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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; Martinerie *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

Table 1 *Clinical data and characteristics of selected patients*

Patient no.	Sex	Age (years)	Seizure type	Origin	Electrodes	Resection/ outcome	No. seizures analysed	Interictal true period/h	No. interictal segments
1	M	38	SP, CP, GTC	H	d	IV	3	24	2
2	F	26	SP, CP, GTC	H	d, g, s	No surgery	5	24	1
3	F	31	CP, GTC	H	d, g, s	I	3	24	1
4	F	42	SP, CP, GTC	H	d	I	3	25	1
5	M	47	SP, CP, GTC	H	d	IV	5	24	1
6	F	42	SP, CP, GTC	H	d, g, s	IV	4	25	1
7	F	22	SP, CP, GTC	H	d, s	II	2	24	1
8	F	50	SP, CP, GTC	H	d, s	I	5	24	2
						Sum	30	194	
						Mean	3.8	24.3	
9	F	15	SP, CP	NC	g, s	III	5	24	1
10	M	14	SP, CP	NC	g, s	I	5	24	1
11	F	16	SP, CP, GTC	NC	g, s	I	5	24	3
12	F	32	SP, CP	NC	g, s	II	2	24	2
13	M	44	CP, GTC	NC	g, s	II	5	24	2
14	F	10	SP, CP, GTC	NC	g, s	II	4	24	1
15	F	41	CP, GTC	NC	d, s	I	4	24	5
16	M	31	SP, CP, GTC	NC	d, s	III	4	24	1
17	M	28	SP, CP, GTC	NC	s	I	5	24	1
18	F	25	SP, CP	NC	s	No surgery	5	25	1
19	F	28	SP, CP, GTC	NC	s	I	4	24	3
20	M	33	SP, CP, GTC	NC	d, s	I	5	26	1
21	M	13	SP, CP	NC	s	I	5	24	2
						Sum	58	315	
						Mean	4.5	24.2	

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.

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

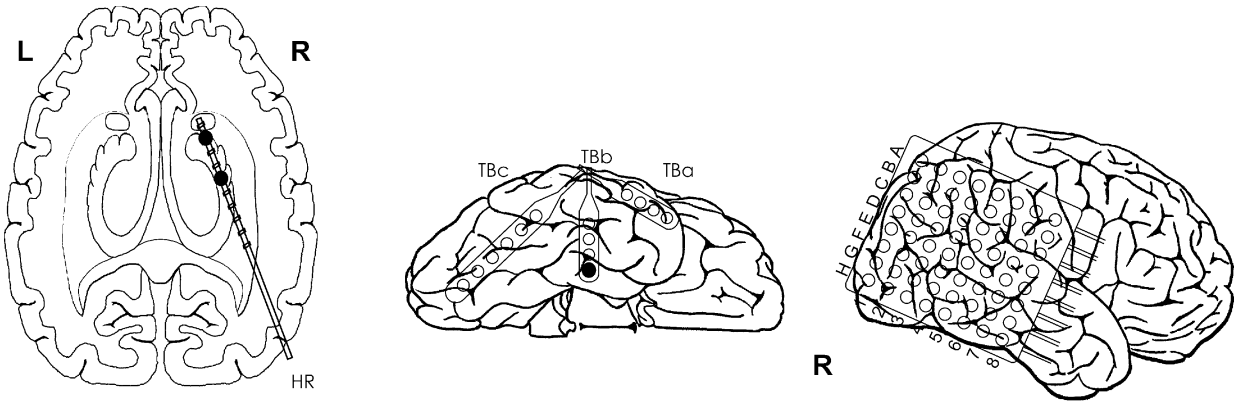

Fig. 1 Implantation scheme with electrode configuration from a non-lesional patient with right hippocampal seizure onset zone. *Left*: Ten-contact depth electrode (HR) implanted from an occipital approach into the right hippocampus with the most anterior contact situated in the amygdala. *Middle*: Subdural strip electrodes (temporo-basal on right side), TBa and TBb (four contacts each) in rostral and mesial direction, TBc (six contacts) in occipital direction. *Right*: Subdural grid electrode covering the lateral temporal and parietal right convexity. The three contacts selected for this study are marked with filled circles.

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^{eff} is a nonlinear feature that is motivated by the correlation dimension D_2 (Grassberger and Procaccia, 1983*a*, *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)

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

where θ is the Heaviside step function ($\theta(x) = 0$ if $x \leqslant 0$, $\theta(x) = 1$ 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:

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

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

We followed the operational method of Lehnertz 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 $C'_m(r_u, m = 1) > 0.975$. The lower bound r_l is defined as:

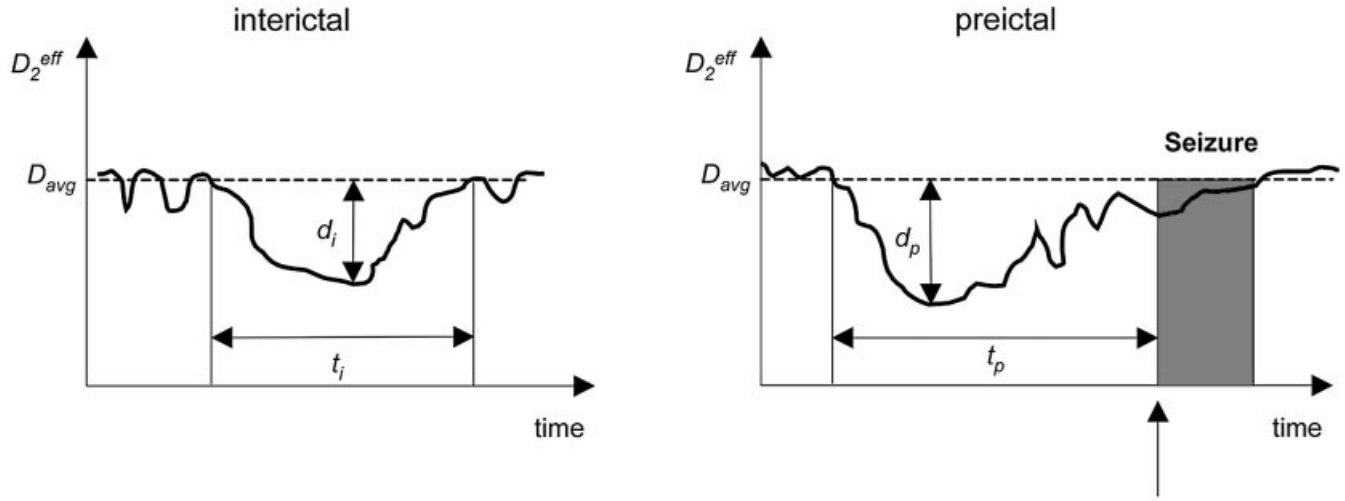

Fig. 2 Schematic illustration of interictal (*left*) and preictal (*right*) dimension drops of the D_2^{eff} feature over time. The dashed line represents the average D_{avg} of all interictal data for each patient and recording site. For interictal data, the time interval t_i is defined as the interval between two crossings of D_2^{eff} with D_{avg}. For a dimension drop that directly precedes a seizure (shaded area), the D_2^{eff} feature must be below D_{avg} at seizure onset (marked in preictal data set by upward arrow). The time interval t_p is defined as the interval between seizure onset and the last crossing of D_2^{eff} with D_{avg}. The amplitude deflections d_i and d_p are defined as the difference between the minimum of D_2^{eff} and D_{avg} during t_i and t_p, respectively.

$$r_l = \min\{r < r_u \| C'_{m_{max}}(r_u) - C'_{m_{max}}(r)| \leqslant \delta\},$$
$$\text{with } \delta = 0.05\ C'_{m_{max}}(r_u),\ m_{max} = 25.$$

Finally, D_2^{eff} is given as:

$$D_2^{eff} = \begin{cases} D^* & \text{if } N_r \geq 5 \\ 10 & \text{else.} \end{cases}$$

If no scaling region could be determined, D_2^{eff} was set to the default value of 10. D_2^{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^{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_{avg} is determined. For interictal data sets, t_i is defined as the longest time interval with D_2^{eff} below D_{avg}. For preictal data, t_p is the time interval between seizure onset and the previous downward crossing of D_2^{eff} with D_{avg}. At seizure onset, D_2^{eff} has to be smaller than D_{avg}. The maximum deflections d_i and d_p are defined as the maximum differences between D_2^{eff} and D_{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 $t_{p,avg}$, $d_{p,avg}$, $t_{i,avg}$ and $d_{i,avg}$, and the medians $t_{p,med}$, $d_{p,med}$, $t_{i,med}$ and $d_{i,med}$ of the parameters of the dimension drops, and of all drops with t_p, $t_i \geqslant 80$ s, corresponding to 10 data points of D_2^{eff}, were

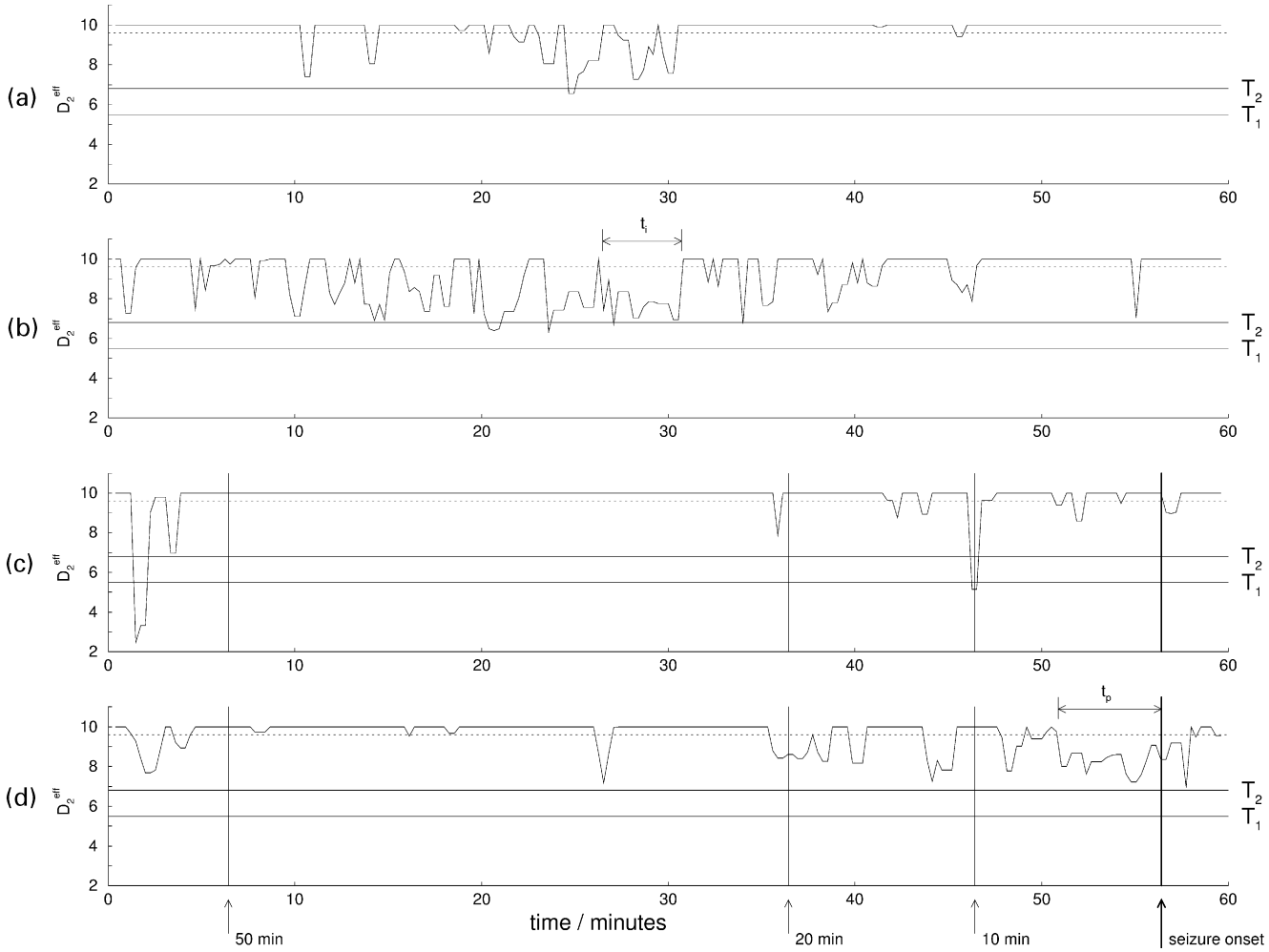

Fig. 3 Examples of D_2^{eff} data from interictal (**a**, **b**) and preictal (**c**, **d**) data sets each of 60 min length from one patient. The mean interictal level D_{avg} is shown by the dotted horizontal line. The dimension drop in **d** directly precedes the seizure onset (marked by vertical bold line). Maximal dimension drop lengths in this example are labelled with t_i and t_p, respectively. The duration t_p exceeds t_i, but the maximum interictal deflection exceeds the preictal one. Hence, the dimension drop is not predictive according to the definition. For the evaluation with allowed false-predictions, the 10, 20 and 50 min alarm windows in **c** and **d** are marked with vertical lines and labelled with arrows. Threshold values T_1 and T_2 resulting from given maximum FPR are denoted with horizontal lines. Alarms are given by downward crossings. For the threshold value $T_1 = 5.5$ and for a small minimal dimension drop duration, alarms are given in **c** in the 10 and 20 min windows. No false alarms are raised in **a** and **b** and no alarm is given in **d**. For a higher FPR and for a minimal drop duration $\geqslant t_i$, the threshold value increases to $T_2 = 6.8$. One false alarm is given in **b**. No alarms are given in **a** and **c**, since the dimension drops are too short. No alarm is given in **d**.

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

Table 2 *Results of the dimension drop analysis*

		Hippocampal origin: 8 patients, 30 seizures (3.8 seizures/patient)	Neocortical origin: 13 patients, 58 seizures (4.5 seizures/patient)
21 interictal recordings (duration = 24 h)			
Mean values of maximal interictal dimension drops within the seizure focus	$t_{i,avg}$	10.9 min	12.4 min
	$t_{i,med}$	8.0 min	5.3 min
	$d_{i,avg}$	3.7	3.7
	$d_{i,med}$	3.6	3.8
Mean values of interictal dimension drops ⩾80 s within the seizure focus	$t_{i,avg}$	2.7 min	3.4 min
	$t_{i,med}$	1.9 min	2.1 min
	$d_{i,avg}$	2.4	2.2
	$d_{i,med}$	2.4	2.0
88 preictal recordings (duration = 50 min)			
Dimension drops directly preceding seizures within the seizure focus		17% (5 seizures)	16% (9 seizures)
Predictive dimension drops		0% (0 seizures)	1.7% (1 seizure)
Mean values of non-predictive dimension drops, fulfilling requirements: (i) being within the seizure focus and (ii) directly preceding the seizures	$t_{p,avg}$	0.4 min	1.7 min
	$t_{p,med}$	0.3 min	0.8 min
	$d_{p,avg}$	2.3	2.8
	$d_{p,med}$	2.7	2.8
Mean values of preictal non-predictive dimension drops ⩾80 s fulfilling only requirement (i)	$t_{p,avg}$	2.9 min	3.4 min
	$t_{p,med}$	1.9 min	2.1 min
	$d_{p,avg}$	2.6	2.5
	$d_{p,med}$	2.5	2.2

Results of the dimension drop analysis of the D_2^{eff} feature for interictal and preictal data for eight patients with hippocampal seizure origin and 13 patients with neocortical seizure origin. Mean values and medians of the drop parameters time interval t_i and t_p and amplitude difference d_i and d_p, respectively, were determined for all dimension drops and for dimension drops exceeding a duration of 80 s. Only one dimension drop fulfilled all three requirements of the definition for predictive dimension drops according to Lehnertz *et al*. (2001).

analysis of the interictal data sets, the alarm mechanism was deactivated for the duration of the respective alarm window of 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 windows 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_{max} can be expressed as the probability $P = FPR_{max} \cdot u$ to produce one false alarm. The probability P for exactly one false alarm within a time interval $W = n \cdot u$, with an integer n, is hence:

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

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

$$P \approx 1 - e^{-FPRmaxW} \quad (2)$$

P describes the sensitivity of a random alert system. For a large window length W, P converges to 1, e.g. if FPR_{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 sets 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: $t_{i,avg}$ = 10.9 min, $d_{i,avg}$ = 3.7, $t_{i,med}$ = 8 min, $d_{i,med}$ = 3.6 for the hippocampal group, and $t_{i,avg}$ = 12.4 min, $d_{i,avg}$ = 3.7, $t_{i,med}$ = 5.3 min, $d_{i,med}$ = 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 $t_{p,avg}$ 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 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, $t_p \geqslant 80$ s were: $t_{i,avg}$ = 2.7 min, $t_{i,med}$ = 1.9 min, $t_{p,avg}$ = 2.9 min, $t_{p,med}$ = 1.9 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. 4. Under most conditions, these are significantly lower than the sensitivities of the prediction algorithm.

Neocortical group

The mean values and medians of all interictal and preictal dimension drops with t_i, $t_p \geqslant 80$ s were: $t_{i,avg}$ = 3.4 min, $t_{i,med}$ = 2.1 min, $t_{p,avg}$ = 3.4 min, $t_{p,med}$ = 2.1 min, and $d_{i,avg}$ = 2.2, $d_{i,med}$ = 2.0, $d_{p,avg}$ = 2.5, $d_{p,med}$ = 2.2. Again, there were no significant differences between the interictal and preictal data. The maximum duration of the individual dimension drops was 3136 s interictally and 3360 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. 5 for optimized minimal dimension drop durations. For FPR_{max} = 0/h the averaged sensitivities were 10.4, 11.9 and 18.5% for the 10, 20 and 50 min windows, respectively. For FPR_{max} = 0.1/h the averaged sensitivities were 13.9, 18.5 and 33.5% for the 10, 20 and 50 min windows, respectively. For increasing FPR_{max}, sensitivities rise up to 84% 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_2^{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*

Patient no.	Sensitivity S_{max}/%																			
	10 min alarm window (FPR_{max})							20 min alarm window (FPR_{max})							50 min alarm window (FPR_{max})						
	0	0.05	0.1	0.25	0.4	0.6	1.0	0	0.05	0.1	0.25	0.4	0.6	1.0	0	0.05	0.1	0.25	0.4	0.6	1.0
1	0	0	0	33	33	33	100	0	0	0	33	33	33	100	0	0	67	67	100	100	100
2	0	0	0	0	0	0	0	0	0	0	0	0	0	20	20	40	40	40	40	60	60
3	33	33	33	33	33	33	67	33	33	33	33	33	33	100	33	67	67	67	100	100	100
4	0	0	33	33	33	33	33	0	33	33	33	33	33	67	0	33	33	100	100	100	100
5	0	0	0	0	0	20	60	20	20	20	20	20	60	60	20	60	60	60	80	80	100
6	0	0	0	50	50	50	50	0	0	0	75	75	75	75	0	0	0	100	100	100	100
7	0	0	0	50	50	50	50	0	0	0	50	50	50	50	0	0	0	50	50	100	100
8	0	0	0	20	20	40	40	20	20	20	40	60	60	80	40	40	40	80	80	80	100
S_{avg}	4.17	4.17	8.33	27.50	27.50	32.50	50.00	9.17	13.33	13.33	35.62	38.12	43.12	68.96	14.17	30.00	38.33	70.42	81.25	90.00	95.00
SE	3.90	3.90	5.10	6.47	6.47	5.42	9.48	4.40	5.00	5.00	7.19	7.74	7.69	8.77	5.46	8.98	8.88	7.20	7.99	5.00	4.68
9	0	0	20	20	20	20	20	0	20	20	20	20	20	20	0	20	20	20	20	40	100
10	20	20	20	20	20	20	40	20	20	20	40	40	40	40	20	40	40	60	60	60	100
11	0	0	0	0	0	0	0	20	20	20	20	20	20	20	20	20	40	40	40	40	40
12	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	50	50	50	50	50
13	20	20	20	40	40	40	40	20	40	40	60	60	60	60	20	40	40	80	80	80	80
14	25	25	50	50	50	50	75	25	50	50	50	50	50	75	25	50	50	75	75	75	100
15	50	50	50	50	50	50	75	50	50	50	50	50	75	75	50	50	50	50	75	75	100
16	0	0	0	25	25	50	75	0	0	0	25	25	75	75	0	0	0	50	75	75	100
17	0	0	0	0	20	20	60	0	0	0	20	40	40	80	20	40	40	80	80	100	100
18	20	20	20	40	40	40	40	20	40	40	60	60	60	80	40	60	60	80	80	100	100
19	0	0	0	0	0	0	25	0	0	0	0	0	25	25	25	25	25	25	25	25	25
20	0	0	0	0	0	0	20	0	0	0	20	20	20	40	20	20	20	40	60	60	100
21	0	0	0	0	20	20	20	0	0	0	0	20	20	60	0	0	0	20	40	80	100
S_{avg}	10.38	10.38	13.85	18.85	21.92	23.85	37.69	11.92	18.46	18.46	28.08	31.15	38.85	50.00	18.46	28.08	33.46	51.54	58.46	66.15	84.23
SE	4.33	4.33	5.13	5.67	5.17	5.61	7.44	4.29	5.64	5.64	6.09	5.67	6.58	7.60	4.33	5.65	5.29	6.21	5.97	6.36	7.55

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.

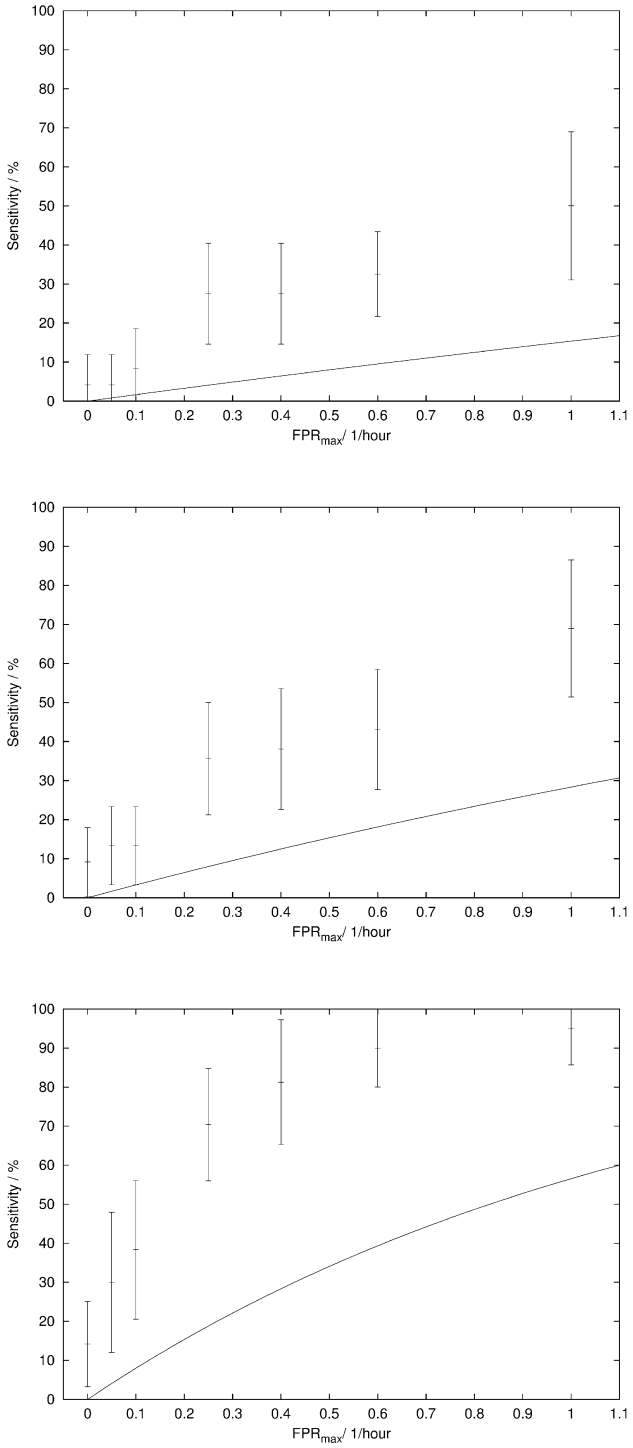

Fig. 4 Averaged sensitivities (±2 SE) of the analysis of the data with hippocampal seizure origin with optimized minimal dimension drop durations for the maximum FPR 0/h, 0.05/h, 0.1/h, 0.25/h, 0.4/h, 0.6/h and 1/h for the 10 (*top*), 20 (*middle*) and 50 min (*bottom*) alarm windows. For comparison,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

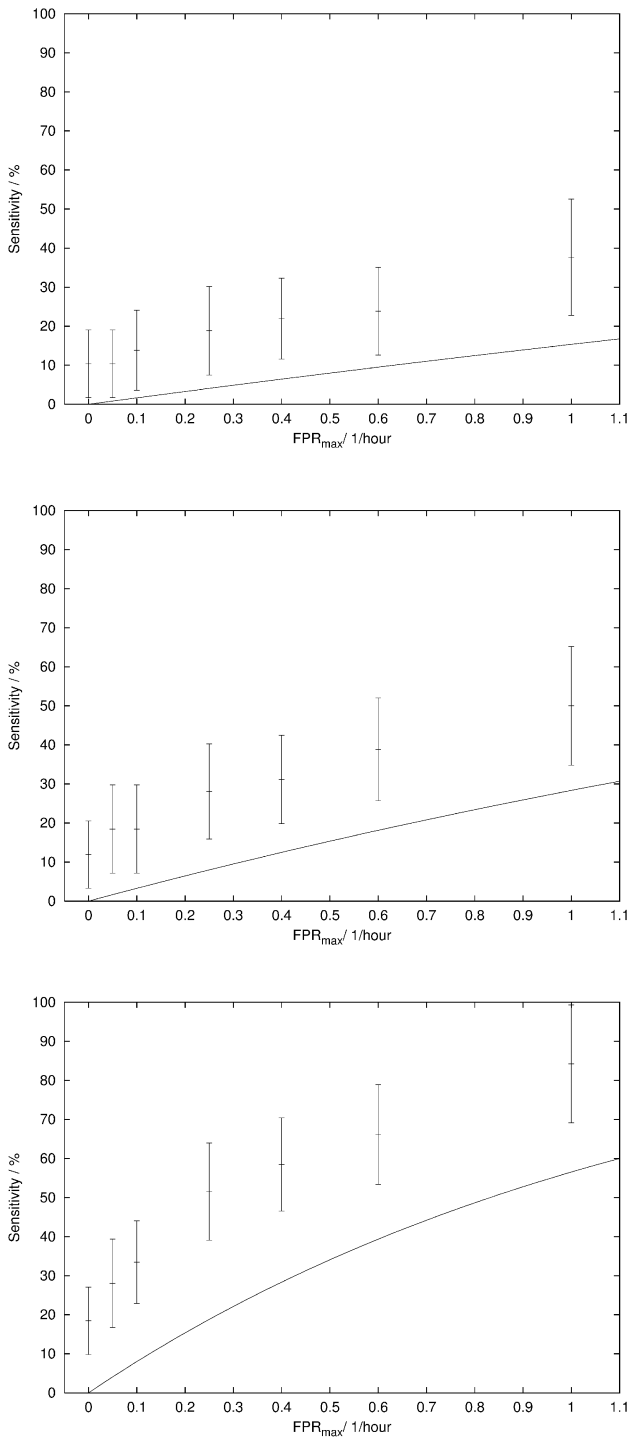

Fig. 5 Averaged sensitivities (±2 SE) of the analysis of the data with neocortical seizure origin with optimized minimal dimension drop durations for the maximum FPR 0/h, 0.05/h, 0.1/h, 0.25/h, 0.4/h, 0.6/h and 1/h for the 10 (*top*), 20 (*middle*) and 50 min (*bottom*) alarm windows. For comparison, the probability of the corresponding random alert system is plotted (solid line).

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

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 pharmacorefractory 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 pharmacorefractoral 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.

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