Discerning Nonstationarity From Nonlinearity in Seizure-Free and Preseizure EEG Recordings From Epilepsy Patients

Christoph Rieke*, Florian Mormann, Ralph G. Andrzejak, Thomas Kreuz, Peter David, Christian E. Elger, and Klaus Lehnertz

Abstract—A number of recent studies indicate that nonlinear electroencephalogram (EEG) analyses allow to define a state predictive of an impending epileptic seizure. In this paper, we combine a method for detecting nonlinear determinism with a novel test for stationarity to characterize EEG recordings from both the seizure-free interval and the preseizure phase. We discuss differences between these periods, particularly an increased occurrence of stationary, nonlinear segments prior to seizures. These differences seem most prominent for recording sites within the seizure-generating area and for EEG segments less than one minute’s length.

Index Terms—EEG, epilepsy, nonlinear time series analysis, nonlinearity, nonstationarity, seizure prediction.

I. INTRODUCTION

APPROXIMATELY 1% of the world’s population suffers from epilepsy [1], [2], a disease that is characterized by recurrent seizures which may occur in virtually every cortical region. These seizures are the clinical manifestations of a highly synchronized discharge of neurons and mostly occur without warning. In certain patients, the region of the brain that primarily generates seizures (epileptic focus) can be removed by surgical intervention which, however, may come at the expense of neurological defects. Other patients require long-term treatment with antiepileptic drugs, which might also cause neurological, particularly neuropsychological deficits. If it were possible to anticipate the occurrence of epileptic seizures, therapeutic possibilities would change dramatically [3]. The unequivocal a priori definition and prospective detection of a preseizure state and with it the possibility to actually predict an impending seizure would allow to develop suitable seizure prevention strategies and would help to study basic mechanisms leading to seizures in humans.

With the advent of the physical theory of nonlinear dynamical systems [4], [5] new analysis techniques were developed [6] that allow to characterize apparently irregular behavior, a distinctive feature of the electroencephalogram (EEG). Over the last decade, univariate nonlinear measures like dimensions, Lyapunov exponents, entropies, or recent bivariate approaches that aim to characterize interdependencies, synchronization, or similarities, were shown to reliably characterize different states of normal and pathological brain function (see [7]–[9] for an overview). In particular, several studies indicate that applying these analysis techniques to EEG recordings allows to define a long-lasting preseizure period [10]–[12].

Due to limitations of the respective methods, it is commonly accepted today that the existence of a nonlinear deterministic or even chaotic structure underlying neuronal dynamics is difficult if not impossible to prove. The discriminative power of nonlinear measures for these dynamical aspects, however, can be enhanced if tests for nonlinearity using surrogate time series [13] are applied [14]–[18].

In a recent study, we have introduced a new measure for nonlinear determinism in EEG time series that exhibits a good sensitivity toward the spatial dynamics of the epileptic brain and correctly lateralizes the epileptic focus in patients with focal epilepsy during the seizure-free interval [19]. A problem with this method is that the null hypothesis includes linearity and stationarity, which may result in spurious detections of nonlinearity due to nonstationarity [20]–[28].

The conventional way of dealing with the problem of nonstationarity is to analyze data by means of a moving-window technique with a short enough segment to assume approximate stationarity. Reducing the segment length, however, also decreases the power of a discriminative statistics.

In this paper, using our recently proposed technique for characterizing nonstationarity on different time scales [29] we further confirm our null hypothesis to avoid spurious detections of nonlinearity due to nonstationarity. Moreover, we pay special attention to the spatiotemporal aspects of the epileptic dynamics by comparing findings for focal and nonfocal EEG recordings.
We also investigate the sensitivity of the above measure for nonlinear determinism toward the temporal dynamics of the epileptic process by examining its capability to distinguish the preseizure (preictal) period from the seizure-free (interictal) interval.

II. MATERIALS AND METHODS

A. Database

Our retrospective study is based on EEG time series recorded intracranially from seven patients with focal epilepsies undergoing presurgical evaluation. Data were recorded independently from the design of the present study and covered different states of the epileptic process (see [30] and [31] for details of electrode implantation and recording techniques). EEG data from 20 to 88 channels were recorded within the 0.5–85 Hz (12 dB/oct.) frequency range using a 12-bit analog-to-digital converter, a sampling rate of 173.61 Hz, and a common average reference. From the available data randomly selected 725 segments from eight recordings during the interictal state (hours to days before seizure) and 132 segments from two recordings before the electrical seizure onset (2–3 min). Recording channels were classified as either focal or nonfocal with the focal area defined as comprising those recording channels that exhibited earliest signs of electrical seizure activity. Surgical removal of the focal area led to complete seizure-freedom in all investigated patients.

In order to test whether short time scales are indeed sufficiently small to assume approximate stationarity of the EEG and to test whether the inherent nonstationarity of the brain can be detected on longer time scales, segments were analyzed on different time scales. The duration of the segments included 23.6 s ($N = 4096$ data points), 47.2 s ($N = 8192$ data points), and 94.4 s ($N = 16384$ data points). Shorter segments were cut out of longer ones amounting to a total number of 857 segments for each segment length.

B. State-Space Reconstruction

The applied analysis techniques require the reconstruction of a state space for which the time-delay embedding scheme proposed by Takens [32] was employed:

Let $\{x_i; i = 1, \ldots, N\}$ denote an EEG time series with zero mean and unit variance, where the physical time is related to the index of $x_i$ by $t = t_0 + i \Delta t$, with the sampling rate $1/(\Delta t)$ and the initial time $t_0$. Time-delay embedding in an $m$-dimensional state space leads to a set of vectors $V = \{\mathbf{x}_n; n = 1, \ldots, M\}$ with $M \leq N$ and $\mathbf{x}_n = (x_n, x_{n-\tau}, \ldots, x_{n-(m-1)\tau})$ where $\tau$ denotes an appropriately chosen time delay.

C. Testing for Nonlinearity

One of the most common tests for nonlinearity is the method of surrogate data [33], which can be used with any nonlinear discriminating statistics that characterizes a time series. The value of such a statistics is computed for the measured data and compared with the distribution of an ensemble of Monte Carlo realizations under a given null hypothesis. We have recently proposed a combination of iterative amplitude adjusted surrogate data (IAAFT) proposed by Schreiber and Schmitz [35] and the coarse-grained flow average $\Lambda$ proposed by Kaplan and Glass [34] in order to discriminate between nonlinear deterministic and linear stochastic dynamics [19].

As a test for determinism, the coarse-grained flow average $\Lambda$ measures the average degree of alignment of nearby segments of a trajectory $\mathbf{x}_n$. The state space $V$ is divided into $b^m$ nonoverlapping rectangular hypercubes, where $b$ denotes the number of hypercubes per state-space axis. If a hypercube with index $j$ is passed $n_j$-times by $\mathbf{x}_n$, for each pass a tangent vector of unit length $\mathbf{t}_{k,j}(k = 1, \ldots, n_j)$ is generated, whose direction is determined by connecting the points where the trajectory enters and leaves the hypercube. Summing up all vectors of passes through hypercube $j$, the resultant vector $\mathbf{T}_j$, normalized by the number of passes $n_j$, is $\mathbf{T}_j = (1/n_j) \sum_k \mathbf{t}_{k,j}$. In case the included trajectory segments are aligned, $\mathbf{T}_j$ is of unit length. The coarse-grained flow average $\Lambda$ is then defined as

$$\Lambda = \sum_j (|\mathbf{T}_j|^2 - R^2)/(1 - R^2),$$

where $R = \langle |\mathbf{T}_j^w| \rangle$ denotes the expectation value for a random walk process with $n$ vectors of unit length. In [34], it has been shown that $R$ scales like $R \propto n^{1/2}$. Choosing the same embedding parameters as in [19], we calculated $\Lambda' = \sum_j \tau \Lambda(\tau)$ in an $m = 6$ dimensional state space. The number of hypercubes $b$ was adjusted with respect to the analyzed time series (ratio between amplitude range and variance) and ranged from 6 to 20. $\Lambda'$ quantifies the local flow in state space regardless of whether this flow reflects determinism or simply preferred directions due to autocorrelations.

In order to test for nonlinear deterministic structures, we used IAAFT-surrogates that reproduce the sample distribution and linear autocorrelations of the original time series but are otherwise random. Under the null hypothesis of a stationary linear stochastic process observed with a monotonic measurement function, we then estimated $\Lambda'$ for each EEG segment (denoted as $\Lambda_{EEG}$) as well as for the corresponding 39 surrogates (denoted as $\Lambda_{Sur}^s$). In contrast to [19] we here define $\Delta \Lambda = \Lambda_{EEG} - \langle \Lambda_{Sur}^s \rangle$ to test for the null hypothesis of the IAAFT surrogate data which we reject at the 95% level of significance (two-sided test) if $|\Delta \Lambda| > 2\sigma(\Lambda_{Sur}^s)$, where $\langle \cdot \rangle$ denotes ensemble average and $\sigma(\Lambda_{Sur}^s)$ the standard deviation for the surrogate ensemble.

D. Measuring Nonstationarity

The method we use to measure nonstationarity has been described in detail elsewhere [29]. This method quantifies the recurrence of vectors in a state space $V$ (see above). For its reconstruction an embedding dimension $m = 10$ and a time delay $\tau = 1$ were used. Although these embedding parameters differ from those used for the test for nonlinearity, we regard this difference as irrelevant since 1) we here compare findings from analysis methods that are independent of each other, and 2) independent random variables are better approximated in a higher dimensional state space.

Subsequently, using every vector $\mathbf{x}_n$ in state space as a reference (denoted as $\mathbf{x}_r$), we calculate the mean distance in time $l_r = (1/k) \sum_{r = 1}^k e_{ul} |n - r|$ of neighboring vectors. This neighborhood is defined as $\mathbf{U}(\mathbf{x}_n) = \{\mathbf{x}_n : \|\mathbf{x}_n - \mathbf{x}_r\| \leq \varepsilon\}$ with $\|\mathbf{x}_n - \mathbf{x}_r\| = \sqrt{\sum_{i=1}^m (x^n_i - x^r_i)^2} / (m k) = |\mathbf{U}(\mathbf{x}_r)|$ denoting the number of neighbors. In the case of a stationary dynamics, the subspaces $\mathbf{U}$ are revisited, which we refer to as re-
currence. Assuming that all vectors $\bar{x}_n \in V$ have the same probability of recurrence, the expected value of $t_r$ is $E(t_r) = (M/2) - (r(M - r)) / (M - 1)$. Contrarily, in the case of nonstationarity the recurrence of related state-space vectors is reduced and the observed distance in time is on average smaller than $E(t_r)$, which we have termed loss of recurrence [29]. Let $\Phi_{M,r,k}(l)$ denote the a priori expected frequency distribution of the mean distance in time under the assumption that for a stationary system each vector (other than $\bar{x}_r$) has the same probability to be found in the neighborhood of $\bar{x}_r$. In this case, \{n; $\bar{x}_n \in U_r(\bar{x}_r)$\} is independent of the time index $r$ of the reference vector. $E(l_r)$ and $\Phi_{M,r,k}(l)$, however, both depend on $r$. In order to solve this problem, we map the mean time distance $l_r$ using the respective distribution function: $l = \Phi_{M,r,k}(l_r)$, with $\Phi_{M,r,k}(l) = \frac{1}{l} \int_0^l \phi_{M,r,k}(l')dl'$. Under the above assumption, $l \in [0, 1]$ is uniformly distributed and independent of $r$.

The distribution of all $l_r$ reflects the (non-)stationarity of the system in the sense that stationarity leads to a uniform distribution whereas in the case of nonstationary capacities lower values of $l_r$ will accumulate and therefore higher values will be diminished. For a stationary system the median $l$ of the set $\{l_r\}$ is equal to 0.5 up to statistical fluctuations. Under the assumption of independent random variables $l_r$, which is, however, not completely met, the significance level of $l$ can be obtained analytically. Instead we use IAAFT-surrogates to estimate the significance level by $(l_{sur} \pm 2\sigma(l_{sur}))$. Note that $(l_{sur})$ can be replaced by 0.5 as IAAFT-surrogates are stationary by construction. In order to define a suitable neighborhood $U_r(\bar{x}_r)$, we use $\varepsilon$ adaptable to the time series under investigation. The median $l$ is calculated for 32 $\varepsilon$-values within the range [0.01, 0.5] using a logarithmic partition. Finally, we choose $l^* := \{l : \max_{\varepsilon} |\{x_r : 0 < U_r(\bar{x}_r) \leq 20\}| \}$ as a suitable measure to test for nonstationarity.

**III. RESULTS**

Fig. 1 shows the frequency distributions of the measure $\Delta\Lambda$ for nonlinear deterministic structure in the EEG for both interictal and preictal segments for different time scales. For the interictal EEG segments values of $\Delta\Lambda$ are symmetrically distributed around zero while they are slightly skewed right-sided for the preictal segments. The distributions are almost identical for the different time scales analyzed. Based on these distributions we estimate the relative number of segments $\rho_{lin}$ that met the null hypothesis of the test for nonlinear determinism $(|\Delta\Lambda| < 2\sigma(l_{sur}))$, independent of the stationarity properties of the EEG segments (Fig. 2). It can be seen that more than 50% of interictal and preictal segments with a duration of 23.6 s can be regarded as the output of a linear stochastic system. With an increasing segment duration, however, we observe a decrease of $\rho_{lin}$ indicating a higher sensitivity of our test for nonlinear determinism. This can be attributed to a better adaption of the IAAFT-surrogates to linear properties of the EEG segments under the given null hypothesis (cf. [13] and [35]). This tendency can be found for recordings from both the interictal and preictal state. When comparing findings from these states we observe a slightly decreased number of linear segments from the latter state. This difference, however, does not allow to clearly distinguish between the two states.

In order to test whether the missing discriminative power of $\Delta\Lambda$ can, at least in part, be attributed to spurious detections of nonlinearity due to nonstationarity, we investigate the frequency distributions of the measure $l^*$ for the analyzed EEG time series (Fig. 3). Values of $l^*$ for both interictal and preictal segments are distributed symmetrically around the expected value for stationary systems, i.e., $l^* = 0.5$. With an increasing segment duration the distribution becomes more narrow, which is in accordance with the dependence of the expected frequency distribution of $l^*$. The relative number of segments $\rho_{stat}$ that meet the null hypothesis of the test for stationarity exceeds 80%, independent of the duration of the analyzed segments (cf. Fig. 4). It must be noted, though, that segments contributing to $\rho_{stat}$ values calculated for the different segment lengths do not necessarily contain identical subsegments, i.e., segments that appear.
stationary on shorter time scales may become nonstationary on longer ones, and vice versa.

Despite the relatively high number of stationary segments we cannot fully exclude false detections of nonlinearity so far because of the remaining nonstationary segments. For the next steps of analysis we therefore restrict ourselves to EEG segments for which $I^*$ indicates stationarity. Typical EEG time series from the interictal and the preictal state which our method classified as either linear and stationary or nonlinear and stationary are depicted in Fig. 5.

The upper plots in Fig. 6 show a subdivision of the relative numbers of stationary segments into linear and nonlinear segments. It is apparent that the number of stationary and linear segments $p_{\text{stat,lin}}$ decreases with an increasing segment length and that this decrease is accompanied by an increased number $p_{\text{stat,nonlin}}$ of stationary and nonlinear segments. Although this tendency is found for both the interictal and the preictal EEG segments during the latter we observe a slightly higher percentage of stationary and nonlinear segments particularly for those of longer duration.

In order to test whether this difference can be attributed to properties of the epileptogenic process, we repeated our analysis steps separately for focal and nonfocal recording channels (Fig. 6, lower plots). Note that the duration-dependent decrease of $p_{\text{stat,lin}}$ is still present for both focal and nonfocal recording sites. In contrast to the interictal state, in the preictal state there is a predominance of nonfocal channels contributing to $p_{\text{stat,lin}}$. Interestingly, the duration-dependent increase of $p_{\text{stat,nonlin}}$ appears to be mostly due to EEG segments from nonfocal sites. When comparing interictal and preictal EEG data we observe a higher percentage of stationary and nonlinear segments recorded preictally and within the focal area. This effect is most pronounced on short (23.6 s) and intermediate (47.2 s) time scales. Generally, we find that the difference between the percentages for focal and nonfocal channels is most distinct during the preictal phase, irrespective of linearity or nonlinearity.

IV. CONCLUSION

In this paper, we have investigated whether an improved characterization of nonlinear deterministic structure in EEG time series allows to distinguish the preseizure period from the seizure-free interval. In order to avoid spurious detections of nonlinearity due to nonstationarity, we identified EEG segments which our method for detecting nonstationarity classified as stationary. Of the 857 analyzed interictal and preictal EEG time series more than 80% fell into this category with a slight preponderance found in the preictal recordings. Restricting our analysis to stationary segments, we found a higher percentage of nonlinear segments in the preictal phase as compared with
the interictal phase. This increase could mainly be ascribed to segments recorded from the epileptic focus. The observed effects were most prominent for short (23.6 s) and intermediate (47.2 s) segments.

The advantage of our measure for nonstationarity is that it does not require a partitioning of the time series which is required for other tests of stationarity that are based, e.g., on the constancy of all conditional probabilities in time [36]. Using this novel method we were able to confine the null hypothesis test of the applied surrogate data to a test for nonlinear determinism. From the high percentage of stationary segments, we conclude that nonlinearity is indeed evident in the EEG and does not exclusively result from spurious detections due to the inherent nonstationary character of the epileptic brain.

The database analyzed in this study is yet too small to draw any definite conclusions concerning the distinction between the interictal and the preictal state. Nevertheless, our results provide some first indications that EEG segments with a duration of a few tens of seconds, recorded from within the epileptic focus and during the preictal period exhibit a higher degree of stationarity and nonlinearity than nonfocal or interictal EEG recordings.

Since nonlinearity and nonstationarity have been shown to be independent properties of the EEG and since a combined characterization of these properties appears to be sensitive to the spatiotemporal dynamics of the epileptic process, we regard further evaluation of this concept as a promising venture.

REFERENCES


Ralph G. Andrejajak was born in Düsseldorf, Germany, in 1970. He studied physics at the University of Bonn and received the physics diploma degree in 1997. He performed the Ph.D. thesis at the Helmholtz-Institute for Radiations and Nuclear Physics, and received the Ph.D. degree in physics from the Fakultät für Physik und Mathematik, University of Bonn, Bonn, Germany. In 2001, he is a Postdoctoral Fellow with the John-von-Neumann Institute for Computing. His main research interests are synchronization of coupled chaotic systems and applications of time series analysis to neuronal dynamics.

Thomas Kreuz was born in Siegen, Germany, in 1973. He studied physics at the University of Bonn, Bonn, Germany, and the University of Edinburgh, Edinburgh, UK, and received the physics diploma degree in 1999. He is now with the Department of Epileptology, University of Bonn and with the John-von-Neumann Institute for Computing, Research Center Jülich, preparing the Ph.D. thesis in affiliation with the University of Wuppertal. His main research interests are quantification of synchronization phenomena and nonlinear time series analysis of the brain electrical activity of epilepsy patients.

Peter David, born in Brskau (Wrocław)/Śląskie in 1938. He studied physics at the University of Bonn, Bonn, Germany, and performed the Ph.D. thesis at the Max-Planck-Institute for Nuclear Physics at Heidelberg. He received the Ph.D. degree in physics from the University of Bonn in 1968. He performed research work in nuclear physics from 1969 to 1990 at Bonn (Institut für Strahlen- and Kernphysik (ISKPK)) and with scientific stays at Trieste (Abdus-Salam-ICTP), Hamburg (DESY), Rochester, NY (NSL) and Brookhaven, NY (NL), Groningen (KVI), Saclay (CEN), and Villigen (Paul-Scherrer-Institute). Since 1991, his teaching and research fields are medical physics, including the physics of medical imaging, neurophysiology, and nonlinear dynamics. He is currently Professor of Physics at the Faculty of Mathematics and Natural Sciences of the University of Bonn, and working at the Helmholtz-Institute for Radiation and Nuclear Physics.

Christian E. Elger was born in Augsburg, Germany, in 1949. He studied biology and chemistry at the University of Tübingen, Tübingen, Germany, and medicine at the University of Münster, Münster, Germany, and graduated from medical school in 1976. In 1982, he received the Ph.D. degree in physiology from the University of Münster. He did his residency at the Department of Neurology and was a Research Fellow at the Institute of Physiology, University of Münster. Since 1990, he is Professor of Epileptology and Director of the Department of Epileptology, University of Bonn, Bonn, Germany, which hosts the only Chair of Epileptology in Germany. In 1997, he became a Fellow of the Royal College of Physicians (London, UK).

Klaus Lehnrz was born in 1960 in Düsseldorf, Germany. He studied physics at the University of Münster, Münster, Germany, and received the Ph.D. degree in physics in 1988 from the Faculty of Mathematics and Natural Sciences, University of Bonn, Bonn, Germany.

From 1986 to 1990, he was a Research Fellow with the Institute of Experimental Audiology, University of Münster and from 1990 to 1996, a Research Fellow with the Department of Epileptology, University of Bonn. He is currently Associate Professor of Physics with the Faculty of Mathematics and Natural Sciences, affiliated with the Helmholtz-Institute for Radiation and Nuclear Physics, University of Bonn and Head of the Neurophysics Laboratory, the Department of Epileptology. His main research interests include medical physics, neurophysiology, and nonlinear systems, nonlinear time series analysis, and their application to physiology and pathophysiology, cognitive neuroscience, and neuromagnetism.