Can Epileptic Seizures be Predicted? Evidence from Nonlinear Time Series Analysis of Brain Electrical Activity

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We evaluate the capability of nonlinear time series analysis to extract features from brain electrical activity (EEG) predictive of epileptic seizures. Time-resolved analysis of the EEG recorded in 16 patients from within the seizure-generating area of the brain indicate marked changes in nonlinear characteristics for up to several minutes prior to seizures as compared to other states or recording sites. If interpreted as a loss of complexity in brain electrical activity these changes could reflect the hypothesized continuous increase of synchronization between pathologically discharging neurons and allow one to study seizure-generating mechanisms in humans. [S0031-9007(98)06221-8]

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The application of concepts from the theory of nonlinear dynamics [1,2] to recordings of brain electrical activity (EEG) has provided a number of interesting insights (see, e.g., Ref. [3] and references therein). In particular, estimates of an effective correlation dimension D_2^{eff} [4,5] have been shown to characterize different states of brain function (e.g., sleeping, awake and resting, nonverbal or verbal cognitive processing). In epileptology, the characterization of pathological activity (i.e., spatiotemporal dynamics of seizure activity) by different nonlinear measures led to a better understanding of basic mechanisms in animal experiments [6,7] as well as in humans [8–15] and promises to be important for clinical practice.

In a strict sense, well known problems in estimating D_2 (as well as other measures) from short (and noisy) data segments or nonstationary data would exclude the use of these measures for a characterization of EEG dynamics [16,17]. However, instead of using D_2^{eff} as an absolute measure to differentiate between periodic, chaotic, or stochastic dynamics one can regard D_2^{eff} as an operational definition and use the term "dimension" in an informal sense. Under these premises, it has been shown in Refs. [10] and [13] that even during seizure-free intervals EEG dynamics of the primary epileptogenic area (the part of the brain giving raise to seizure activity) is characterized by temporary transitions to system states of lower "complexity" defined by changes towards reduced D_2^{eff} values obtained from successive data segments. These transitions (a) allow one to reliably delineate the primary epileptogenic area from brain regions not involved in the epileptogenic process and (b) reflect properties of factors influencing the latter (e.g., drugs). Furthermore, they can be observed even in intervals in which EEG recordings fail to show steep, high-amplitude epileptiform potentials (so called spikes, the hallmark of the epileptic brain) that are known to resemble the simultaneous pathological discharging of neurons within a volume of at least several mm^3. Thus, system states of reduced complexity can be assumed to reflect more subtle or even hidden pathological synchronization phenomena of the underlying neuronal networks.

Up to now there is only limited knowledge about seizure-generating mechanisms in humans. Model simulations and animal experiments led to the hypothesis that seizure activity will be induced when a "critical mass" of neurons is progressively involved in closely time-linked high-frequency discharging [18]. However, evident markers in the EEG representing the transition from asynchronous to synchronous states on longer time scales have not yet been described. Traditional linear methods of time series analysis indicate that changes in the electroencephalographic activity that can be regarded as characteristic precursors may, at the most, be detectable a few seconds before the actual seizure onset [19].

In this Letter we demonstrate the capability of nonlinear time series analysis methods to identify a preseizure state. The early identification of such a transition state with a sufficient duration is of special interest since it will provide a key for the study of mechanisms generating seizures in humans. Furthermore, it may be extremely beneficial for the treatment of patients suffering from epilepsy enabling specific pharmaco- or electrotherapeutic possibilities to prevent seizure generation. In the present study we applied a time-resolved D_2^{eff} analysis to EEG signals recorded during both intervals temporally far away from any seizure as well as prior to and during seizures, where the former recordings served as a control. Again we want to emphasize that we determine D_2^{eff} as an operational measure of complexity of the EEG. Absolute values of D_2^{eff} are not considered and presumably do not agree with the true D_2 (if it exists). Instead, only differences with respect to time and location of the EEG registration are assumed reliable and are used to characterize the complex spatiotemporal dynamics of the epileptogenic activity (cf. Ref. [10]).

We recorded brain electrical activity directly from the cortex and from within relevant structures of the brain, hence with a high signal-to-noise ratio. Up to

128 implanted electrodes in 16 patients with pharmacoresistant epilepsy were used (see [10,20] and references therein for details of the clinical evaluation and recording techniques). EEG signals were sampled at 173 Hz using a 12 bit analog-to-digital (A/D) converter and filtered within a frequency band of 0.53 to 40 Hz. We subjected 68 data sets to nonlinear time series analysis.

State-1.—Intervals with a minimum distance to any seizure of 24 h; 52 data sets; duration: 6–40 min; awake.

State-2.—Preceding seizure; seizure onset directly following; 16 data sets; duration: 10–30 min; seizure onset was defined as earliest sign typical for seizure activity; awake.

For the present investigation, analysis was restricted to recordings from electrode contacts within the primary epileptogenic area (i.e., exhibiting earliest signs of seizure activity) as well as from adjacent and remote brain areas. Recordings from the last category served as controls. Adjacent areas were defined as those regions of the brain where a spreading of seizure activity was observed in the course of the seizure.

In order to overcome some of the shortcomings associated with the estimation of D_2^{eff} from EEG signals, we employed manipulations that have been described in detail elsewhere [10]. Since we do not interpret D_2^{eff} as an estimate of the correlation dimension, our considerations are aimed solely at maximizing its discriminative power. Briefly, following Ref. [21] EEG signals of each recording site were segmented into half-overlapping consecutive normalized epochs of 30 sec duration representing a reasonable tradeoff between approximate stationarity and epoch length. For each epoch, correlation sums $C(r)$ [4] as well as the local derivatives $C'(r) = \frac{d \log C(r)}{d \log r}$ were calculated from time-delay reconstructed phase space vectors [22] using a fixed time delay, an embedding dimension range $m = 1, \ldots, 30$, and the maximum norm [23]. The range of possible values for the hypersphere radius r was selected to match the resolution of the A/D converter. To limit autocorrelative effects we selected a cutoff W to be of the order of the first zero-crossing of the autocorrelation function as proposed by Ref. [16]. Using criteria derived from analyses of state–1 data sets of another patient population we define D^* as an estimator of D_2^{eff} given by (cf. [24]),

$$D^* = \frac{1}{N_r} \sum_{r=r_l}^{r_u} C'(r)\,, \tag{1}$$

where N_r is the number of r values in $[r_l, r_u]$. The upper bound r_u of a "quasiscaling" (cf. Fig. 1), if it exists, is attributed to those r values where $C'(r, m = 1)$ is close to 1 (depending on the r step size we here used $C'(r_u, m = 1) > 0.975$). The lower bound r_l is defined as

$$r_l = \{r \,||C'(r_u) - C'(r)| \le \epsilon \wedge r < r_u\}_{\min} \tag{2}$$

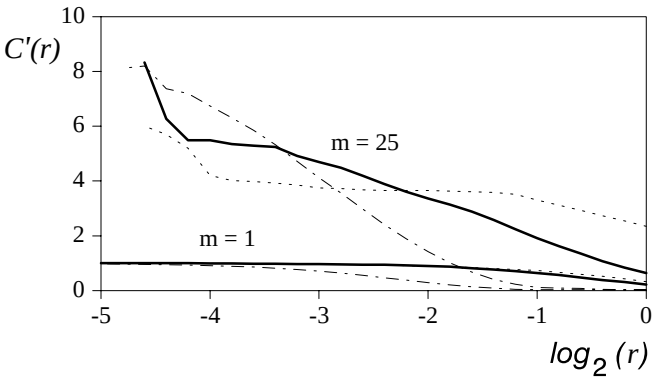

FIG. 1. Local slopes of correlation sums $C'(r)$ vs hypersphere radius r of representative EEG recordings during state-1 (dash-dotted lines) and state 2 (thick lines). For comparison data obtained during the seizure state are included (dotted lines). Only $C'(r)$ values of the latter and of state-2 exhibit a "quasiscaling" resulting in D_2^{eff} estimates of 3.7 and 5.3, respectively.

using $C'(r)$ of a high embedding dimension ($m = 25$) and $\epsilon = 0.05 C'(r_u, m = 25)$. Finally,

$$D_2^{\text{eff}} = \begin{cases} D^*, & \text{if } D^* \le D_{\max} \text{ and } N_r \ge 5\,, \\ D_u, & \text{else,} \end{cases} \tag{3}$$

where $D_{\max}$ is a maximum resolvable dimension dependent on the number of data points as proposed by Ref. [25]. D_u is an arbitrary but fixed threshold value of 10.

We stress that this determination of D_2^{eff}—while being arbitrary—was done fully automatically and without human interference. Furthermore, it is important to note that we did not use a fixed r value or r interval for each analyzed data segment but instead searched for an appropriate r interval above the noise floor. At larger r values, $C(r)$ is especially sensitive to high-amplitude spikes. Thus, relying on large r values would simply represent a detection of spikes (cf. Ref. [14]). Because of the aforementioned restrictions we want to suppress the influence of large-amplitude spikes since it is not intended to characterize occasionally occurring sharp transients that are known to be of only minor predictive relevance (cf. [26]).

In Figs. 2 and 3 we present typical examples of D_2^{eff} profiles (as functions of time) obtained from state-1 and state-2 EEG recordings within the primary epileptogenic area, adjacent and remote areas of the brain. During state-1, temporary transitions to less complex system states attributed to synchronization (cf. Refs. [10,13]) are less frequent with increasing distance from the primary epileptogenic area. When approaching the epileptic seizure (state-2) these effects become more and more pronounced in the primary epileptogenic area and at adjacent recording sites. This holds true for both the strength S_σ (the maximum deflection from an upper threshold T_u which was defined as the mean D_2^{eff} level obtained for the patient state-1 recordings of this site) and the duration S_τ [the longest time

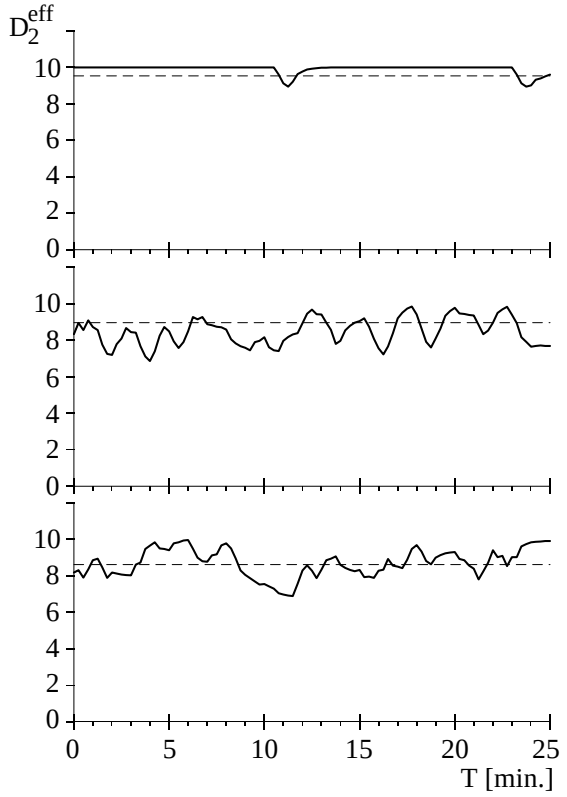

FIG. 2. Bottom to top: D_2^{eff} profiles (solid lines) from within the primary epileptogenic area, adjacent and remote areas obtained from state-1 (seizure-free) EEG recordings. Dotted horizontal lines denote site specific upper threshold values T_u. Profiles are smoothed using a 3-point moving average.

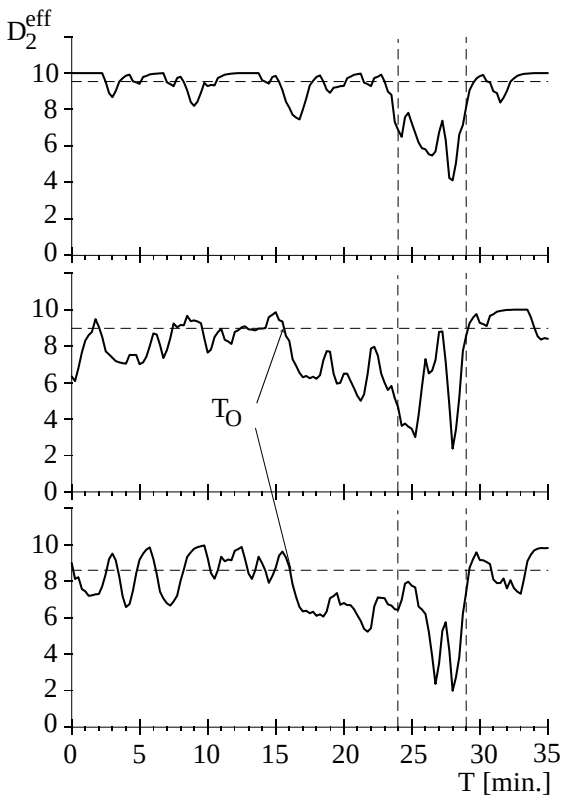

FIG. 3. Same as Fig. 2 but for state-2 recordings. For completeness, data obtained from the seizure and postseizure state were included. Dotted vertical lines denote beginning and end of the seizure state.

interval with D_2^{eff} below T_u for state-1 profiles; for state-2 profiles, S_τ is defined to reach from seizure onset back to the previous intersection (T_0 in Fig. 3) of the D_2^{eff} profiles with T_u].

Maximum synchronization (S_σ and S_τ) was always found inside the primary epileptogenic area. During state-2, maximum synchronization was always observed in time windows immediately preceding seizures (preseizure state). We therefore used these values as reference for comparison (cf. Fig. 4) with maximum synchronization values achieved during control recordings (state-1). Here the mean values amounted to $S_\sigma = 1.0$ (range: 0.5–2.5) and $S_\tau = 5.25$ min (range 1.00–10.75 min). For the preseizure state we observed $S_\sigma = 2.0$ (range: 1.0–3.5) and $S_\tau = 11.50$ min (range: 4.25–25.00 min). In all but one patient we found both S_σ and S_τ to be enlarged during the preseizure state. Thus, it is concluded that a reduced dimensional complexity of brain activity, as soon as it is of sufficient size and duration, can be regarded a specific feature defining states which proceed to a seizure.

In addition to these temporal synchronization phenomena, state-2 D_2^{eff} profiles from within the primary epileptogenic area and adjacent areas also exhibit features of spatially variant synchronization phenomena. In Fig. 3, T_0 denotes a time instant in the preseizure state that can

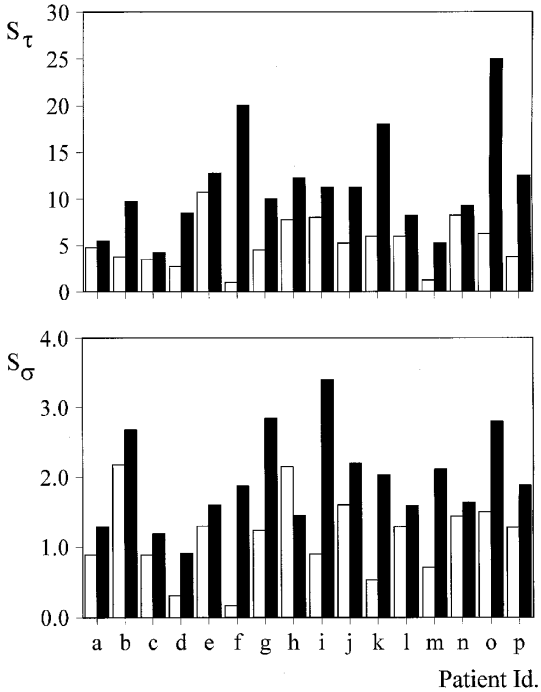

FIG. 4. Synchronization duration S_τ[min] (upper part) and strength S_σ (lower part) for all investigated patients. Empty bars denote maximum values found during state-1 intervals. Filled bars denote values for the preseizure state.

be regarded characteristic for a coupling between different regions of the brain. While D_2^{eff} profiles seem to be *out of phase* for $T < T_0$ (as they do in state-1; cf. Fig. 2) they tend to become *in phase* for $T > T_0$. This impression, however, requires further investigations.

In summary, it can be concluded from the present findings that nonlinear time series analysis bears potential capability to extract features from ongoing brain electrical activity that can be regarded as precursors of an impending seizure. It could be demonstrated that the synchronization phenomena of the preseizure state differ clearly from the one found during seizure-free intervals under various conditions [10,13]. Both synchronization duration and strength are of sufficient size to open a time frame that provides possibilities for pharmacological or electrotherapeutic interventions in the preseizure period. As concerns to basic research, it remains to be established whether different methods of nonlinear time series analysis (e.g., [27–33]) could furnish additional precursors that allow one to extend the knowledge about seizure-generating mechanisms in humans.

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