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Anticipating epileptic seizures in real time by a non-linear analysis of similarity between EEG recordings

M. Le Van Quyen,[CA] J. Martinerie, M. Baulac and F. Varela

Laboratoire de Neurosciences Cognitives et Imagerie Cérébrale (CNRS UPR 640) and Unité D'epileptologie, Hôpital de la Salpêtrière, 47 Blvd. De L'hôpital, 75651 Paris Cedex 13, France

[CA]Corresponding Author

IN a previous publication we showed that non-linear analysis can extract spatio-temporal changes of brain electrical activity prior to epileptic seizures. Here we describe a new method to analyze this long-term non-stationarity in the EEG by a measure of dynamical similarity between different parts of the time series. We apply this method to the study of a group of patients with temporal lobe epilepsy recorded intracranially during transitions to seizure. We show that the method, which can be implemented on a personal computer, can track in real time spatio-temporal changes in brain dynamics several minutes prior to seizure. *NeuroReport* **10:2149–2155 © 1999 Lippincott Williams & Wilkins.**

Key words: Epilepsy; Non-linear analysis; Non-stationarity; Prediction; Real time

Introduction

A characteristic feature of epilepsy is the spontaneous occurrence of seizures, most often without warning and for no apparent reason. The unpredictability of seizure onset is the most important cause of morbidity for persons with epilepsy [1]. A reliable anticipation of a seizure several minutes ahead would provide a window of time during which automated warning or a therapeutic intervention could be undertaken to minimize risk of injury and perhaps abort the seizure. It is, however, notoriously difficult to predict seizure onset more than a few seconds in advance from a visual inspection or a traditional signal analysis of the EEG [2,3]. In particular, the quantification of the spike rate occurring prior to seizure onset has given mixed or negative results [4,5]. A deeper characterization of the underlying neuronal dynamics would be relevant to gain new insights in the mechanisms of seizure generation on a longer time scale.

The non-linear time series analysis of EEG data has been shown to provide additional information about the dynamics of epileptogenic networks [6–8]. Applied to the analysis of seizure generation, our group recently provided evidence that non-linear time series analysis is capable to recognize dynamical changes of brain electrical activities several minutes prior to seizure [9]. Other studies have confirmed the usefulness of non-linear measures for the detection of pre-ictal changes [10,11]. Although these results are very promising, further studies are necessary to allow an early and accurate anticipation of seizure. In particular, most of the studies have been conceived from the perspective of a decrease in complexity in the pre-seizure brain activity. According to this hypothesis, estimations of non-linear invariants, such as the correlation dimension [10] or the largest Lyapunov exponent [11], are specifically used to characterize transitions from a high- to low-dimensional dynamics. However, these applications to EEG recordings meet some difficulties. First, the link between the changing profile of the EEG and the dimension of an underlying attractor remains problematic [12]. Second, EEG recordings are not stationary over periods of sufficient length to permit a reliable estimation of these non-linear quantities. Third, the computational effort for the estimation of these parameters restricts the ability to develop a rapid analysis over a long time scale.

In order to overcome some of these limitations, we propose here a new non-linear strategy adapted to the detection of gradual non-stationarities prior to seizure. Results of our previous study [9] support the view that pre-ictal changes can be interpreted in terms of a gradual increasing neuronal recruitment which does not vary significantly over a shorter time scales of a few seconds, but exhibits variations over

a larger time scale. In the present paper we show that these pre-ictal changes can directly be estimated by the dynamical closeness between pairs of windows using a similarity measure. The comparison of distant windows from the viewpoint of their dynamical properties offers a greater sensibility to changes than a moving-window paradigm and a reduced computational effort. The computational speed of the algorithm represents a important step toward a real time strategy for seizure prediction and clinical applicability of our strategy.

Materials and Methods

Our study is based on a homogeneous group of 13 patients (including the 11 patients of our previous study [9]) presenting with medial temporal lobe epilepsy associated with hippocampal sclerosis (see [13] for a detailed presentation of the patients). They required intracranial recordings and video monitoring to confirm the exact site of the structures generating seizure onsets. The EEG-video recordings were performed on a 32 channel BMSI system (Nicolet-BMSI, Madison, Wisconsin, USA). The raw data were digitized at 200 Hz, with 12 bit resolution, and were passed to a 32 channel amplifier system with band-pass filter settings of 0.5–99 Hz using an external reference over linked ears. Our study is based on 23 long-term recordings of 40 min duration including 20 min prior to seizure.

We introduce a new non-linear technique inspired by the approach of Manuca and Savit [14] to track long-term non-stationarity in time series. The proposed method consists of dividing the recording into small segments and quantifying the extent to which the underlying dynamics differs between pairs of distant segments. More precisely, our algorithm can be divided in two main steps. The first step is to construct a reference dynamics of the non-seizure state. We choose for this purpose a long EEG segment S_{ref} (typically of a few minutes) recorded during an interval quite distant in time from any seizure. The standard way of reconstructing the underlying dynamics is given by a time-delay embedding of the amplitudes [15]. Unfortunately, this reconstruction is computationally cumbersome for practical applications and requires a large data set. Another way to reconstruct qualitatively the dynamics has been recently introduced [16] and derived from the sequences of time intervals between positive-going crossings of a fixed threshold [17]. From a theoretical standpoint, the reason for this is that time crossings can be interpreted as the phases of the system's flow in a Poincaré section [18]. An important advantage of this approach is that these timings are not affected by the fluctuations of the signal amplitude (like spiking activity) and the noise components are to some extent filtered out, leaving a relatively pure dynamical component. Above all, the method achieves a significant reduction (by ten orders of magnitude) in the volume of data without loss of potentially valuable dynamical information.

Let the times of threshold crossing (set here to the zero of the signal) be denoted by T_n, and let $I_n = T_{n+1} - T_n$ be the time intervals between two successive crossings. From this sequence of intervals, delay vectors are formed $A_n = (I_n, I_{n-1}, ..., I_{n-m+1})$ defining an m-dimensional embedding of the dynamics. We used $m = 16$. In order to further improve this dynamical reconstruction for shorter time series and reduce the noise level, we applied a single value decomposition (SVD) of this m-dimensional embedding space, identifying the optimal space that contains the trajectory. Let $\underline{\underline{\mathbf{A}}}(S_{\mathrm{ref}})$ be the trajectory matrix of the reference segment S_{ref} (i.e. the matrix whose rows are the embedding vectors A_n), then a SVD can be computed with conventional algorithms by the transformation $\underline{\underline{\mathbf{A}}}(S_{\mathrm{ref}}) \rightarrow \underline{\underline{\mathbf{X}}}(S_{\mathrm{ref}}) = \underline{\underline{\mathbf{A}}}(S_{\mathrm{ref}}).\underline{\mathbf{V}}$ where $\underline{\underline{\mathbf{X}}}(S_{\mathrm{ref}})$ is the trajectory matrix projected onto the basis $\underline{\mathbf{V}}$ defined by the eigenvectors of the covariance matrix $\underline{\underline{\mathbf{A}}}(S_{\mathrm{ref}})^T.\underline{\underline{\mathbf{A}}}(S_{\mathrm{ref}})$. The dynamics in the space defined by the largest singular values is identical to the original embedding space [19].

The second step is to compare this reference dynamics with the dynamics of distant test segments S_t. In the present study, we split the recording into non-overlapping consecutive test segments of 25 s each. In order to allow comparisons between these smaller test windows consisting of a few hundred points and the reference window, we only consider a basic skeleton of reference dynamics built by a random selection of a sub-set of points. This provides an adapted picture $\underline{\underline{\mathbf{Y}}}(S_{\mathrm{ref}})$ of the reconstruction, extracting the most frequent occupations of the phase space flow. The dynamic similarities are then estimated between the reference dynamics $\underline{\underline{\mathbf{Y}}}(S_{\mathrm{ref}})$ and the projection $\underline{\underline{\mathbf{X}}}(S_t)$ of a 16-dimensional reconstruction of S_t on the principal axes of the reference dynamics (i.e. $\underline{\underline{\mathbf{X}}}(S_t) = \underline{\underline{\mathbf{A}}}(S_t).\underline{\mathbf{V}}$, where $\underline{\mathbf{V}}$ is the eigenvector matrix of the reference window). For this, we used statistical measure of similarity based on the cross-correlation integral [20]:

$$C(S_{\mathrm{ref}}, S_{\mathrm{t}}) = \frac{1}{N_{\mathrm{ref}} N_{\mathrm{t}}} \sum_{i=1,N_{\mathrm{ref}}} \sum_{j-1,N_{\mathrm{t}}} \Theta(|| Y_{\mathrm{i}}(S_{\mathrm{ref}}) - X_{\mathrm{j}}(S_{\mathrm{t}})|| - r)$$

where Θ is the Heaviside step function, $\| \ \|$ the euclidian norm and N_{ref} (resp. N_{f}) denotes the number of elements in each set.

This measure gives the probability of finding points within a neighborhood r in the reconstruc-

tion of S_{ref} close to points in the reconstruction of S_t. In the present application, we define a distance r typically at 30% of the cumulative neighborhood distribution of the reference set. This gives stable results with EEG segments of several seconds duration, and guarantees a robust measure of similarity between two segments. In order to further improve the discriminatory power between two dynamics, we used a modified variant of this measure given by cross-correlation ratio:

$$\gamma(S_{ref}, S_t) = C(S_{ref}, S_t)/\sqrt{C(S_{ref}, S_{ref})C(S_t, S_t)}$$

γ ranges from 0 to 1 and provides a sensitive measure of closeness between two dynamics. If the reference S_{ref} and test S_t segments share the same underlying dynamics, the value of γ is around 1. On contrary, if changes in the dynamical state occur, the similarity γ goes down to below 1.

Using this measure, we computed the similarities over the entire EEG recordings by sliding the test window S_t every 25 s. The corresponding time course provides information about long-term changes before seizure onset. In order to give a statistical significance to these changes, we have to quantify the deviation from the interictal period, taken at the initial part of the recording period. We take here as baseline activity the first 250 s of the recording. Let μ and σ be the mean and s.d. of similarity variations during this baseline. We define here the significance Σ of the deviation by the ratio $\Sigma = (\gamma - \mu)/\sigma$, whose p-value is given by the Chebyshev's inequality (for any statistical distribution of γ): $P(|\Sigma| \geq k) \leq 1/k^2$, where k is the chosen statistical threshold.

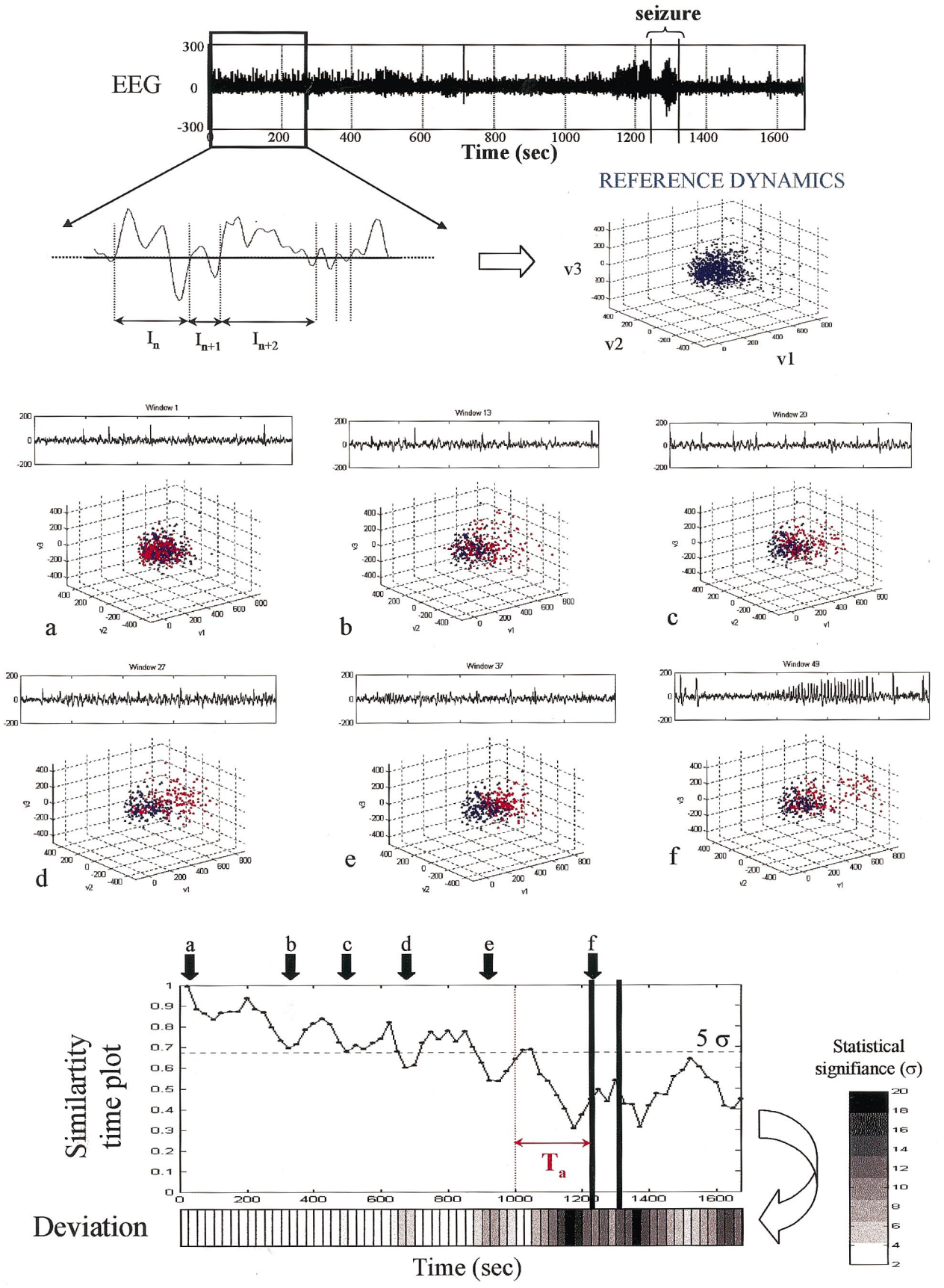
Results

Figure 1 illustrates the application of the proposed method to a long recording covering 20 minutes before a spontaneous seizure. The recording site we used in this example is localized in the epileptogenic zone and the earliest signs of seizure activity are identified by expert visual inspection of the EEG. Following the first step of the similarity method, we begin by constructing a reference dynamics of the non-seizure state (Fig. 1, top). This dynamics has to take into account the most salient features of the interictal EEG. To accurately distinguish changes that are specifically caused by seizure emergence, we incorporate in the reference window various interictal patterns, including epileptiform discharges (spikes) and activity of extracerebral origin (artifacts). On this basis, we capture the underlying dynamics from the sequences of time intervals between positive-going crossings of a threshold and after noise reduction by SVD.

The second step is to compare this reference dynamics with the dynamics of moving test windows (Fig. 1, middle). Here we use the SVD of the non-seizure reference signals, and apply its corresponding eigenvector matrix for all later data segments. Visually, dynamics of a test window can be represented by a cloud of points distributed in a 3D space defined by the three largest principal axes of the reference dynamics. The similarity can then be viewed as the average number of common points between these reference and test clouds. If the EEG is stationary, there will be no difference in the statistical properties of these clouds and the similarity index yield a value close to 1. On contrary, if changes in the dynamical state occur (i.e. modifications of quantities like the mean, the variance, or more hidden kinds of non-stationarity like local modifications of the phase space), the similarity index between the two clouds decreases to below 1. This comparison offers a great sensibility in the detection of changes with a minimum of computational cost. In fact, the quantification of 25 s single-channel recording can be performed in ~2 s using MATLAB (Math Works Inc.) on a 233 MHz personal computer. A further substantial improvement can be obtained by compiling the MATLAB program in C/C++ code file.

In order to facilitate inspection over longer time scales, the similarity profile can be plotted over the entire data set (Fig. 1, bottom). This plot reveals that the similarity gradually decreases during the preseizure period. When approaching the seizure this effects become more and more pronounced, over several orders of magnitude before the clinical seizure onset. The seizure corresponds to the lowest value, while post-ictally the similarity increases again, and tends to reach the initial level. Figure 1 (bottom) depicts the statistical significance of the deviation from the reference dynamics in multiples of standard deviation, used here to establish a criterion to determine the distinctness between normal and pathological states, and thus be able to quantify the anticipation of the seizure. Specifically,

FIG. 1. Top: Construction of a reference dynamics of the non-seizure state from a long EEG segment (here of 250 s) recorded during an interval temporally far away from the seizure. This reference dynamics is represented by a cloud of particles distributed in a space defined by the three largest singular values (v1, v2, v3). Middle: Characterization of the similarity between the reference dynamics (blue) and the dynamics of moving test windows (red) of 25 s length. The similarity estimates the average number of common points between the reference and test clouds. Bottom: Similarity as function of time over the entire data set. It can be observed that the profile gradually decreases during the preseizure period over several order of magnitude before the seizure onset. The deviations from the initial part of the recording period are depicted in standard deviations using a gray scale plot. From this deviation, we estimate an anticipation time of $T_a = 250$ s indicated by a red arrow in the figure.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we characterized an anticipation time T_a when the similarity reaches a critical level, and remains at or above this fixed deviation threshold k during a length of time D before the decrease is classified as a seizure precursor. In this study a positive detection is defined by a sustained deviation of the similarity above a threshold of $k = 5$ ($p = 0.04$) during $D = 150$ s. With this setting, we estimated in our example an anticipation time of $T_a = 250$ s (see arrow in Fig. 1). The analysis of the inter-relationship between the threshold k and duration D constraints, and their effects on sensitivity, provided a mean for individual or group optimization of the algorithm.

The localization of the site or sites presenting the earliest deviation can also be used to optimize the algorithm. In this respect, Fig. 2 shows the application of the proposed method to all recording contacts of two typical patients. The deviations from the baseline of each contact are depicted as a function of time in s.d. and give then a spatio-temporal plot of pre-seizure changes. The anticipation times of each contact are indicated in the right side of each plot. We can observe in the two cases that long-lasting decreases in similarity prior to the seizure were found at many recording sites. The spatial distribution of the deviations presents an extended topography which is not only confined to the region of the ictal onset zone. Nevertheless, some individual contacts (at the frontal cortex for patient 1/1, at the occipo-temporal junction and temporal cortex for patient 2/2) allow the earliest seizure anticipation.

Figure 3 summarizes the global results of seizure anticipation obtained from our group of 13 patients. The results confirm our previous finding that the extraction of dynamical properties allows in most of the cases (19/23) the seizure anticipation several minutes in advance (mean −345 s). Moreover, the proposed method provides a substantial improvement of our previous anticipations (where 17/19 seizures were anticipated with a mean of −158 s see [9] for details). Although the small number of patients with multiple seizures precludes formal statistical analysis, it can be observed that the various anticipation times for one patient are highly variable in duration. This intriguing observation, in line with our previous results [9], suggests that seizure emergence is a complex, non-repetitive process even for an individual patient.

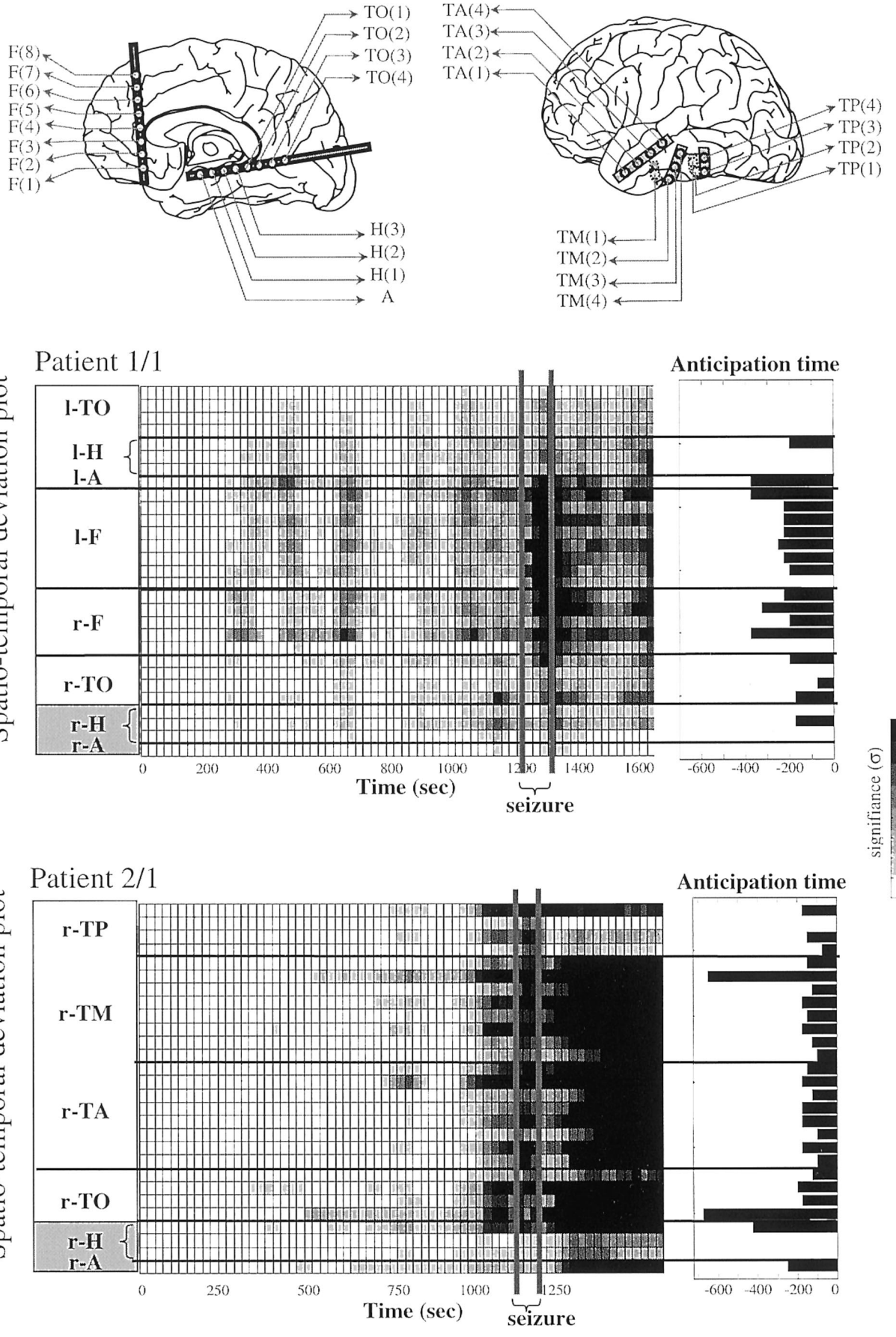
Discussion

Based on our first observations that the epileptic processes are governed by long-term recurrent trends in the spatio-temporal dynamics [9], we propose here a method to rapidly provide detailed information about gradual pre-ictal changes in the EEG dynamics. In the field of non-stationarity characterization, a number of statistical tests have been proposed in the literature. However, many of these tests are applications of linear (frequency-based) time series analysis, implying that the stationarity is usually defined on the basis of the second moments like the mean, the variance or the power spectrum. Thus, descriptions of the non-stationarity from the viewpoint of non-linear dynamic system are attractive because they test more hidden changes [21]. This is the rationale behind our non-linear technique which is based on a statistic testing the dynamic similarity between segments of the time series [13,21]. A similar approach led to promising results in the special context of the classification of the morphology of EEG recordings [22].

The proposed method has a number of practical advantages over previous studies [7,9,10,23]. First, the dynamic similarities provide insights into non-trivial changes in phase space before seizure onset. This is compatible with the viewpoint of a decrease of complexity, but does not presuppose it. Second, a significant advantage is the ability to check directly the dynamic similarity between two windows, rather than differences between quantities evaluated separately on each one. Third, the method is robust against changes in embedding dimension and window length. High sensitivity is obtained with low dimensions and for relatively short time series. In addition, the dynamic reconstruction based on threshold crossings affords a substantial reduction in the volume of the investigated data without undue loss of dynamically important information in the primary signal. Fourth, the computational cost is relatively small and can be implemented with a personal computer, facilitating the possibility of clinical application. Fifth, the method is virtually unaffected by noise by the use of threshold crossings and SVD reduction. Finally, the method does not require specific a priori knowledge or a template, as is the case for other detection algorithms [24].

To conclude, we wish to point to some unresolved

FIG. 2. Top: Schematic location of the multicontact intracranial electrodes including (left) intrahippocampal and fronto-orbital intracerebral electrodes (eight contacts) and (right) subdural strips. The exact location of the electrode was dependent on the clinical situation. r- or l- A: right or left amygdala, H: hippocampus, TO: lateral temporo-occipital junction, F: frontal cortex. Bottom: Spatio-temporal plots of pre-seizure changes for two typical patients. Their epileptogenic regions are in both cases in the right amygdalo-hippocampal structures. The deviations from the baseline of each contact are depicted as a function of time in gray scale. The corresponding anticipation times are indicated in the right side of each plot. In the two plots, we can observe that long lasting decrease prior the seizure was found at a large number of the recording sites.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TM(4)
Patient 1/1
Anticipation time
Spatio-temporal deviation plot
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l-H
l-A
l-F
r-F
r-TO
r-H
r-A
0 200 400 600 800 1000 1200 1400 1600
Time (sec)
seizure
-600 -400 -200 0
significance (σ)
Patient 2/1
Anticipation time
Spatio-temporal deviation plot
r-TP
r-TM
r-TA
r-TO
r-H
r-A
0 250 500 750 1000 1250
Time (sec)
seizure
-600 -400 -200 0

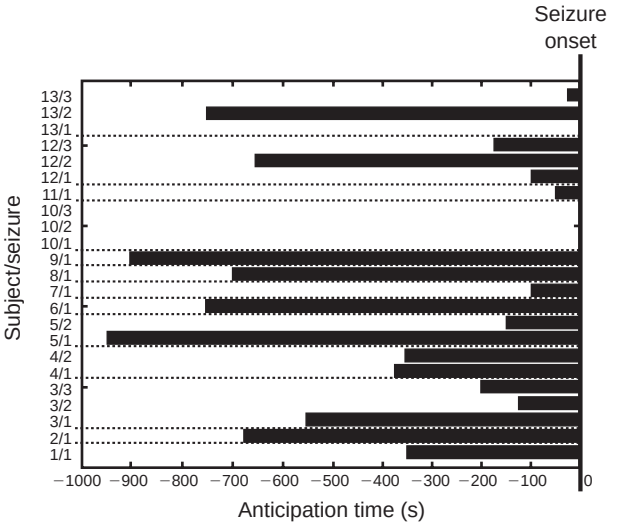

FIG. 3. Anticipation times (defined as the earliest anticipation found across all the channels) for all the patients and seizures under investigation.

questions raised by the method introduced here, and which only further studies based on a larger patient group and EEG recordings of long duration will answer. The performance of the analysis should be refined in terms of its selectivity, i.e. it should be determined whether the changes observed in pre-ictal activity are unique to this period, or whether they are cyclic in nature and can occur at periods remote from ictal events. The rate of false detections indicates the sensitivity of the method. In this study, the threshold values (k,D) were determined empirically for our data set of seizure/subjects so as to avoid any false positives and still anticipate the actual crisis. For a larger, more varied data set it remains to be seen if a (k,D) combination is also possible, that is, if the parameter space is sufficiently adequate. Our results militate in favor of a view of epilepsy in terms of epileptogenic networks, rather than local focal changes. Thus, it will be of interest to explore if one could not combine indicators over multiple recording sites in order to obtain a better discrimination. Despite these unresolved questions, our method using non-linear analysis of similarity opens a computationally effective door towards the development of automated seizure warning.

Conclusion

We report here a new method for the detection of changes in dynamic properties of electrical brain activity that anticipate epileptic seizures. The algorithm, which can be implemented on a personal computer, substantially improves the speed and accuracy of our previous method for seizure anticipation, and provides a real time solution to the problem of seizure prediction. This study of spatio-temporal anticipation window of time of the pre-seizure period having a sufficient length opens new possibilities for automatic warning and therapeutic interventions.

References

1. Murray J. *Seizure* **2**, 167–178 (1993).
2. Rogowski Z, Gath I and Bental E. *Biol Cybern* **42**, 9–15 (1981).
3. Osorio I, Frei M-G and Wilkinson SB. *Epilepsia* **39**, 615–127 (1998).
4. Lange HH, Lieb JP, Engel J and Crandall PH. *Electroencephalogr Clin Neurophysiol* **56**, 543–555 (1983).
5. Katz A, Marks DA, McCarthy G and Spencer SS. *Electroencephalogr Clin Neurophysiol* **79**, 153–156 (1991).
6. Pijn JP, Van Neerven J, Noest A and Lopes da Silva F. *Electroencephalogr Clin Neurophysiol* **79**, 371–381 (1991).
7. Casdagli M, Iasemidis L, Savit R *et al. Electroencephalogr Clin Neurophysiol* **102**, 98–105 (1997).
8. Le Van Quyen M, Adam C, Baulac M *et al. Brain Res* **792**, 24–40 (1998).
9. Martinerie J, Adam C, Le Van Quyen M *et al. Nature Med* **4**, 1173–1176 (1998).
10. Lehnertz K and Elger CE. *Phys Rev Lett* **80**, 5019–5022 (1998).
11. Iasemidis LD and Sackellares JC, Measuring Chaos in the Brain. In: Duke DK and Pritchard WS, eds. *Measuring Chaos in the Brain*, Singapore: Word Scientific, 1991: 49–82.
12. Theiler J and Rapp PE. *Electroencephalogr Clin Neurophysiol* **98**, 213–223 (1996).
13. Adam C, Clemenceau S, Semah F *et al. Acta Neurol Scand* **94**, 1–11 (1996).
14. Manuca R and Savit R. *Physica D* **99**, 134–161 (1996).
15. Takens F. Detecting strange attractors in turbulence. In: Rand DA and Young LS, eds. *Lecture Notes in Mathematics 898*. Berlin: Springer Verlag, 1981: 366–381.
16. Sauer T. *Phys Rev Lett* **72**, 3811–3814 (1994).
17. Janson NB, Pavlov AN, Neiman AB and Anishchenko VS. *Phys Rev E* **58**, R4–7 (1998).
18. Pikovski AS, Rosemblum MG, Osipov GV and Kurths J. *Physica D* **104**, 219–238 (1997).
19. Albano AM, Muench J, Schwartz C *et al. Phys Rev A* **38**, 3017–3027 (1988).
20. Kantz H. *Phys Rev E* **49**, 5091–5097 (1994).
21. Schreiber T. *Phys Rev Lett* **78**, 843–846 (1997).
22. Hernandez JL, Biscay R, Jimenez JC *et al. Int J Bio-Med Comput* **38**, 121–129 (1995).
23. Widman G, Lehnertz K, Jansen P *et al. Physica D* **121**, 65–74 (1998).
24. Gabor AJ, Leach RR and Dowla FU. *Electroencephalogr Clin Neurophysiol* **99**, 257–266. (1996)

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