



Evaluation of selected recurrence measures in discriminating pre-ictal and inter-ictal periods from epileptic EEG data



Eulalie Joelle Ngamga^a, Stephan Bialonski^b, Norbert Marwan^{a,*}, Jürgen Kurths^{a,c,d}, Christian Geier^{e,f}, Klaus Lehnertz^{e,f,g}

^a Potsdam Institute for Climate Impact Research, Telegraphenberg A 31, 14473 Potsdam, Germany

^b Max-Planck-Institute for the Physics of Complex Systems, Nöthnitzer Straße 38, 01187 Dresden, Germany

^c Department of Physics, Humboldt University Berlin, 12489 Berlin, Germany

^d Institute for Complex Systems and Mathematical Biology, University of Aberdeen, Aberdeen AB24 3UE, United Kingdom

^e Department of Epileptology, University of Bonn, Sigmund-Freud-Straße 25, 53105 Bonn, Germany

^f Helmholtz Institute for Radiation and Nuclear Physics, University of Bonn, Nussallee 14–16, 53115 Bonn, Germany

^g Interdisciplinary Center for Complex Systems, University of Bonn, Brühler Straße 7, 53175 Bonn, Germany

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ABSTRACT

We investigate the suitability of selected measures of complexity based on recurrence quantification analysis and recurrence networks for an identification of pre-seizure states in multi-day, multi-channel, invasive electroencephalographic recordings from five epilepsy patients. We employ several statistical techniques to avoid spurious findings due to various influencing factors and due to multiple comparisons and observe precursory structures in three patients. Our findings indicate a high congruence among measures in identifying seizure precursors and emphasize the current notion of seizure generation in large-scale epileptic networks. A final judgment of the suitability for field studies, however, requires evaluation on a larger database.

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1. Introduction

Recurrence plots (RPs) are graphical representations of times during which two states of a system are neighbors in phase space [1]. They have been widely used over the last 25 years as a tool to study changes and transitions in the dynamics of a system (even high-dimensional), or to detect synchronization and coupling [2–4]. This has been achieved by using the visual aspects of structures encountered in RPs as well as different statistical quantification approaches [2,3]. One important and widely used approach is *recurrence quantification analysis* (RQA), which is based on diagonally and vertically aligned recurrence points in the RP [5,6]. These lines characterize the temporal interdependences between individual observations or segments of the phase-space trajectory. Several substantial measures of complexity (MOC) have been defined on the base of these temporal structures of the RP and are related to predictability, stationarity, or intermittency. RQA has

demonstrated its potential through many successful applications in different fields [7]. Among others, they were applied to electroencephalographic (EEG) data from epilepsy patients as well as from epileptic rats. For example, Acharya and colleagues [8] have used RQA measures to classify EEG data from normal, during seizures (ictal), and between seizures states (inter-ictal). Further, RQA measures have been reported to exhibit sudden abrupt changes occurring up to some minutes before seizure onsets [9–12]. The latter findings can contribute to better understand this neurological disorder that affects about 65 million individuals worldwide [13] as well as to develop alternative therapies, e.g. based on the prediction of seizures [14–20], particularly for the 20–30% of patients that remain poorly treated or untreated [21]. It remains elusive, however, whether the described phenomena can be regarded as seizure precursors, since their statistical validity has not sufficiently or not at all been investigated, and since the analyzed EEG recordings were of rather short duration.

Recently, another quantification approach has been introduced that combines time series recurrence with complex networks [22–24]. Here, the recurrence matrix is considered as the adja-

* Corresponding author.

E-mail address: marwan@pik-potsdam.de (N. Marwan).

gency matrix of an undirected and unweighted complex network. The resulting *recurrence network* (RN) can be characterized with well-known network measures, i.e., further diagnostic tools become available for time series analysis [25,26]. In contrast to RQA, where the MOC characterizes the *dynamical properties* of the system, these network-based measures capture the *geometric properties* associated with a trajectory in phase space [24]. Such complementary information can be useful when studying regime changes [25], characterizing different dynamics [27,28], or even for the detection of coupling directions [29]. First applications in different scientific disciplines have demonstrated the usefulness of these additional characteristics. Very promising findings have been discussed, e.g., by Lang and colleagues [30] in a RN-analysis of synchronous EEG time series from normal subjects and from epilepsy patients. Among other findings, the authors observed that RNs of normal subjects exhibited a sparser connectivity and a smaller clustering coefficient compared to those of epilepsy patients (cf. [31]). These findings have been confirmed by another study, reporting an increasing degree of structural complexity in the EEG of normal subjects compared to the EEG from epilepsy patients [32].

It has been suggested that the conceptual difference between RQA and RN measures may allow to capture complementary aspects of the underlying dynamics under investigation, and that the combined use of both quantification approaches may improve the detection of dynamical changes [24]. In certain applications, however, a higher performance of RN measures in comparison to that of RQA measures has been observed. For example, this has been reported in Ref. [33] where a classification of healthy women and preeclamptic patients based on cardiovascular time series has been performed with the aim of performing early prediction of preeclampsia. Another example is found in Ref. [27], where a classification of periodic and chaotic behavior is performed using short time series of observables from continuous-time dynamical systems.

We observed a lack of literature describing such a comparison of performance between RQA and RN measures when applied to time series from complex systems such as the brain, and in particular in the analysis of EEG data. In the present work, we compare selected RQA and RN measures for a specific problem of multivariate EEG data analysis. In particular, we investigate the suitability of these measures for an identification of pre-seizure states in multi-day, multi-channel, invasive EEG (iEEG) recordings.

2. Data and methods

2.1. Patient characteristics and data

We analyze iEEG recordings from five epilepsy patients (see Table 1 and Fig. 1) who underwent presurgical evaluation of drug-resistant epilepsy at the University of Bonn Epilepsy Program [34]. The patients signed informed consent that their clinical data might be used and published for research purposes. Further, the study protocol had received prior approval by the ethics committee of the University of Bonn.

The iEEG data was recorded from chronically implanted intrahippocampal depth and/or subdural grid and strip electrodes (on average of 54 contacts) with a total recording time of 929 h during which 32 seizures (five to seven seizures per patient) occurred. The data was band-pass-filtered between 0.1 and 70 Hz, sampled at 200 Hz using a 16 bit analog-to-digital converter, and referenced against the average of two recording contacts outside the focal region. Reference contacts were chosen individually for each patient. Some recording gaps have been encountered and they were mainly due to diagnostic procedures that required the patient to be temporarily disconnected from the recording system.

Table 1

Clinical data. ID: patient identification number; age (yrs.) and gender: female (f), male (m); D_{epi} : duration of epilepsy (yrs.); FH: focal hemisphere, left (L), right (R); FR: focal region, MT mesial aspects of temporal lobe, LT lateral aspects of temporal lobe; N_{rs} : number of recording sites; N_{sz} : number of seizures; D_{rec} : duration of iEEG recording (hrs).

ID	age/gender	D_{epi}	FH	FR	N_{rs}	N_{sz}	D_{rec}
1	37/f	5	R	MT	70	7	169
2	55/m	10	L	LT	20	6	232
3	44/f	44	L	LT	52	5	220
4	22/m	19	L	LT	62	7	167
5	35/f	6	R	LT	70	7	141

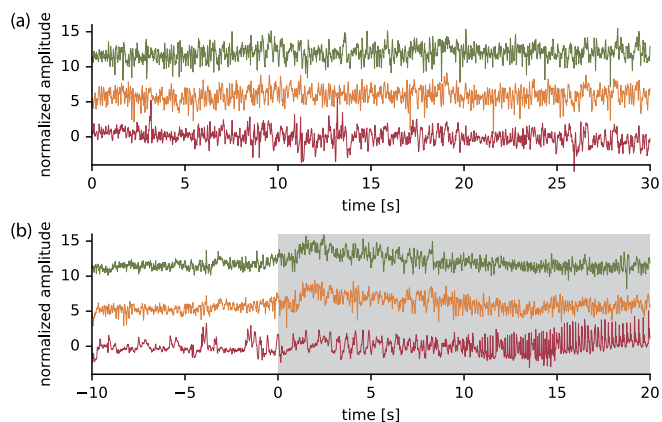


Fig. 1. Example of iEEG data from an inter-ictal (a) and a pre-ictal/ictal period (b) of patient 3 from recording sites within the epileptic focus (red), from its neighborhood (orange), and from a remote brain region (green). The latter two time series were shifted to enhance readability, and amplitude values were normalized to zero mean and unit variance. The gray-shaded area marks the initial phase of the seizure. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2.2. RQA- and RN-based measures of complexity

The basis of the MOC that we here used to characterize the iEEG is the recurrence plot (RP). It was introduced to visualize the time-dependent behavior of the dynamics of a system and particularly the recurrences of the phase-space trajectory to a certain state [1,2]. Let us consider x as an exemplary univariate time series with T sampling points and let x_i denote the value of x at discrete time i . In order to observe the recurrences of states from this time series, we compute the $T \times T$ matrix

$$\mathbf{R}_{i,j} = \Theta(\varepsilon - |x_i - x_j|), \quad i, j = 1, \dots, T \quad (1)$$

where $\Theta(\cdot)$ is the Heaviside function, ε is a predefined threshold, and $|\cdot|$ denotes absolute value. In general, Eq. (1) can be applied on phase-space trajectories in \mathbb{R}^m (where m is the dimensionality and the absolute value is replaced by a norm [2]), but here we apply it on time series directly (i.e., without embedding of time series in the phase space, similarly to Ref. [35]). This choice is motivated by the fact that several recurrence properties are invariant under embedding [36] and by the highly non-stationary character of brain dynamics [37–39], which complicates the choice of appropriate embedding parameters. Moreover, embedding can cause spurious correlations which affect mainly the recurrence analysis of stochastic signals [40].

An RP is a graphical representation of the above defined matrix \mathbf{R} . For the coordinate (i, j) of an RP we choose black color to plot a point if $\mathbf{R}_{i,j} = 1$, i.e., in the recurrent case, and white color otherwise. An example is shown in the left part of Fig. 2 for 10.24 s of an iEEG recording. The white and black points can form different lines and structures, which are related to the properties of the underlying dynamics.

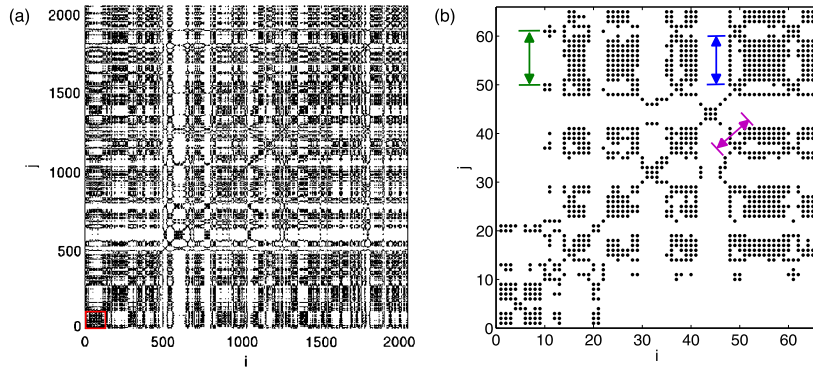


Fig. 2. (a) Exemplary recurrence plot of 10.24 s iEEG recording ($T = 2048$ data points). The corresponding recurrence matrix was calculated using the recurrence threshold $\varepsilon = 0.3$. (b) Enlargement of the area marked by the red rectangle (lower left corner). The green, blue and magenta double arrows exemplify a white vertical, black vertical, and black diagonal line, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Among these lines and structures encountered in an RP, we consider in our analysis the white vertical, black vertical, and black diagonal lines, respectively (see right part of Fig. 2). These lines are commonly used in RP-based analyses [2,5–7]. The lengths of white vertical lines are an estimator of the recurrence time [41, 42]. A black vertical line marks a time length in which a state does not change or changes very slowly, and is thus related to laminar states. A black diagonal line occurs when a segment of the trajectory runs parallel to another segment, and is thus related to the divergence of states [2]. By counting how many times a length of a line occurs in an RP, we evaluate the frequency distributions of the respective lengths of these three types of lines. From the frequency distributions, we compute the following MOC: *determinism* (DET), *laminarity* (LAM), and *mean recurrence time* (MRT) [2].

Furthermore, we use MOC that characterize complex networks, in particular the *average shortest path length* (APL) and *network transitivity* (CI). The analogy between the recurrence matrix and the adjacency matrix of an undirected and unweighted complex network [23,24] allows us to apply complex network measures on RPs in order to quantify the geometrical properties of the system's attractor encoded in the RP. For more details on this approach we refer to Refs. [23,24,43]. A brief description including the mathematical equations of the MOC considered in the present work is given in the appendix.

Using a sliding-window analysis, we calculated time profiles of the above mentioned MOC separately for each iEEG time series from each channel. Non-overlapping windows of 4096 data points, corresponding to a duration of 20.48 s, were used in accordance with previous studies [44,45]. This window length can be considered as a compromise between the required statistical accuracy for the calculation of a measure and the approximate stationarity within a window's length [46,47]. A fixed value of the threshold $\varepsilon = 0.3$, Eq. (1), was chosen following the discussion in Refs. [40, 48] and the data in each analysis window were normalized to zero mean and unit standard deviation.

2.3. Investigating the suitability of MOC for an identification of pre-seizure states

We tested whether time profiles of the MOC carry potential information about seizure precursors by estimating their classification performance in terms of their ability to distinguish between inter-ictal and pre-ictal (before a seizure) periods. Following Mormann and colleagues [44], we here assumed the existence of a pre-ictal period with a duration of 30 min [49,50]. In order to exclude effects from the post-ictal period (after a seizure), data recorded within 1 h after the electrical onset of a seizure was discarded from the analysis. Eventually, we defined inter-ictal periods to include all data except from the pre-ictal, ictal, and post-ictal

periods. In cases where the time interval between two successive seizures was less than the assumed pre-ictal duration plus one hour, the maximum amount of data available from the seizure onset back to the end of the post-ictal phase of the preceding seizure was used. Applying these selection criteria reduced the number of seizures accessible for our analysis to 26.

For each channel, we then investigated whether the MOC amplitude values allow us to distinguish between inter-ictal and pre-ictal periods. To do so, we tested the separability of the pre-ictal P_{pre} and inter-ictal P_{int} distributions of MOC amplitude values in terms of sensitivity and specificity using receiver operating characteristic (ROC) statistics. With this statistics, a threshold for amplitude values is continuously shifted across P_{pre} and P_{int} . The ROC curve is obtained by plotting sensitivity (ratio of true positives to total number of positives) against one minus specificity (ratio of true negatives to total number of negatives).¹ The capability of the considered MOC to distinguish between inter-ictal and pre-ictal periods was then quantified using the area under the ROC curve (AUC). For identical distributions P_{pre} and P_{int} (i.e., periods are indistinguishable) $AUC = 0.5$, while for distributions that are completely non-overlapping, values of 0 or 1 are attained, depending on the ROC hypothesis used for the definition of sensitivity and specificity (pre-ictal decrease: $AUC > 0.5$; pre-ictal increase: $AUC < 0.5$). We performed analyses for both ROC hypotheses and selected the larger one thus achieving an AUC value that is always ≥ 0.5 by construction.

Next, in order to test whether the predictive performance – as quantified by the largest AUC value – is better than random, we employed the concept of seizure time surrogates [51]. With this Monte-Carlo-based resampling technique, the original seizure times are replaced with times randomly chosen in the inter-ictal interval (seizure time surrogates) using the total number of original seizures and the distribution of inter-seizure intervals as constraints. In addition, seizure time surrogates were not allowed to coincide with original seizure onset times or to fall into a recording gap. For each patient and each channel, ROC analysis was repeated for 100 seizure time surrogates (the available data from patient 3 allowed to generate 20 seizure time surrogates only), and the significance of a given predictive performance was determined by calculating the fraction of AUC values obtained with seizure time

¹ The definitions of sensitivity and specificity are based either on the ROC hypothesis of a *pre-ictal decrease* (H^{\downarrow} ; MOC amplitude values from P_{pre} are lower than those of P_{int}) or on a *pre-ictal increase* (H^{\uparrow} ; vice versa). For H^{\downarrow} , the terms 'positive' and 'negative' correspond to whether an amplitude value is below, respectively above the threshold, while the terms 'true' and 'false' indicate whether values below the threshold belong to P_{pre} and values above the threshold belong to P_{int} or not. For H^{\uparrow} , these correspondences need to be adjusted accordingly.

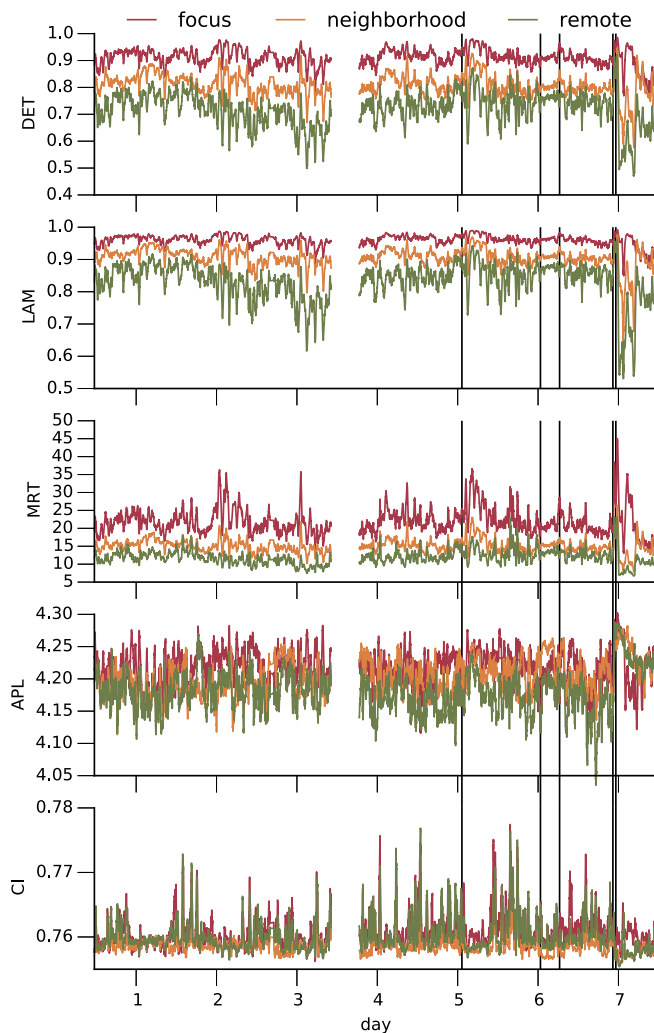


Fig. 3. Time profiles of the measures of complexity DET, LAM, MRT, APL, and CI (from top to bottom) estimated from iEEG data of patient 3. Data recorded from within the epileptic focus (red), from its neighborhood (orange), and from a remote recording site (green). Moving average over 60 windows corresponding to 20.48 min. There was a recording gap on day 3. Seizures are marked by black vertical lines, and ticks on x-axes denote midnight. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

surrogates, which exceeded AUC values obtained with the original seizure times.

Eventually, we controlled for falsely rejected null hypotheses due to multiple testings (1370 hypothesis tests for five MOC and for a total of 274 channels) by applying the Benjamini–Hochberg procedure [52] with a false discovery rate of 0.1.

3. Results and discussion

In Fig. 3 we show, as an example, time profiles of the MOC calculated from iEEG data of patient 3, which were recorded from within the epileptic focus (as defined by the pre-surgical workup), from its neighborhood (not more than two electrode contacts apart), and from a remote recording site. The temporal variability of the RQA-based measures DET and LAM appears to increase with an increasing distance to the epileptic focus, while the reverse appears to hold for MRT. The temporal means of these MOC decrease with an increasing distance to the epileptic focus, and similar observations could be made for all other patients. This finding is in line with previous studies that employed other measures of complexity [53–62]. In contrast, no such clear dependence of the temporal mean could be observed for the RN-based measures APL and

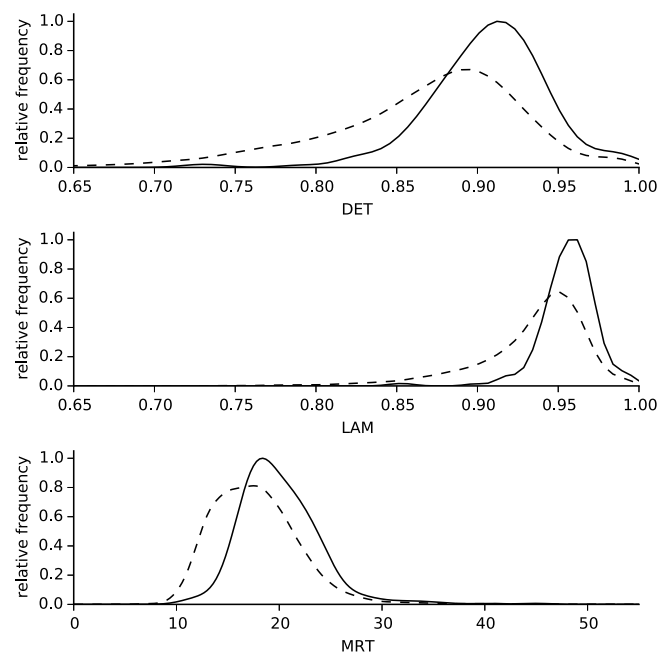


Fig. 4. Frequency distributions of the inter-ictal (dashed lines) and pre-ictal (solid lines) values of the measures of complexity DET, LAM, and MRT (from top to bottom) estimated from iEEG data of patient 3. Data from a recording site near the epileptic focus carrying predictive information.

CI, although their evolutions exhibit some periodic temporal structure that appears to be related to daily rhythms. Indeed, estimating their power spectral densities (Lomb–Scargle periodogram [63]) revealed a strong component at about 24 h (data not shown) particularly for recordings from remote sites and near the epileptic focus when using APL and for recordings from remote sites and from within the epileptic focus when using CI. Similar observations could be made for all other patients, and comparable dependences on daily rhythms had been reported for global and local statistical measures of functional epileptic brain networks [19,45,64].

With the methods described in Sec. 2.3, we observed statistically significant differences between MOC values from the pre-ictal and inter-ictal periods in three out of five patients. In patient 1, both LAM and MRT indexed the dynamics of the same remote brain site (one recording site) to carry information predictive of impending seizures. Both MOC attained lower values during the 30 min pre-ictal periods than during inter-ictal periods. In patient 3, all RQA-based MOC provided predictive information (pre-ictally increased values, see Fig. 4) from the dynamics near the epileptic focus (two recording sites). In addition, APL identified other nearby brain sites (two recording sites) to carry potential seizure precursor dynamics (pre-ictally decreased values). With both APL and CI remote but adjacent brain regions (one recording site each) could be identified, however, either through pre-ictally increased (APL) or decreased values (CI). In patient 4, all RQA-based MOC provided predictive information (pre-ictally decreased values) from the dynamics of the epileptic focus (one recording site), of nearby (one site) and of remote brain regions (five sites). In addition, similar information could be achieved with CI from the dynamics of remote brain regions (three sites).

When judging the predictive performance of RQA- and RN-based measures, we note first that the RQA-based measures DET, LAM, and MRT pinpointed the same brain region to carry predictive information in all patients. Although these MOC assess different characteristics of an RP, they here provided redundant spatial information. Nevertheless, seizure precursors were mostly found in brain regions off the epileptic focus, which would favor the recent concept of seizure generation in an *epileptic network* rather than

from a circumscribed area of the brain (epileptic focus) [19]. Pre-ictal alterations of these MOC (increase vs. decrease) exhibited a high interindividual variability, rendering an interpretation of the pre-seizure brain dynamics difficult.

Second, RN-based measures APL and CI identified precursory structures in two patients only, and particularly CI clearly decreased during the 30 min pre-ictal periods. If CI is interpreted as a global measure of the effective dimensionality of the underlying attractive set [65], its pre-ictal decline is in line with previous observations using other dimensionality estimates [66]. As with the RQA-based measures, APL and CI also identified seizure precursors in brain regions off the epileptic focus.

Third, taking into account the redundancies provided by RQA-based MOC, both RQA- and RN-based measures had a comparable predictive performance, which compares to the one seen previously for other linear and nonlinear univariate measures [44].

4. Conclusion

We investigated the suitability of selected measures of complexity based on recurrence quantification analysis (RQA) and recurrence networks (RN) – characterizing dynamical and geometrical properties of a system – for an identification of pre-seizure states in multi-day, multi-channel, invasive EEG recordings from five epilepsy patients. We employed a number of downstream statistical techniques to avoid spurious findings due to various influencing factors and due to multiple comparisons. With these approaches, statistically significant precursory structures could be identified in three patients. Findings indicate a high redundancy in predictive information that can be achieved with RQA-based measures. In the two patients for which RN-based measures identified precursory structures, these measures did not provide additional information about brain regions from which possible precursors emerge. We thus conclude that the combined use of both quantification approaches does not appear to improve the detection of dynamical changes preceding seizures in the human epileptic brain. Clearly, a final judgment of the suitability of these recurrence-based time series analysis approaches for seizure prediction studies needs to be evaluated on a larger data base.

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Appendix A. Measures of complexity

The following measures of complexity have been used and their description is detailed in Refs. [2,23,24,41,42]:

1. *Determinism* (DET) is the percentage of recurrence points which form a diagonal line of minimal length l_{\min} . It quantifies the predictability of the system. Processes with stochastic behavior will render a DET value which tends to 0, while it will be equal to 1 for purely periodic processes.

$$\text{DET} = \frac{\sum_{l=l_{\min}}^T lP(l)}{\sum_{i,j=1}^T R_{i,j}}, \quad (\text{A.1})$$

where $P(l)$ denotes the frequency distribution of the lengths l of the diagonal lines in the RP.

2. *Laminarity* (LAM) is the percentage of recurrence points which form a black vertical line of minimal length v_{\min} . It represents slowly changing states and, thus, the occurrence of laminar

states in the system. High values of LAM are an indication of dynamics that is trapped more often to certain states.

$$\text{LAM} = \frac{\sum_{v=v_{\min}}^T vP(v)}{\sum_{v=1}^T vP(v)}, \quad (\text{A.2})$$

where $P(v)$ denotes the frequency distributions of the lengths v of black vertical lines.

3. *Mean recurrence time* (MRT) is the average length of white vertical lines in the RP.

$$\text{MRT} = \frac{\sum_{w=1}^T wP(w)}{\sum_{w=1}^T P(w)}, \quad (\text{A.3})$$

where $P(w)$ denotes the frequency distribution of the lengths w of white vertical lines. MRT estimates the main time-scale of variations (e.g., for an harmonic oscillation it corresponds to the period length) [67].

In accordance with previous works [2], the minimal lengths were chosen as $l_{\min} = 2$ and $v_{\min} = 2$.

As mentioned in section 2, by considering the phase space vectors as nodes of a network and their recurrences in the phase space as links, an analogy between the recurrence matrix and the adjacency matrix of an undirected and unweighted network can be built. The network is represented by an adjacency matrix \mathbf{A} , which is the recurrence matrix from which the identity matrix is subtracted ($A_{ij} = R_{ij} - \delta_{ij}$; where δ_{ij} is the Kronecker delta used to avoid self-loops in the network).

4. *Average shortest path length* (APL) is the average length of shortest paths between all pairs of nodes in the network and is given by:

$$\text{APL} = \frac{1}{T(T-1)} \sum_{i,j=1}^T d_{ij}, \quad (\text{A.4})$$

with the minimum number of links d_{ij} that have to be crossed to move from node i to node j . Disconnected pairs of nodes are not included in the average. In recurrence networks, APL characterizes the average phase space separation of states [24].

5. *Network transitivity* (CI) considers the average probability that two neighbors of any state are also neighbors and is given by:

$$\text{CI} = \frac{\sum_{i,j,k=1}^T A_{jk}A_{ij}A_{ik}}{\sum_{i,j,k=1}^T A_{ij}A_{ik}}. \quad (\text{A.5})$$

CI can be interpreted as a global measure of the underlying attractive set's effective dimensionality [65].

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