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REVIEW

Epilepsy and Nonlinear Dynamics

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Abstract This overview summarizes findings obtained from analyzing electroencephalographic (EEG) recordings from epilepsy patients with methods from the theory of nonlinear dynamical systems. The last two decades have shown that nonlinear time series analysis techniques allow an improved characterization of epileptic brain states and help to gain deeper insights into the spatial and temporal dynamics of the epileptic process. Nonlinear EEG analyses can help to improve the evaluation of patients prior to neurosurgery, and with an unequivocal identification of precursors of seizures, they can be of great value in the development of seizure warning and prevention techniques.

Keywords Nonlinear EEG analysis · Epilepsy · Seizure prediction · Presurgical evaluation

1 Introduction

The human brain is probably one of the most complex systems in nature. The neocortex of a human is a thin, extended, convoluted sheet of tissue with a surface area of $\sim 2{,}600\ \mathrm{cm}^2$, and a thickness of 3–4 mm. It contains up to 28×10^9 neurons and approximately the same number of glial cells. Cortical neurons are connected with each other and with cells in other parts of the brain by a vast number of synapses, of the order of 10^{12} [1]. The highly interconnected neuronal networks can generate a wide variety of synchronized activities, including those underlying epileptic seizures, which often appear as a transformation of otherwise normal brain rhythms.

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Following [2], epilepsy is defined "as a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition." This definition requires the occurrence of at least one epileptic seizure. With a prevalence of approximately 1% of the world's population [3, 4], epilepsy represents one of the most common neurological disorders, second only to stroke. Worldwide, 50 million individuals are affected. An epileptic seizure is defined as "a transient occurrence of signs and/or symptoms due to abnormal, excessive or synchronous neuronal activity in the brain" [2, 5]. Generalized onset seizures involve almost the entire brain, while focal onset (or partial) seizures originate from a circumscribed region of the brain (epileptic focus) and remain restricted to this region [5]. Epileptic seizures may be accompanied by an impairment or loss of consciousness; psychic, autonomic, or sensory symptoms; or motor phenomena. It should be noted that, with the aforementioned definition, the term *synchronous* is controversially discussed. Several authors have suggested that seizures do not necessarily involve an increase in neuronal synchrony [6–10].

In many patients with epilepsy, seizures are well-controlled with currently available antiepileptic drugs (AEDs). Nevertheless, despite carefully optimized drug treatment, approximately 30% of patients continue to have seizures [11]. In patients suffering from seizures that originate from a circumscribed region of the brain and that cannot be controlled sufficiently by AEDs (refractory focal epilepsy), neurosurgery can have a 60–70% chance of bringing long-term remission [12]. For epilepsy patients who do not achieve complete seizure control with currently available therapies, there is a strong need for new curative treatments. Given the fact that it is the sudden, unforeseen occurrence of seizures that represents one of the most disabling aspects of the disease [13], a method capable of predicting the occurrence of seizures could significantly advance therapeutic possibilities [14, 15] and improve the quality of life for epilepsy patients. Preventive treatment strategies (e.g., long-term medication with AEDs, which can cause cognitive or other neurological deficits) could be replaced by an *on-demand therapy*, e.g., by excretion of fast-acting anticonvulsant substances or by electrical or other stimulation in an attempt to reset brain dynamics to a state that will no longer develop into a seizure [16, 17].

The aforementioned deficiencies and the desire to help patients with uncontrollable epilepsies clearly indicate the need for refined analysis techniques that allow one to extract relevant information from observables of brain dynamics. In epileptology, electroencephalographic (EEG) recordings are regarded as being indispensable for clinical practice. This is due to the high temporal resolution of the EEG and its close relationship to physiological and pathophysiological functions of the brain. Long-term digital video-EEG monitoring in epilepsy is an established technique, and advances in technology have led to miniaturization of equipment and have allowed for multiday, multichannel (up to 300) recordings at high sampling rates (up to kilohertz). In selected cases, chronically implanted intracranial electrodes allow the recording of brain electrical activity from the surface of the brain (electrocorticography; ECoG) and/or within specific brain structures (stereo-EEG; SEEG) at a high signal-to-noise ratio and at a high spatial resolution. Nevertheless, visually scoring large amounts of EEG data is a challenging task, and limitations become obvious particularly in clinical problems when rather sophisticated questions are being asked. In order to allow an improved characterization of EEG dynamics, a number of *linear* analysis techniques have been developed over the last few decades (see [18] for a comprehensive overview), and these techniques are now widely used for clinical purposes. Although linear techniques are important contributors to understanding physiological and

pathophysiological conditions in the brain, they provide only limited information as to the dynamical aspects of the EEG. Thus, it is argued that they cannot fully characterize the complicated, apparently irregular behavior of the complex dynamical system *brain*. In this system, nonlinearity is already introduced on the cellular level since the dynamical behavior of individual neurons is governed by integration, threshold, and saturation phenomena. Despite these well-known physiological facts, it has been repeatedly argued that it might not be valid to expect that a huge network of such nonlinear elements also behaves in a nonlinear way (see, e.g., [19]). In contrast to normal background activity, however, epileptic seizures are highly nonlinear phenomena.

Based on the celebrated embedding theorems by Takens [20] and by Sauer et al. [21] – stating that the system's behavior in state space can be approximated using only a single observable (e.g., the EEG) – a variety of new concepts and time series analysis techniques have been developed that allow one to characterize the dynamical behavior of an unknown system [22–26]. Within this framework of nonlinear dynamical systems, a number of univariate and bivariate nonlinear approaches are now available (see [27–33] for an overview and for implementation details for EEG analysis). Univariate quantities, such as an effective correlation dimension [34], correlation density [35, 36], entropy-related measures [37–41], or Lyapunov exponents [42–46], allow one to draw inferences about the number of degrees of freedom (or complexity), the amount of order/disorder, or the degree of chaoticity or predictability in a single EEG time series. Other univariate measures aim at discriminating between deterministic and stochastic dynamics [47, 48] or provide an estimate of the amount of nonstationarity [49, 50]. Bivariate measures, such as similarity index [51, 52], phase synchronization [53–56], nonlinear interdependency [57, 58], and other measures for generalized synchronization [59], allow one to estimate dynamical interactions between two time series. More recent developments aim at providing information about both the strength and the direction of interdependence [58, 60–67].

In order to allow for an improved characterization of spatial–temporal aspects of the epileptic process, analysis methods are usually applied to long-lasting, multichannel recordings in a moving-window fashion. The duration of a window is chosen in such a way that it represents a reasonable trade-off between approximate stationarity of the system and sufficient number of samples that are required to achieve a statistically reliable estimate. The moving-window analysis renders time profiles of a characterizing measure for different channels or channel combinations. This permits reduction of large amounts of EEG data to a small number of parameters, for downstream processing, which usually consists of scanning for, and processing of, prominent characteristics that can be related to the epileptic process. Although these approaches have a great potential to detect subtle spatial–temporal changes in brain dynamics, the results obtained should be interpreted with great care, particularly with respect to the underlying physiological and pathophysiological conditions. Many techniques place great demands on the recorded EEG with respect to the precision of the data and the absence of noise, and almost all techniques assume the underlying dynamical system to be stationary. In practice, however, none of these requirements can be exactly fulfilled. Moreover, a number of factors have been identified that might alter the absolute value of some nonlinear measure. These include properties of EEG electrodes, the precision of the analog-to-digital converter, amplifier and filter settings, and different recording montages, to name just a few. In addition, problems specific to the individual algorithms have to be taken into account. Despite these potential limitations, nonlinear EEG analysis is able to provide new and relevant information as long as nonlinear measures are used as tentative indices of different brain states [31, 68].

2 Value of Nonlinear EEG Analysis in the Presurgical Evaluation of Candidates for Resective Therapy

As already mentioned above, neurosurgery can have a 60–70% chance of bringing long-term remission for patients with refractory focal epilepsy. Successful surgical treatment of focal epilepsies requires exact localization of the *epileptogenic zone* (i.e., the brain region that can generate seizures) and its delineation from eloquent cortex that is indispensable for defined cortical functions. By definition, total removal or disconnection of this zone is necessary and sufficient for complete seizure control. Different presurgical evaluation methodologies are currently in use (see [69] for a comprehensive overview). Clinical review and neuropsychological examinations are complemented by neuroimaging techniques that aim at identifying potential morphological or metabolic correlates. Together with recording of seizures with prolonged EEG and video, these techniques aim at establishing converging evidence that there is a single epileptogenic zone and that the rest of the brain is functioning normally. If the epileptogenic zone cannot be determined unequivocally by noninvasive investigations, invasive ECoG/SEEG recordings can help to substantially improve the presurgical workup. Localization of the epileptogenic zone mostly relies on the observation of typical seizures on the video-EEG, which is currently regarded as the gold standard (to simplify matters, the term EEG shall refer to both noninvasive and invasive recordings in the following). In this context, localization refers to the identification of electrodes that exhibit the earliest signs of seizure activity on the EEG, preceding concomitant behavioral changes, as observed on the video (see [70] for a comprehensive overview). Epileptic seizures, however, often represent a rather infrequent phenomenon—under normal conditions, about 3 ± 4 seizures per month occur [71] (note that during presurgical monitoring an artificially high seizure frequency (more than three seizures per day [72]), seizure clustering, and atypical seizures may occur due to the reduction of anticonvulsive medication). Thus, the question arises as to what extent information obtained from the seizure-free interval (*interictal state*) can help to identify and to delineate the epileptogenic zone.

It is well known that the epileptic brain is far from being normal even between seizures. Epilepsy patients frequently exhibit pathological activity (but without concomitant behavioral changes) in their EEG between seizures. Spikes, sharp waves, and spike–wave discharges are considered the hallmark of epilepsy, and currently available automated spike detection systems provide quantitative parameters like spike rates at different recording sites, amplitude, duration, and temporal variances of discharge rates. Although these systems allow one to extract and to compress diagnostically relevant information from interictal long-term EEG recordings, system accuracy is still regarded as not sufficient. This is due to fact that it is problematic to clearly differentiate between steep potentials of quite physiological character and specific epileptiform events because exact definitions are still lacking. Moreover, interictal epileptiform discharges are always generated from a rather extensive area of cortex, which substantially limits their value for identifying the epileptogenic zone.

Research findings obtained over the last 10–15 years indicate that univariate nonlinear time series analysis techniques allow an improved localization of the epileptogenic zone during the seizure-free interval, i.e., without the necessity to record seizures [28, 48, 73–87]. A recent study indicates that focusing on nonlinearity by using a combination of nonlinear measures with surrogates [88] appears as the key to a successful characterization of the spatial distribution of the epileptogenic process [89]. The term *localization* here again refers to the identification of electrode sites from which pathophysiological activities

can be dominantly recorded on the EEG. At present, EEG analysis techniques discussed here do not allow a full three-dimensional localization of the epileptogenic zone. It should be noted, however, that the spatial–temporal distributions of *dynamical* changes of the EEG (as characterized by a time-resolved estimation of some nonlinear measure) do not necessarily coincide with the spatial–temporal distributions of obvious interictal epileptiform discharges. They do, however, coincide quite well with the epileptogenic zone (as determined by established presurgical evaluation techniques) in a large number of patients with focal epilepsies in the mesial or lateral temporal lobe or in frontal, parietal, or occipital neocortex. Thus, it is argued that these techniques allow us to identify more subtle spatial–temporal changes in brain dynamics that are of high relevance for clinical purposes. Despite these advantages, univariate nonlinear EEG analysis techniques may be more difficult to relate to the neurophysiology of epilepsy than other quantitative tools.

Univariate approaches characterize dynamical EEG changes related to only a single recording site, and thus, they cannot reflect any interactions between different regions of the brain. Since the epileptic process is commonly accepted to be closely associated with changes in neuronal synchronization in a network of components, which may be spatially distributed, the analysis of synchronization in the EEG can a priori be regarded as a promising approach. Indeed, a growing number of studies has investigated the merit of bivariate [55, 58, 66, 90–95] and, more recently, genuinely multivariate EEG analysis approaches [96–98] for a localization of the epileptogenic zone. Although findings indicate an increased level of synchronization/interdependence between interictal EEG recordings from sites covering the epileptogenic zone, physiologically-induced synchronization changes in other brain areas might attain similar levels, which limits the spatial resolvability of pathophysiological interactions. When comparing the efficiency of univariate and bivariate approaches (i.e., the percentage of successfully surgically treated patients for which nonlinear EEG analysis – in retrospective studies – identified the epileptogenic zone as determined by established presurgical evaluation techniques), values of about 90% can be achieved with univariate techniques [28, 89], while bivariate analysis techniques range between 60% and 75% only [91], which may not be sufficient for clinical applications. Despite these limitations, bivariate (or, in general, multivariate) approaches, which allow one to infer both strength and direction of interdependences, can help to identify pathological interactions in the epileptic brain and to distinguish between interactions that are locally restricted to the immediate surroundings of the epileptogenic zone and those that involve remote brain regions, and even brain regions in the opposite hemisphere [33, 66, 99]. Given the growing evidence for the concept of a localized and well-defined epileptogenic zone to be replaced by an *epileptic network* whose interactions extend over large regions of the brain (see, e.g., [100–103]), the aforementioned properties of bivariate approaches can provide deeper insights into the complex spatial–temporal dynamics of the epileptic process. Eventually, this can help to further improve presurgical evaluation of candidates for resective therapy.

Most of the aforementioned analysis techniques (implicitly) assume some (nonlinear) deterministic and low-dimensional structure underlying the epileptogenic process, and there is strong evidence from different laboratories that this assumption is valid (see, e.g., [48, 75, 104]). Very often, however, the dynamics of the epileptic process in between seizures must be regarded as high-dimensional and nonstationary, which might prevent its detailed characterization when using these techniques. Addressing this issue, we recently [105] evaluated the merit of previously proposed data-driven analysis techniques that allow one to estimate drift and diffusion terms of a corresponding Fokker–Planck equation

[106–109]. With these techniques, deterministic laws and fluctuating forces of EEG dynamics can be identified. Focusing on interictal EEG recordings, we observed that the spatial distribution of the drift term indicated the extent of the epileptogenic zone in six out of eight patients suffering from uncontrollable seizures of mesial temporal lobe origin. This is in line with previous findings [48] that have shown the epileptic process to enhance or induce nonlinear, deterministic structures in an otherwise linear stochastic appearance of the EEG. Interestingly, in all patients, the spatial distribution of the diffusion term correctly indicated the extent of the epileptogenic zone. Using our recently proposed technique to measure interdependences in dissipative dynamical systems with estimated Fokker–Planck coefficients [67], we again observed that a more detailed characterization of spatial and temporal aspects of the epileptic process in between seizures can be achieved when focusing on interactions in the stochastic part of the dynamics. Although these findings need to be validated on a larger patient group and including other types of epilepsies, they indicate the high relevance of this approach for diagnostic purposes.

3 Nonlinear EEG Analysis and Seizure Prediction: State-of-the-art and Current Deficiencies

For patients with refractory focal epilepsy and for whom epilepsy surgery is not an option, there is a strong need for alternative therapy concepts. As already stated above, it is the sudden, unforeseen occurrence of seizures that represents one of the most disabling aspects of the disease. If it were possible, however, to detect a preseizure (preictal) state with high sensitivity and specificity, even seconds before seizure onset, therapeutic possibilities would change dramatically. Side effects from treatment with AEDs could be reduced by on-demand therapies during the preictal state with short-acting drugs, electrical stimulation, or other suitable interventions, such as focal cooling [110] or biofeedback operant conditioning [111, 112]. Even a simple warning system would be capable of decreasing both the risk of injury and the feeling of helplessness that results from seemingly unpredictable seizures. Such applications could reduce morbidity and mortality and greatly improve the quality of life for people with epilepsy. More importantly, the unequivocal identification of a preictal state would significantly advance our understanding of the basic mechanisms leading to seizure initiation in humans (note that current knowledge about seizure-generating mechanisms is mainly derived from animal experiments).

Following [113], there are two different scenarios of how a seizure could evolve. The first scenario is based on the so-called reservoir theory proposed by Lennox in 1946 [114] and considers some random (endogenous and/or exogenous) fluctuations that cause a sudden and abrupt transition to a seizure. Such a *noise-induced* transition in a bistable network would be conceivable for the initiation of generalized onset seizures, and it is widely assumed that these types of seizures would not be preceded by detectable dynamical changes on the EEG (see also [115, 116]). The notion of a primary generalized epilepsy, however, has been repeatedly challenged [5], and the search for possible precursors of generalized-onset seizures has begun only recently [117–119].

The second scenario considers a gradual change (or a cascade of changes) in dynamics responsible for seizure generation. These changes might reflect alterations (acting on different time scales) of some cellular, synaptic, or molecular properties of neurons with the epileptic network that may lead to a deformation of an otherwise stable attractor

representing the interictal state. With certain changes in some critical unstable parameters (under the influence of fluctuating endogenous and/or exogenous factors), the distance between an interictal and an ictal attractor may gradually become smaller such that a transition to a seizure eventually occurs. These changes could, in theory, be detected. This scenario could be more likely in focal epilepsies, and research over the last three decades indicates that (mostly nonlinear) EEG analysis techniques appear to be capable of identifying spatial–temporal changes in the ongoing EEG that can be regarded as precursors of an impending seizure (see [30, 120–126] and references therein for comprehensive overviews). After preliminary descriptions of preictal phenomena and proof-of-principle studies, recent studies focus on the analysis of continuous multiday, multichannel recordings together with a more rigorous methodological design using statistical methods for performance assessment [127–131]. Recent studies provide evidence that particularly measures quantifying interactions between different regions of the epileptic brain allow one to identify precursors preceding focal-onset seizures. This evidence, however, is based on retrospective analyses of mostly intracranial EEG data recorded during evaluation for resective surgery. Moreover, no study has been published that demonstrates preictal state identification in blinded, prospective, randomized clinical trials with accuracy sufficient for clinical application. Since many previous studies provided an over-optimistic view of prediction algorithms (note that the term *prediction* refers to the identification of a preictal state), guidelines have been proposed recently in order to assure the methodological quality of future studies [30].

The design of a prospective seizure prediction study (along with the assessment of its performance) strongly relies on a number of assumptions that need to be validated in future studies. Given the aforementioned scenarios for seizure generation, it still remains an open issue whether the epileptic process is optimally sampled both in time and space. The placement of (scalp and intracranial) EEG electrodes typically follows roughly common protocols, guided by the demands of the presurgical evaluation and limited by the need to protect patients. Some recent studies reported on seizure precursors that were not in close vicinity to the epileptogenic zone but could be located in remote brain structures or even in the opposite brain hemisphere [132–136]. Although this finding might appear to be counterintuitive, it underlines the importance of brain tissue outside the epileptogenic zone but within the epileptic network in generating clinical seizures. Another crucial aspect is the lack of an adequate interictal-to-preictal transition scenario, both in time and space. It should be noted that there is very likely no single such scenario. Currently available information indicates that a preictal state might last from minutes to hours, depending on the applied analysis technique [126]. When estimating the performance of a seizure prediction algorithm, however, an inappropriately selected duration would lead to an increased number of false classifications. The interictal-to-preictal transition is usually assumed to follow some rectangular function, with a sharp boundary between states. If, however, this transition follows another function (e.g., linear, exponential, or log-periodic), very early or intermittently occurring precursors would wrongly be classified as false-positive predictions. The situation becomes even more complicated when taking into account spatial aspects of the interictal-to-preictal transition. From our synchronization studies, we concluded that an epileptic seizure might be interpreted as the climax of a process of changes in brain dynamics that starts long before the seizure [55]. The field of seizure prediction would strongly benefit from improving the physiological or dynamical understanding to exactly delineate a preictal state both in time and space, particularly from a level that relates to neurophysiology on the cellular and network level. This would also be of great value for exactly defining what constitutes a seizure [137].

4 Conclusions

Research over the last two decades has provided strong evidence that the application of concepts and methods from nonlinear dynamics to electroencephalography significantly advances our understanding of the complex spatial–temporal dynamics underlying normal and disturbed brain function. In epileptology, nonlinear EEG analysis has opened new directions to improve presurgical evaluation of patients that are candidates for resective therapy. More importantly, nonlinear EEG analyses may enable the prediction of epileptic seizures, which may allow the development of both warning and therapeutic antiepileptic devices, particularly for individuals with refractory focal epilepsy and for whom epilepsy surgery is not an option. This is now an area of active research [138], and recent studies indicate that approaches that are based on the nonlinear dynamics of interacting nonlinear elements [139–141] or biologically inspired computing approaches [142, 143] can provide the computational power needed for the development of miniaturized, possibly implantable, prediction and prevention systems. Despite these advantages, considerable development is required before such systems can enter clinical practice. A major challenge is to establish – in prospective studies – convincing evidence for the existence of a preictal state together with an appropriate model for its characteristics in human epilepsy. Since this requires large, high-quality data archives that are well-characterized and represent the heterogeneity of patterns and patients found in human epilepsy, efforts are currently underway to create such a database [137, 138]. Another major challenge is to improve the understanding of brain dynamics during the seizure-free interval and all of its confounding variables. This might help to refine already existing approaches in order to increase predictive performance, to develop new analysis concepts and measures, and to guide basic science investigations to specific mechanisms. Of equal importance is to improve the understanding of mechanisms underlying seizure termination, which, in turn, might provide valuable information about seizure-initiating mechanisms [9, 10, 144–148] and might guide new developments for seizure control [149]. Since such studies might require access to deep brain structures and other locations in the epileptic network that cannot be explored in human studies, due to safety concerns, there is a strong need to improve existing and develop new spontaneously seizing animal models of epilepsy.

Given these challenges, there is a also great need for refined time series analysis techniques that allow one to disentangle the temporal and spatial patterns of interactions in the epileptic brain. An improved knowledge about the characteristics of the underlying functional and anatomical networks may contribute substantially to our understanding of the epileptic process. This may be achieved through improving the detectability of directional interactions with bivariate analysis techniques, with genuinely multivariate analysis approaches, from synchronization theory and random matrix theory, and with recent techniques from graph theory and network theory [150, 151].

Last but not least, it is of potential importance to develop neurocomputational models for the dynamics of neuronal networks underlying the epileptic process [152, 153]. Using concepts from network theory, recent modeling studies already indicate the importance of network topology in epileptogenesis and seizure generation [154–158], which may help in interpreting the complex phenomena seen on the EEG during the interictal-to-preictal transition [159]. An improved understanding of the interplay between structure and function in the epileptic brain may help to integrate the plethora of experimental data available, to test various hypotheses concerning interictal and preictal brain dynamics and their relation to endogenous and exogenous control parameters, and to improve analysis concepts and measures.

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