dimension drop durations.

Random alert system

A minimum requirement for a useful prediction method is its superiority to a random alert system. Within a small time interval $u$ a maximum FPR $FPR_{\text{max}}$ can be expressed as the probability $P = FPR_{\text{max}}/u$ to produce one false alarm. The probability $P$ for exactly one false alarm within a time interval $W = nu$, with an integer $n$, is hence:

$$P = 1 - (1 - FPR_{\text{max}}u)^W$$

If $u$ is small compared with $W$, $P$ can be approximated as:

$$P = 1 - e^{-FPR_{\text{max}}W}$$

$P$ describes the sensitivity of a random alert system. For a large window length $W$, $P$ converges to 1, e.g. if $FPR_{\text{max}} = 0.1/h$ and $W = 50 \, h$, Equation 2 yields $P = 0.9933$.

Results

Predictive dimension drops directly preceding seizures

The results of the dimension drop analysis for interictal and preictal data of the hippocampal and neocortical groups according to the definition from Lehnertz et al. (2001) are given in Table 2. Mean values and medians of the maximum interictal dimension drop parameters were: $t_{i,\text{avg}} = 10.9 \, \text{min}$, $d_{i,\text{avg}} = 3.7$, $t_{i,\text{med}} = 8.0 \, \text{min}$, $d_{i,\text{med}} = 3.6$, for the hippocampal group, and $t_{i,\text{avg}} = 12.4 \, \text{min}$, $d_{i,\text{avg}} = 3.7$, $t_{i,\text{med}} = 5.3 \, \text{min}$, $d_{i,\text{med}} = 3.8$ for the neocortical group. Dimension drops directly preceded seizures in five out of 30 (17%) seizures of hippocampal origin, and in nine out of 58 (16%) seizures of neocortical origin. The mean time intervals $t_{p,\text{avg}}$ of all dimension drops directly preceding seizures were 0.4 and 1.7 min for the hippocampal and neocortical group, respectively. For only one dimension drop from the neocortical group, the parameters ($t_p = 8 \, \text{min}$ and $d_p = 3.8$) exceeded the maximum values of the interictal dimension drops. Following the criteria of Lehnertz et al. (2001), this was the only correct...
seizure prediction. No dimension drop from the hippocampal group was predictive.

**Predictive dimension drops within preictal time windows**

**Hippocampal group**

The mean values and medians of all interictal and preictal dimension drops with \( t_i, t_p \geq 80 \text{ s} \) were: \( t_{i,avg} = 2.7 \text{ min}, t_{i,med} = 1.9 \text{ min}, \) \( t_{p,avg} = 2.9 \text{ min}, t_{p,med} = 1.9 \text{ min}, \) and \( d_{i,avg} = 2.4, d_{i,med} = 2.4, d_{p,avg} = 2.6, d_{p,med} = 2.5. \) The means and medians differ due to the skewed distribution with many short drops compared with few long drops. There were no significant differences between the interictal and preictal data. The maximum duration of the individual dimension drops was 1504 s interictally and 1952 s preictally.

For seven given FPR between 0/h and 1/h based on thresholds derived from the interictal data, the sensitivities for each patient for the 10, 20 and 50 min windows are given in Table 3. The values of the averaged sensitivities \( S_{avg} \) for all patients are displayed for the 10, 20 and 50 min alarm windows in Fig. 4 for optimized minimal durations of dimension drops. For \( FPR_{max} = 0/h \) the averaged sensitivities were 4.2, 9.2 and 14.2% for the 10, 20 and 50 min windows, respectively. For \( FPR_{max} = 0.1/h \) the averaged sensitivities were 8.3, 13.3 and 38.3% for the 10, 20 and 50 min windows, respectively. For increasing \( FPR_{max} \), sensitivities rise up to 95% for a 50 min alarm window and FPR of 1/h.

The sensitivities from the corresponding random alert systems according to Equation 2 are displayed in Fig. 5. These are significantly lower than the sensitivities of the prediction algorithm.

There was no consistent difference in the performance of seizure prediction between patients who became seizure-free after surgery and those who did not.

**Discussion**

**Importance of interictal data for the evaluation of seizure prediction algorithms**

The successful identification of preictal periods by extracting features from EEG data critically depends on the comparison with the behaviour of the feature during interictal periods. Both specificity and sensitivity of a prediction method can be quantified, but only based on long-term EEG recordings comprising a sufficient number of preictal periods, ictal events and interictal data representing the natural variability, e.g. including the effects of circadian rhythms (Litt and Lehnertz, 2002; Litt and Echauz, 2002). In other words, whether an algorithm that detects preictal changes in the EEG is of clinical value depends on the number of false predictions for interictal data. To determine this relation quantitatively, our evaluation of a nonlinear method to predict epileptic seizures was based on a representative long-term EEG data set, comprising 50 min of preictal and 24 h of interictal periods.

**Predictive dimension drops**

Using an algorithm based on drops in the effective correlation dimension \( D_{t,eff} \), Lehnertz and Elger (1998) reported that a reduced dimensional complexity of brain activity, as soon as it is of sufficient size and duration, can be regarded as a specific feature defining states that precede a seizure. Analysing data from the epileptogenic area, they reported seizure preceding predictive dimension drops in 67% of hippocampal and 29% of neocortical epilepsy (Lehnertz et al., 2001). Predictive dimension drops were defined as being more pronounced than during interictal periods. This is where the amount and representativity of interictal data come into play. Our analysis resulted in only one successful prediction out of 88 preictal periods. The natural explanation for this dramatic loss of performance is the greater and more representative variability of the dimension drops within interictal periods of longer duration (24 h) compared with the 30–50 min blocks in the former study.

**Permitting false predictions**

In their study, Lehnertz et al. (2001) considered only dimension drops that exceeded interictal ones and directly preceded the seizure. Our analysis suggests that these criteria are too stringent to be successfully applied to long-term data.
### Table 3 Detailed results with sensitivities and maximum FPR

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**S_{avg}**

| 4.17 | 4.17 | 8.33 | 27.50 | 27.50 | 32.50 | 50.00 |
| 4.40 | 5.00 | 5.00 | 7.19 | 7.47 | 6.89 | 9.48 |
| 5.46 | 8.98 | 8.88 | 7.20 | 7.99 | 5.00 | 4.68 |

**SE**

| 3.90 | 3.90 | 5.10 | 6.47 | 6.47 | 5.42 | 9.48 |
| 4.40 | 5.00 | 5.00 | 7.19 | 7.47 | 6.89 | 9.48 |
| 5.46 | 8.98 | 8.88 | 7.20 | 7.99 | 5.00 | 4.68 |

Detailed results with the sensitivity $S_{max}$ (in %) and maximum FPR, $FPR_{max}$ (per hour), of the effective correlation dimension analysis obtained with the optimized minimal dimension drop durations. The maximum FPR constraints are 0/h, 0.05/h, 0.1/h, 0.25/h, 0.4/h, 0.6/h and 1/h. Three alarm windows of 10, 20 and 50 min length were applied. Mean values $S_{avg}$ for the patients with hippocampal (patients 1–8) and neocortical (patients 9–21) seizure origin are listed. SE = standard error of the mean.
We have thus loosened both restrictions in order to investigate whether dimension drops of sufficient size are indicative of an imminent seizure: (i) an acceptable FPR is allowed for; and (ii) the prediction is based on dimension drops occurring within certain time windows before the onset of the seizure. Regarding (i), a range of maximum FPR was specified and

**Fig. 4** Averaged sensitivities (±2 SE) of the analysis of the data with hippocampal seizure origin with optimized minimal dimension drop durations for the maximum FPR 0/h, 0.05/h, 0.1/h, 0.25/h, 0.4/h, 0.6/h and 1/h for the 10 (top), 20 (middle) and 50 min (bottom) alarm windows. For comparison, the probability of the corresponding random alert system is given (solid line).

**Fig. 5** Averaged sensitivities (±2 SE) of the analysis of the data with neocortical seizure origin with optimized minimal dimension drop durations for the maximum FPR 0/h, 0.05/h, 0.1/h, 0.25/h, 0.4/h, 0.6/h and 1/h for the 10 (top), 20 (middle) and 50 min (bottom) alarm windows. For comparison, the probability of the corresponding random alert system is plotted (solid line).
Corresponding thresholds of the extracted features were determined based on the interictal data. With respect to (ii), dimension drops occurring at any time within windows of length 10–50 min before the seizure’s onset were considered.

Under these conditions, the prediction methods result in a sensitivity of 38% in hippocampal seizures and 33% in neocortical seizures if a FPR of 0.1/h is permitted for interictal data and a 50 min time window is considered preictally. The algorithm outperforms a random alert system significantly. This shows that the preictal EEG carries information about the forthcoming seizure, and that the extracted feature indeed captures this information to some degree. This is remarkable, as there is an ongoing debate with respect to the applicability of methods from nonlinear dynamics to biological data (Rapp et al., 1993; Jedynak et al., 1994; Kantz and Schreiber, 1997; Schreiber, 1999; Timmer et al., 2000).

**Clinical applicability**

Apart from the statistical superiority of a prediction algorithm to a random alert system, clinical applicability depends on a number of additional factors. To determine the sensitivity of a method, three steps have to be applied: (i) the choice of a maximum FPR; (ii) the derivation of a threshold based on representative long-term interictal data; and (iii) the determination of the sensitivity based on preictal data. The allowed FPR depends on clinical and technical requirements as well as on individual factors of the patient. In this study, we regarded a range of maximum FPR between 0/h and 1/h. Reasonable FPR should be at most on the order of the patient’s seizure frequency. On average, patients suffering from pharmacoresistant epilepsy have a seizure frequency of three seizures per month, corresponding to a rate of 0.0042 seizures per hour (Bauer and Burr, 2001), which may increase up to 0.15 seizures per hour if medication is discontinued (Haut et al., 2002). Applying the results for hippocampal prediction performance to such a patient, one out of three seizures would be predicted correctly within 1 month, while about 70 false predictions have to be accepted. This would mean that <2% of the predictions are correct, whereas more than 60% of the seizures would occur unpredicted. Used as a pure warning system, a prediction method of this quality would probably be ignored after a short time. If used as an automatic therapeutic device, most interventions would be obsolete and potentially harmful to the patient.

**Conclusions**

An analysis of 88 seizures from 21 patients with pharmacoresistant focal epilepsy showed that dimension drops (Lehnertz and Elger, 1998; Lehnertz et al., 2001) are not sensitive indicators of upcoming seizures. Basing specificity on long-term interictal EEG recordings, only one out of 88 seizures could be predicted successfully. An analysis of dimension drops occurring within certain time windows preceding seizures showed that dimension drops predict seizures with a better performance than a random alert system. Considering clinical applicability, however, sensitivity and specificity of the method are not sufficient. A gain in specificity can only be achieved at the expense of sensitivity and vice versa.

Our analysis showed that dimension drops in the epileptic focus in interictal data can be observed to an extent comparable to preictal data. Lehnertz and Elger (1995) reported that drops in the effective correlation dimension method correctly lateralize the seizure onset zone based on an analysis of even interictal data alone. That is, at times far from seizure onset, dimension drops take place that typically occur in the focal area. The duration and amplitude of these interictal dimension drops have a wide overlap with preictal drops if sufficiently long interictal periods are considered. The limited performance of the dimension drops with regard to the preictal period may thus be related to the very fact that dimension drops occurring during interictal periods are a hallmark of the epileptogenic area, as has been shown by Lehnertz and Elger (1995). Thus, the sensitivity of the method to detect changes during interictal periods may pose a fundamental limitation to its ability to predict seizures with sufficient specificity.

**Acknowledgements**

We wish to thank Dr Klaus Lehnertz, Clinic of Epileptology (Bonn), for his support and discussions; in particular, for providing short reference data sets for validation of the algorithm.

**References**


Iasemidis LD, Principe JC, Czaplewski JM, Gilmore RL, Roper SN, Sackellaes JC. Spatiotemporal transition to epileptic seizures: a nonlinear dynamics analysis of scalp and intracranial EEG recordings. In: Lopes da Silva FH, Principe JC, Almeida LB,
Evaluation of nonlinear seizure prediction


