Nonlinear Dynamics of 3 Hz Spike-and-wave Discharges Recorded During Typical Absence Seizures in Children

One-channel routine recordings of the scalp electroencephalogram (EEG) from unmedicated children strictly classified as unprovoked typical (3 c/s) absence seizures were selected. The dynamics of spike-and-wave discharges (SWD) were then examined by means of autocorrelation, correlation dimension, averaged pointwise dimension and largest Lyapunov exponent. For one EEG signal with pronounced spike-and-wave (SW) patterns, these measures were used complementary to a surrogate data method, a nonlinear (SETAR) modeling approach, and a SW simulation procedure providing five types of SW test signals. The SETAR model exhibited stationary SW dynamics, visually very similar to the EEG target signal, and with clear nonlinear structure. According to the results, the EEG episodes investigated represent low-dimensional dynamics, possibly recorded during nonstationary periods. Arguments that justify the assumption of deterministic chaos in our EEG signals were not obtained with the current methods. From the results one may conclude that two global oscillatory modes are present for the model, and three modes are active during the EEG recording period.

Introduction

One distinct phenomenon that may emerge within the thalamicocortical system is the hypersynchronous collective firing of neurons at 2–4 Hz. It is related to physiological (sleep) states as well as abnormal behavioral (seizure) states and has been the object of study on various levels.

The classical generalized rhythmic 3 Hz spike-and-thalamic wave discharge (SWD; IFSECN, 1974) has one of the highest correlations of an electroencephalogram (EEG) pattern occurring in association with a distinct seizure disorder (typical absence seizure, TAS; see Appendix). The relatively stereotyped clinical manifestations, together with frequent occurrence, ease of precipitation (sleep, hyperventilation), and obvious and consistent expression in the EEG have made TAS the most extensively studied type of epileptic seizure. However, there are many questions to which the clinical evaluation cannot provide answers.

Most assumptions about SWD have been derived from in vitro and in vivo animal studies using models of epilepsy which possess a high level of face validity for human TAS and have therefore remained the most productive way to understand the disorder. During the past few years, an impressive body of data has been published (for reviews see Niedermeyer and Lopes da Silva, 1993; Avoli and Glower, 1994; Malafosse et al. 1994; Snead 1995). This work has unraveled basic neuronal structures, synaptic circuitry and mechanisms that lead to the generation of TAS/SWD in animals (see Appendix). Relationships between the EEG and the underlying cortical and thalamic activity have already been characterized (Steriade and Amzica, 1994; Steriade and Contreras, 1995). Nevertheless, the EEG patterns during TAS suggest that the dynamics of SWD on the network level are controlled by deterministic laws of evolution, and these dynamics have not yet been understood. Theoretical, i.e. mathematical, approaches have been considered for their description. This method of investigation is even more important for the study of human TAS, since in this case the application of invasive techniques is commonly precluded (see Appendix). In addition, the findings obtained from animal models may not be fully relevant to human SWD.

Mathematical (computerized) analysis of the EEG in general and SWD in particular can be divided into two fundamental approaches (Jansen, 1991): (i) the phenomenological (or black box) approach, describing the state(s) of a neuronal system according to features of its output (see Niedermeyer and Lopes da Silva, 1993; a recent example is the work of Sherman et al., 1997); (ii) the nonlinear modeling approach (an attempt to look inside the black box), which aims at mathematical system equations by means of which the dynamic behavior can be described in conformity with data from the biological tissue. The fact that the dynamics of the model can be understood and even predicted (Theiler, 1995) makes this approach particularly attractive. Related attempts have been made with respect to the generation (Skarda and Freeman, 1987) and controlling (see Glanz, 1994) of specific processes underlying the EEG. (See also Lopes da Silva, 1991; Lopes da Silva et al., 1994.) A relatively simple model of the dynamics of ‘petit mal’ absence seizures has been presented by Friedrich and Uhl (1996). Owing to the heterogeneous nature of disorders subsumed under the term ‘petit mal’, comparable models will hardly have perfect validity for all types of absence seizures.

The creation of a feasible model that can reproduce a type of EEG activity realistically based on nonlinear system equations remains a difficult task. In the absence of such models, it has been suggested that characteristic properties of the state of a nonlinear dynamic system – such as the correlation dimension and largest Lyapunov exponent – be estimated because they may allow one to infer something about the nature of the system, in particular whether the system involves deterministic chaos (Rapp et al., 1985; Pritchard and Duke, 1992, for review). Only a few studies on human SWD with this intention have been published (Babloyantz and Destexhe, 1986; Frank et al., 1990; Theiler, 1995). Since the seizures analyzed were not classified exactly, the comparison of these and current results is difficult. In any case, the findings of these studies relied on single EEG data sets, yielded ambiguous results and led to different interpretations of the seizure dynamics.

Because of this fact and the ongoing need for solutions to the problem from the theoretical point of view we were motivated to start another analysis of human SWD. This study comprised two parts. The first part aimed at determining the intra- and interindividual variability of nonlinear characteristics among comparable SWD. Therefore, a number of TAS for several subjects were analyzed. Because of the known heterogeneity

M. Feucht1, U. Möller1,2, H. Witte2, K. Schmidt3, M. Arnold2, F. Benninger1, K. Steinberger1 and M.H. Friedrich1

1University Clinic of Neuropsychiatry for Children and Adolescents, 1090 Vienna, Austria, 2Institute of Medical Statistics, Computer Sciences and Documentation and 3Institute of Pathophysiology, Friedrich Schiller Universität, 07740 Jena, Germany

Cerebral Cortex Sep 1998;8:524–533; 1047–3211/98/$4.00
of conditions associated with SWD in humans, only SWD corresponding to a distinct seizure type (TAS) and a distinct syndrome (childhood absence epilepsy, CAE) were selected. Only unmedicated patients were considered in order to prevent possible data bias.

Jansen (1991) argued that nonlinear characteristics are less appropriate as ‘magic’ single features, but could be better used as constraints for the build-up of models or as evaluation criteria for models already created, i.e. the outputs of the model(s) and the data actually observed are compared through estimates of those characteristics. The second part of our study was therefore directed towards qualitative statements: we created a few relatively simple models that either emphasized or omitted particular features included in prototypical SWD from a real EEG. The resulting spike-and-wave (SW) data sets were then compared with the EEG signal by means of estimates of certain dynamic properties. The qualitative statements obtained involve, for natural reasons, some elements of judgment and interpretation.

The current analysis strategy was applied for the first time with respect to the selection of the experimental data and the complementary use of the several methods. The aim of this strategy was to describe as adequately as possible structural properties of the neuronal system generating typical SWD. More generally it was intended to facilitate the understanding of at least the pure SW dynamics and to support the development and evaluation of models generating the basic dynamic features according to real patterns.

Materials and Methods
EEG raw data (Schwarzer Picker ED 24 electroencephalograph, bandwidth set at 0.3–70 Hz, 19 scalp electrodes placed in standard 10/20 montage positions, referenced to averaged ears, impedance kept below 5 kΩ; data were digitized at 256 Hz) were collected from the data base of the Department for Seizure Disorders at the Vienna University Clinic of Neuropsychiatry for Children and Adolescents. Selection criteria were: clear-cut diagnosis of CAE according to medical records and EEG/video evaluation. Atypical patterns during the initial and final seizure stage in conjunction with high-amplitude spikes was selected (visual inspection). Therefore, the channel with the most pronounced SW rhythm is not necessarily accompanied by additional events; if they still occur, they may more likely reflect individual peculiarities.] The analysis methods applied include the autocorrelation function (a standard method in signal analysis) and three nonlinear characteristics (correlation dimension $D_2$, averaged pointwise dimension $D_p$ and the largest Lyapunov exponent $\lambda_1$). During some earlier EEG applications, low fractal $D_2$ and positive $\lambda_1$ estimates have led analysts to state the existence of chaos. In the meantime several studies (such as Theiler, 1995) have shown that in this way one cannot obtain a formal proof of chaos. Nevertheless, one can show that some statistical and dynamic properties of the system are (or are not) consistent with deterministic chaos. Considering these experiences, three further techniques were used for the generation of artificial SW data to be tested against the real SWD by means of the aforementioned features.

Characterization of the Linear Properties of a Signal

Autocorrelation Function (ACF)
The ACF reflects the linear dependencies of a (stationary) signal. It quantifies how strongly two data points, separated by a given time lag $L$, are correlated on average. The ACF contains information equivalent to the power spectrum (Grassberger et al. 1991). The ACF was used in the present study (i) to accomplish the comparison of the linear dependencies of different SW signals with each other, and (ii) as an indicator for the adaptation of the embedding technique.

Characterization of the Nonlinear Properties of a Signal

Attractor Reconstruction
The attractor of a stationary dynamic system (see Appendix) is a topological structure that reflects time-invariant characteristics of the dynamics, in particular nonlinear relationships. The embedding technique (Packard et al., 1980; Takens, 1981) makes it possible to reconstruct the attractor and to assess its properties based on a one-channel time series obtained from the system. In the present study, this technique was applied to all SW signals. The resulting reconstruction sets provided the basis for the estimation of correlation dimension, averaged pointwise dimension and largest Lyapunov exponent.

Correlation Dimension
The correlation dimension $D_2$ (Grassberger and Procaccia, 1985) can be intuitively characterized as the number of dimensions of the smallest-dimensional space that is completely filled by an attractor. A regular (periodic or quasiperiodic) motion with $n$ independent variables fills an $n$-dimensional space, whereas a chaotic process provides a fractal spatial structure. Therefore, a regular motion has an integer $D_2$, and $D_2$ of a chaotic signal is a fractal number. $D_2$ was used in this study for the following tasks: (i) to determine whether the neuronal system generating a SW signal is low-dimensional (i.e. its dynamics can be described with only a few degrees of freedom), and (ii) to distinguish SW signals from each other which differ in a specific property.

Figure 1. Examples of the EEG sequences of five children clipped for investigation of the dynamics. The lower trace was selected for detailed analysis (see Fig. 2).
Averaged Pointwise Dimension

The pointwise dimension $D_p$ (Farmer et al., 1983) quantifies the same property for a point on the attractor as $D_2$ does on average for the entire attractor. $D_p$ is useful for evaluating a reconstruction set which does not adequately represent all parts of the attractor. These parts can be excluded on the basis of certain criteria for the acceptance of $D_p$ estimates. The mean value of the remaining $D_p$ estimates provides the averaged pointwise dimension $D_{p\bar{a}}$. This technique was demonstrated by Holzfuss and Mayer-Kress (1986). Our approach to $D_{p\bar{a}}$ involves more comprehensive examination of the data and an extended set of criteria (see Appendix). $D_{p\bar{a}}$ was used for the same tasks as $D_2$.

Largest Lyapunov Exponent

The Lyapunov exponents define the average rate of contraction or expansion of initial errors along the main axes of the system in the phase space. They quantify the influence of small initial errors over time and are measures of the predictability of time series. The dynamics of a system is primarily defined by the largest Lyapunov exponent (LLE) $\lambda_1$. A positive LLE indicates unpredictable (possibly chaotic) behavior, whereas an LLE $= 0$ stands for predictable deterministic (periodic, quasi-periodic) or stochastic behavior. For the present analysis, algorithms according to Wolf et al. (1985) and Schmidt et al. (1998) were used. The tasks of the LLE in the study were (i) to provide evidence of chaos in case it is present in the data, and (ii) to distinguish SW signals differing in a specific property from each other.

Derivation of New SW Sequences with Specific Properties from One EEG Signal

Nonlinear Modeling of SW Signals

A self-exciting threshold autoregressive (SETAR) model (Tong, 1978; Tong and Lim, 1980) is an extension of the classical autoregressive concept and applicable in nonlinear time sequence analysis (Grassberger et al., 1991). It has been shown (Tong, 1983) that such models can generate patterns which are characteristic of nonlinear dynamic systems such as oscillations with amplitude-dependent frequencies, (asymmetric) limit cycles, jump resonances and synchronization phenomena. Since SETAR models seem to be promising for model-based analysis of time series with nonlinear (quasi)periodic oscillations, this approach was considered in order to model the selected EEG signal. For the parameter estimation we used a novel adaptive stochastic gradient procedure (Arnold et al., 1997). This approach was used to serve as a simple nonlinear model providing a noise-free SW sequence from a stationary (steady) state which is a realistic reproduction of an EEG target SW signal.

Generation of Surrogate SW Signals

Chaos represents a deterministic nonlinear structure in the long-term relationships of a signal. Convincing evidence of chaos in the time course of a signal is provided by a clearly positive estimate of the LLE. Nevertheless, this might be difficult for a nearly periodic signal if chaos is coded in the form of cycle-to-cycle variability.

Theiler (1995) suggested a test by means of which at least the existence of nonlinear structure (also called dynamic correlations) can be indicated in a nearly periodic signal. Possible long-term relationships are destroyed by separating out the individual patterns and scrambling them, i.e. the intact patterns are rearranged in a new, random order. The resulting time series is termed surrogate data. [The statistical method of surrogate data (Theiler et al., 1992) was introduced with a phase randomization technique and the null hypothesis that the data arise from a linear stochastic process. As shown by means of `mixed' sine waves, this technique `may not distinguish chaotic time series and colored noises of low frequency content' (Prathavan and Sadasivan, 1997). Since the null hypothesis does not apply for SW data either (Theiler, 1995), cycle-shuffling has been suggested for the indication of dynamic structure in almost periodic signals.] The removal of dynamic correlations will then be detected by changes in characteristic nonlinear properties. Comparing $D_2$, $D_{p\bar{a}}$ and $\lambda_1$ estimates of a signal with those of surrogate data sets, we assessed whether there is any dynamic correlation at all between one pattern and another in the selected EEG signal and a SW signal derived from the EEG by means of a nonlinear (SETAR) model. The SW cycles were separated at the beginning of each spike, i.e. where the rising part crossed an appropriate threshold.
be quantified. In the judgment of the authors, the minimal criteria for a reliable estimation of $D_2$ were not fulfilled (see subsequent detailed analysis).

The averaged pointwise dimension $D_{{ap}}$ was found to be between 2.6 and 3.2 for most configurations applied to each data set respectively. Typical signs of reliable estimation were observed for a subset of configurations yielding $D_{{ap}}$ estimates within the interval (2.93, 3.05). The largest Lyapunov exponents for all 14 signals — spread over the interval (0.04, 0.10) — were close to zero ($0.081 \pm 0.017$). Thus, the results for the EEGs of all seizures are comparable, where $D_{{ap}} \approx 3$ and $\lambda_1 \approx 0$. The variability of the absolute results can be ascribed to differences of the signals investigated (length of the data sets, SW morphology, irregular signal components) and differences of the algorithmic configurations tested with each data set.

**Results Derived from One EEG Signal with Typical SW Characteristics**

**SW Sequences Derived from the EEG Target Signal**

The impulse response of the SETAR model strongly assimilated the SW characteristics of the selected EEG (Fig. 3). Visual and time-variant spectral analysis revealed, however, that the prolongation of the wave components was not adopted.

Thirty-nine surrogate data sets (see Theiler, 1995) were derived from both the EEG signal and the model-generated SW sequence. The cutting points are not obvious in the surrogate signals (Fig. 4).

The first SW simulation (S5, Fig. 5a) approximately matches the EEG patterns (S1) of the initial and final phases (Fig. 5c). During the intermediate phase the EEG patterns led for some time, indicating that the increase in the duration of the EEG waves is not exactly linear.

**Linear properties of the signals**

The ACFs of all signals included in the detailed analysis are depicted in Figure 6. The periodicity of the SW simulation with constant duration of the waves (S6) is manifest in its almost periodic ACF (Fig. 6c). [The modest decrease of the peak size...]

---

**Figure 3.** (a) Reproduction of SW dynamics by the SETAR model (S3), (b) segment of the EEG target signal (S1).

**Figure 4.** Segments of the original SW and one surrogate set from the EEG (S1 = a, S2 = b) and the SETAR model (S3 = c, S4 = d). The SW cycles were separated out where the rising parts of the spikes intersect the dotted line.

**Figure 5.** SW simulation S5 with increasing (a) and S6 with constant (b) duration of the waves. (c) Signal of (a) (fat) and the selected target EEG (thin) superimposed.

**Figure 6.** Autocorrelation functions of SW signals: (a) EEG (S1, solid) and 39 surrogate data sets (S2, dotted); (b) model (S3, solid) and 39 surrogate data sets (S4, dotted). The latter are best recognizable from the fifth to the seventh negative peak. (c) Simulated SW with increasing (S5, fat solid) and constant (S6, thin solid) duration of the waves.
reveals a discretization effect: even though all waves in this time series have the same shape (per definition of the series), the sample values forming this shape are slightly lagged (decorrelated) between the cycles. The ACF of the SW simulation with successively prolonged waves (S5) shows a collapse of the rhythmic oscillations near the value \( L = 1.8 \). This characteristic course of this ACF results from the wave prolongation because this property makes up the specific difference between both simulations.

The global shape of the ACF obtained from the EEG signal S1 (Fig. 6a) is very similar to that of the EEG simulation S5. Hence, the ACF of the EEG is mainly determined by the prolongation of the wave patterns. This effect became weakened by the SW cycle randomization: the ACFs of the surrogate sets S2 show continued oscillations.

The shuffling of the SW cycles of the signal S3 has no effect on the autocorrelation, although the SW complexes have a different morphology (Fig. 3). The ACF, derived from the nonlinear model, can hardly be distinguished from the ACFs of its surrogate sets (Fig. 6b). Hence, the evaluation of linear dependencies did not reveal structure in the order of successive SW cycles.

### Table 1

<table>
<thead>
<tr>
<th>SW data</th>
<th>( D_2 )</th>
<th>( D_\infty )</th>
<th>( \lambda_1 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1 original scalp EEG data</td>
<td>a</td>
<td>-2.94</td>
<td>0.081</td>
</tr>
<tr>
<td>S2 surrogates from EEG data</td>
<td>a</td>
<td>1.81</td>
<td>0.083 ± 0.002</td>
</tr>
<tr>
<td>S3 response of the SETAR model</td>
<td>a</td>
<td>1.90–2.00</td>
<td>0.005</td>
</tr>
<tr>
<td>S4 surrogates from SETAR data</td>
<td>b</td>
<td>1.86–1.90</td>
<td>0.057 ± 0.006</td>
</tr>
<tr>
<td>S5 simulation with prolonged waves</td>
<td>b</td>
<td>1.80c</td>
<td>0.005</td>
</tr>
<tr>
<td>S6 simulation with constant waves</td>
<td></td>
<td>0.76–0.80</td>
<td>0.97–1.00</td>
</tr>
</tbody>
</table>

The given intervals denote the range of results obtained for different algorithmic configurations. *a* estimation not possible; *b* estimation in the context of the analysis not necessary (see text).

The choice of algorithmic parameters involves heuristic elements (see Appendix). More optimal parameters may be found, yielding \( D_\infty \) values even closer to 2 for the simulation S5. An application of the \( D_2 \) estimation procedure to the data selected by the pointwise technique provided values between 1.95 and 2.05 for S5 and 1.00 for the simulation S6 (estimation interval: 0.91–0.94 \( r_{\max} \), see also above 'Correlation Dimension \( D_2 \)').

The ACF of the simulated SW signal with constant waves (S6) reveals structure in the order of successive SW cycles. This effect became weakened by the SW cycle randomization: the ACFs of the surrogate sets S2 show continued oscillations.

The shuffling of the SW cycles of the signal S3 has no effect on the autocorrelation, although the SW complexes have a different

Figure 7. Log–log plots of correlation integrals (upper) and local slopes of the graphs (lower): (a) EEG (S1, solid) and 39 surrogate data sets (S2, dotted), embedding dimensions 5–9; (b) model SW (S3, solid) and 39 surrogate data sets (S4, dotted), embedding dimensions 6–10.
The dimension estimates are close to integers, where the values depend on the properties included in the signals (see Fig. 2): $D = 1$ for pure SW simulation (S6), $D = 2$ for SW with prolongation of the wave components (S5), $D = 2$ for SW without prolongation but with superimposed events of smaller amplitudes (S3), and $D = 3$ for a signal including all three properties (S1).

Under these circumstances, it may be noted that the dimension estimates are close to integers, where the values depend on the properties included in the signals (see Fig. 2): $D = 1$ for pure SW simulation (S6), $D = 2$ for SW with prolongation of the wave components (S5), $D = 2$ for SW without prolongation but with superimposed events of smaller amplitudes (S3), and $D = 3$ for a signal including all three properties (S1).

The surrogate data test made it obvious that the model SW signal and its surrogate sets can be distinguished from the EEG in the different types of SW signals investigated. Like D2, the LLE does not permit a clear distinction between the EEG and its surrogate sets. Also similarly to D2, the model SW signal and its surrogate sets can be distinguishable. The difference is larger than one magnitude. Since the LLE of the simulated SW with constant patterns (S6) is zero by definition, the estimated value 0.003 indicates the precision of the algorithm used. All LLEs computed were no larger than 0.1. The mean value of the point prediction error (Schmidt et al., 1998) minus its standard deviation was 0.003 for the EEG and even negative for the model and the simulation S6.

Since the ACFs of the EEG signal S1 and EEG simulation S5 change considerably if distinct blocks (SW complexes) of the signals are shuffled, both signals represent — in a statistical sense — realizations of nonstationary processes. On the other hand, a stationary process is associated with the field of nonlinear dynamics with the long-term behavior of a dynamic system during a steady-state in contrast to a transient period after initialization or perturbation. From this point of view, the SWD may represent either a short episode during a steady-state, or a transient phase, i.e. the (unmodified) system generates SWD in the observed fashion as a part of already stable long-term behavior, or during a period of stabilization of the behavior. [An example for the problem indicated has been presented in Argyris et al. (1994) by means of the Duffing equation (discussion of dynamic behavior, effects of a long transient period on the phase space structure, consequences for the estimation of related properties.) This question cannot be answered on the basis of the EEG data available. By means of the signal and the methods at hand it is possible to describe the dynamic features at least during the specific observation period.

For the interpretation of estimated dimensions it is relevant whether evidence for deterministic chaos was obtained or not. Although we were able to differentiate most types of SW signals (S1–S6) by means of the LLE (Table 1), the estimated LLEs for all algorithmic configurations used and all signals investigated were not consistent with deterministic chaos. [Theiler (1995) argued that an LLE much larger than 1 would be expected for chaos occurring on a time scale smaller than one SW period. Further, an LLE not substantially different from those of surrogate data should not be interpreted as a true value.] On this basis, a generation of SWD by interaction of regular modes of behavior can be taken into account.

Dimension 1 for simulation S6 means that the corresponding SW pattern is generated by just one oscillatory event. The increase in the estimated dimension of one unit due to the additional change in the patterns for simulation S5 was shown to be a systematic effect. [The same effect was also measured for sine waves with steadily decreasing frequency. In this case, the phase portrait no longer shows a limit cycle. Instead the reconstruction set is arranged on a spiral that forms a flat (two-dimensional) loop.] This can be regarded as the detection of a second, independent variable, i.e. a delay element reducing the frequency of SW repetition.

The surrogate data test made it obvious that the model SW sequence S3 involves nonlinear structure (i.e. relationships over more than one SW cycle, not represented by the ACF). The time series seems to reflect a stationary process in the statistical and the dynamic sense. This is indicated by the invariance of the ACF with respect to SW shuffling and the invariance of the spatial extent of the reconstruction set with respect to the signal length. The dimension estimates suggest that two oscillatory modes are necessary in order to reproduce the SW morphology of the EEG adequately. Under these circumstances the value $D_{ap} = 3$ is the
expected result for the EEG signal S1 because it additionally exhibits an organized alteration of the patterns. Regardless of the unknown long-term behavior corresponding to the EEG signal S1, the third variable is effective at least during the observation period.

Discussion
The problem of stationarity seems to play a crucial role in the analysis of the nonlinear dynamics of SWD. Our results permit the conclusion that the system investigated was not (as yet) stationary over (almost) the entire period during which the SW patterns were recorded. The same conclusion can be drawn from experimental findings in animals (Steriade and Amzica, 1994; Steriade and Contreras, 1995). [Simultaneous cellular and EEG recordings of SWD in anaesthetized cats demonstrated a close time relation between the activity of cortical neurons and the surface EEG. Whereas equivalent observations in humans are precluded for ethical reasons, similarities were manifested in the EEG and behavioral features during SWD. It was hypothesized that the electrophysiological processes revealed by the invasive recordings are homologous at least to some (clinical) forms of seizures (Steriade and Amzica, 1994).] The following results from this work (and former studies) should be noted.

Generally, the synchronization of neuronal activity increased during the seizure to reach its highest level during unitary SW discharges around 5 Hz. The authors demonstrated that SW paroxysms are generated progressively by synaptic build-up, and are sequentially distributed through short- and long-scale linkages within the cortex and most probably through reciprocal corticothalamic networks. A spike train causes the spike component of a SW complex, whereas the subsequent period of silence is responsible for the wave component in the EEG. The progressive synchronization leads to a shortening of the duration of spike trains and a prolongation of silent periods. At least the prolongation was clearly observed in the above EEG example. Thus, the conjecture that the SWD (restricted to the measurable period) might be nonstationary from a mathematical point of view is in fact related to the nonstationary behavior of the neuronal network generating the EEG signals.

The authors cited above provided two arguments that may explain irregular EEG events. If the action potentials were fired in two or more clusters, double- or poly-spike components can be observed in the EEG. This corresponds to a lower level of neuronal synchronization. Therefore, such spike complexes might reflect initial states of the network rather than a stationary (chaotic) state. Further, inhibitory processes increasing during the seizures were thought to clean up the background firing, whereas activities from strong interneuronal connections are preserved. This means that low-amplitude events beside or superimposed on SW patterns may occur in the EEG if either the inhibition of other activities is not (yet) perfect or if the pool of neurons projecting to the scalp electrode has strong connections to other neuronal populations not involved in the SW rhythm. The latter argument provides an explanation of why in some instances irregular events do not disappear until the end of a seizure. Generally, one would expect that preferentially SW patterns would survive the progressive inhibition. This was indeed observed in the data inspected and chosen for this study.

The above authors considered exhaustion as one reason for the arrest of seizures. Hence, it is conceivable that the duration and/or cessation of the global SW activity is determined by external factors and not necessarily by the dynamic process itself. This argument supports the assumption that the observable SWD describe only a temporary state of the dynamics (whether stationary or not).

Babloyantz and Destexhe (1986) and Frank et al. (1990) concluded that they had each found chaos in one human SW sequence respectively based on small $D_2$ and clear positive $\lambda_1$ values. From information given in the first paper the second authors inferred $\lambda_1$ to be only a little larger than zero. Theiler (1995) re-examined the data first analyzed by Frank et al. (180 SW cycles taken from the scalp EEG of an epileptic seizure not exactly classified) using similar, but not identical algorithms (ACF, $D_2$ and LLE with the SW shuffling technique). The differences between original and surrogate data with respect to the correlation integrals were ‘not large enough to imply that the data are low-dimensional’, and ‘interesting dynamical structure’ was not found (the LLE was even negative). Thus, the arguments supporting the assumption of chaos for specific data sets were weakened by reconsideration later on. The results of Theiler are similar to those in our study, if only $D_2$ and LLE, applied to the real EEG, are considered. This demonstrates the importance of additional or alternative tools such as the averaged pointwise dimension or nonlinear models. The autocorrelation between original and surrogate data differed much less than in our study. Thus, the problem of stationarity may be of particular relevance in CAE.

Babloyantz and Destexhe (1986) analyzed a petit mal (the term ‘petit mal’ does not indicate the precise epileptic syndrome which may be different from CAE) EEG sequence of 5 s, containing $\sim$15 SW complexes. Due to the high sampling rate (1200 Hz) and the reconstruction parameters, they obtained distinct subsets for the spike events on the one hand and the wave components on the other. They inferred that the data ‘emanating from wave activity have a tendency to remain in a plane’ and estimated $D_2 \approx 2.05 \pm 0.09$. Some considerations show that their result may be consistent with our findings: the waves are more similar to each other than the spiky elements and the waves provide more reconstruction points due to their length versus spike length. Therefore, the correlation integrals $C(r)$ for small values of $r$ will probably be dominated by data from the waves, as in our case (see above: Averaged Pointwise Dimension $D_{wp}$). The duration of the wave patterns in their EEG signal, however, seems to be more or less constant. Thus, the situation for $D_2$ estimation seems more similar to that of our SW model ($D_2 \approx 2$) than our EEG example ($D_{wp} \approx 5$). Finally, it may be noticed that the spike events in their data (channel 1) develop from single spikes towards double or poly-spikes. This fact is amazing, because it seems to disagree with the above arguments concerning the progressive neuronal synchronization. If, however, the coherence of neuronal firing during SWD may indeed decrease or oscillate, it would apparently constitute an independent variable as indicated by the pointwise dimension for our EEG signal.

A comparison of the dynamic and spatiotemporal properties between the spike and the wave components shows that the variability of the dynamic patterns can be related to the variability of spatial patterns: during most absence seizures the EEG waves of different SW complexes — recorded at the same site — were more similar to each other and more regular than the spike events [this was quantified by our estimates of the pointwise dimension and the local LLE according to Schmidt et al. (1998)]; Lemieux and Blume (1986) found that the topographical patterns of the field distribution at a single time point were quite symmetrical over the scalp for the EEG waves and often asymmetrical for the spikes, where the patterns tended...
to remain stationary during the evolution of the wave, in contrast to clearly changing patterns during the spike period. However, the findings of both approaches overlap only in part: the effects of the dynamic changes of neuronal synchronization on the nonlinear measures (see above) or the nonlinear structure in the order of SW complexes did not find an adequate expression in the topological description; the topological aspects of the long-term dynamics remain to be investigated.

Since the field distribution during EEG spikes was relatively discrete and changed systematically (Lemieux and Blume, 1986) a search for determinism in their long-term dynamics may yield improved results using higher sampling rates and methods that can distinguish different types of dynamics on ‘nonuniform attractors’, e.g. the semi-local Lyapunov exponents and metric entropy (Gallez and Babloyantz, 1991) or the pointwise dimension (applied in our study).

Nonlinearities in electrographic signals of paroxysmal activity have already been demonstrated in animal studies (Pijn et al., 1991) and human epilepsies (Casdagli et al., 1997). The detection of nonlinear features in our SW model, which was derived from a real EEG signal, can be seen as new evidence for nonlinear dynamics in surface EEG data, even though this is not a rigorous proof. This type of nonlinear structure in the EEG would be consistent with chaos, but this would not yet justify the assumption of chaos in the EEG signal S1. In order to look for nonlinear structure also in the time series of the interspike intervals (Longtin, 1993; Rapp et al., 1994) one would need more SW cycles than there are available from typical childhood absence seizures.

Friedrich and Uhl (1996) applied an analytical approach to two multigrid EEGs of different persons suffering from petit mal epilepsy. They found that a petit mal seizure obeys a deterministic law of evolution with few degrees of freedom. In particular, they were able to decompose the experimental patterns into three dominant spatial modes and to explain the dynamics as a kind of mode interaction. Their conclusion of low-dimensionality and the quantification of three variables for the complete seizure dynamics is in striking conformity with our results.

Summary and Final Remarks
The essential results of the present nonlinear EEG analysis of childhood absence seizures are as follows. (i) Indications for nonlinear structure in SWD were found. (ii) Mathematical analysis of SWD on the macroscopic (EEG) level gave rise to the conjecture that the system, while generating the SWD, was either not (as yet) stationary or only partially exhibited characteristics of a steady-state. (iii) Arguments that justify the assumption of deterministic chaos in our EEG signals were not obtained. (iv) Dimensional analysis provided clear indications of low-dimensional dynamics underlying the EEG. This means the dynamics of hypersynchronous neuronal firing during SWD in terms of the scalp EEG can be equivalently generated by a system of few, most probably three types of motion. One of these modes can be associated with a process of modifying the strength of interaction between the neurons participating in the SWD.

The above findings are of value for attempts to model almost pure SWD. The results indicate that this can be done with deterministic equations. Such models help to increase our understanding of the basic dynamic features of most SWD. Nevertheless, it is clear that SWD do not arise from isolated neuronal circuits, i.e. interconnections with ‘external’ structures must be taken into account. In order to explain mechanisms responsible for the start and cessation of seizures or irregular EEG events during the seizures, approaches to nonlinear stochastic dynamic systems (Tong, 1995) may be useful.

The results were obtained based only on segments of one EEG channel respectively and are restricted to CAE. Multichannel evaluation and comparisons with SWD of other syndromes remains the subject of further studies. The current results and the material cited indicate that nonlinear models may substantially support the explanation of dynamic phenomena underlying the EEG, among them epilepsy. The discussions in Skarda and Freeman (1987) and Glanz (1994) also show that the relevance of chaos to the EEG is the subject of a controversial debate.

Notes
This study was supported by the Austrian Fonds zur Förderung der Wissenschaftlichen Forschung (grants P 10598-MED and P 10460-MED) and the German BMBF (grant 01ZZ9602).

Address correspondence to Martha Feucht, Währinger Gürtel 18–20, A-1090 Wien, Austria. Email: Martha.Feucht@univie.ac.at.

References
Nonlinear Dynamics During Childhood Absence Seizures • Feucht et al


Appendix

Typical Absence Seizures

Although SWD are sometimes also seen with other conditions and even without any observable clinical symptoms, as many as 98% of patients have generalized non-convulsive (grade type 1), i.e. absence seizures (Avoli and Gloor, 1994). Typical absence seizures (TAS), as defined by the International League against Epilepsy (ILAE; see ILEA, 1981), occur in various epileptic seizure disorders. Based on differences in clinical and EEG presentation, age at seizure onset, response to antiepileptic drug (AED) treatment and prognosis, a number of syndromes have been individualized (reviewed by Panayiopoulos, 1994) and are listed in the current ILAE classification (CCTILAE, 1989).

Results of Animal Studies

According to the current hypothesis, SWD reflect a widespread phase-locked oscillation of ~250–300 ms between excitation (spike) and inhibition (wave) in mutually connected thalamocortical networks with the nucleus recesscularis thalami having a crucial gateway function. The main features are thought to be the critical involvement of those thalamocortical mechanisms that mediate spindles and recruiting responses, and of γ-amino-butyric acid (GABA)ergic transmission. In contradistinction to focal spikes, during SWD there is preservation of the GABAergic function, sparing of classical inhibitory postsynaptic potentials (IPSPs) and absence of paroxysmal depolarization shifts (PDS).

Reasons that Preclude Invasive Investigations of Human TAS

SWD/TAS almost exclusively occur in otherwise normal children between 4 and 12 years of age, they usually respond to specific AED treatment and remit before puberty in the majority of cases. Consequently, ethical considerations rule out the application of techniques that are commonly used in patients with drug-resistant, localization-related epilepsies during presurgical evaluation and epilepsy surgery (i.e. electrophysiological studies of epileptic tissue using in vitro slice techniques, in vitro depth electrode recordings).

In addition, it has been stressed by several authors that the insertion of depth leads is unlikely to yield precise information on the origin and propagation of primary generalized seizure discharges. Consequently, reports about studies in pediatric patients with implanted depth electrodes are rare and the results published so far have remained inconclusive and therefore debatable (reviewed in Niedermayer and Lopes da Silva, 1993, p. 508).

The same holds for brain-slice experiments, as the face validity of in vitro models for generalized seizures (by definition, these seizures are bilateral and widespread – features that can seldom be modeled in single cells or regional brain slices) is somewhat limited (reviewed in Wyllie, 1997, p 58).

Stationarity and Attractor

A nonlinear dynamic system can be mathematically described by a differential equation including variables and control parameters. Defined by this equation, the motion of the system
yields a trajectory in the phase space (whose coordinates are defined by the system variables). Provided that the equation and parameter values are not modified, the trajectory for infinite time describes a compact subregion in the phase space, i.e. the attractor. If the initial point of the trajectory lies outside the attractor, the system has to pass through a transient phase. Eventually arrived on the attractor, the system persists in a steady-state. This is the stationary phase (see, for example Argyris et al., 1994 and refs therein).

**Correlation Dimension versus Averaged Pointwise Dimension**

The local space-filling properties of the attractor are quantified by the normalized mass \( C_p(r) \) of points on the attractor within a ball of radius \( r \) around a reference point. The pointwise dimension \( D_p \) can be estimated as the slope of a linear region \((r_0, r_1)\) for small \( r \) in a plot \( \log C_p(r) \) against \( \log r \). The global space-filling properties can be characterized in two ways. (i) If the average of \( C_p(r) \) over the entire attractor, called the correlation integral \( C(r) \), is used instead of \( C_p(r) \), then the correlation dimension \( D_2 \) is obtained. (ii) The mean value of the slopes obtained for a set of reference points leads to the averaged pointwise dimension \( D_{2p} \). The relevance of a slope value for an interval in the log-log plot is confirmed by a plateau of \( D_{2p} \) around a reference point. The pointwise dimension \( D_p \) is obtained. Further, saturation of the slope estimates with increasing embedding dimension is required.

**Algorithmic Parameters**

In order to apply \( D_2 \), \( D_{2p} \) or the LLE, several parameters must be fixed. Up to now, this problem needs some judgment (see Theiler, 1994, 1995). The choice of parameters within appropriate ranges usually leads to very similar, although not identical results. Therefore, numerical results cannot be understood as absolute solutions. In order to avoid biased values, each data set was examined with various different parameter configurations according to common rules (see cited literature). If no solution among the results obtained was clearly favorable, we gave an interval for the estimated quantity (Table 1). Using a graphical user interface for dimension estimation, the related parameters were tuned interactively (heuristic approach). In the tests with surrogate data, all parameters were selected for the EEG and modeled SW signal and then kept constant for the surrogate sets.

**Attractor Reconstruction**

The embedding technique is also known as delay method, since \( m \) time-delayed sample values of the signal are joined to one point in the reconstructed phase space of embedding dimension \( m \).

After fixing the EEG recording parameters, the time lag \( L \) and the embedding dimension have a strong influence on the phase space reconstruction. \( L \) was tested between 1 and 1.5 \( L_0 \) (\( L_0 \) is the value where the ACF first intersects the zero line). This range was found to be relevant for EEG signals of epileptic seizures, based on simultaneous analysis of ACF and the mutual information function (Graf and Elbert, 1990). The lag \( L_c \), where the ACF crossed the value \( 1/e \), produced consistent results (see also Albano et al., 1988) and was selected for the above presentation.

Based on an estimated dimension \( D \), the embedding dimension \( m \) was varied from \( m_1 > D \) to \( m_2 \geq 3D \) (\( m = D + 1 \) is the minimum required, \( m = 2D + 1 \) is theoretically sufficient).

**Correlation Dimension and Averaged Pointwise Dimension**

In the calculations the Euclidean norm was used for the radius scale. The correction parameter \( W \) (Theiler, 1986) was considered. \( W = L \). It is furthermore necessary to define which qualities a plot region must have for slope estimation. We preferred a stricter regime for the acceptance of pointwise dimension estimates compared to the approach of Holzfuss and Mayer-Kress (1986): each reference point was tested. It was required that the linear region (i) spreads over small radii \( (r_0 \leq 5\% r_{\text{max}}) \), (ii) covers at least 100 embedding points, and (iii) has a minimum length of 2 on the log_{10} plot (other configurations were also tested). Considering the small data size \( N \approx 5400 \), these constraints have the effect that only those embedding regions are admitted for estimation where the density is relatively high and the spatial properties are relatively constant.

**Largest Lyapunov Exponent**

The evolution time \( k \), used to quantify the influence of initial errors, was varied between 1 and 100 (–400 ms). The LLEs converged to small values (<0.1). \( k = 10 \) was used for presentation throughout the computations.