NONLINEAR EEG ANALYSIS IN EPILEPSY

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Abstract- **This overview presents potential applications of nonlinear time series analysis using EEGs derived from epilepsy patients. Apart from diagnostically oriented topics including localization of epileptic foci in different anatomical locations during the seizure-free interval I discuss possibilities for seizure anticipation which is one of the most challenging aspects of epileptology.**
Keywords - **Nonlinear time series analysis, EEG, epilepsy, seizure anticipation**

I. Introduction

The disease epilepsy is characterized by a recurrent and sudden malfunction of the brain that is termed *seizure*. Epileptic seizures reflect the clinical signs of an excessive and/or hypersynchronous activity of neurons in the cerebral cortex. Depending on the extent of involvement of other brain areas during the course of the seizure, epilepsies can be divided in two main classes. Generalized seizures involve almost the entire brain while focal (or partial) seizures originate from a circumscribed region of the brain (*epileptic focus*) and remain restricted to this region. Epileptic seizures might be accompanied by an impairment or loss of consciousness, psychic, autonomic or sensory symptoms or motor phenomena.

Knowledge about basic mechanisms underlying the generation of seizures mainly stems from animal experiments. Although there is a considerable bulk of literature the underlying electrophysiological and neurobiochemical mechanisms are not yet fully explored. Moreover, it remains to be proven whether these findings are fully transformable to human epilepsies. Recordings of the membrane potential of neurons under epileptic conditions indicate an enormous change, which by far exceeds physiological changes occurring with neuronal excitation. This phenomenon is termed paroxysmal depolarization shift (PDS, [1, 2]) and represents a shift of the resting membrane potential that is accompanied by a raise of intracellular calcium and a massive burst of action potentials (500 - 800 per second). PDSs originating from a larger cortical region are associated with steep field potentials (known as *spikes*) recorded in the scalp EEG. Focal seizures are assumed to be initiated by abnormally discharging neurons (so-called *bursters* [3, 4]) that recruit and entrain neighboring neurons into a "critical mass". This build-up might be mediated by an increasing synchronization of neuronal activity that is accompanied by a loss of inhibition, or by facilitating processes that permit seizure emergence by lowering a threshold.

Approximately 0.6 - 0.8 % of the world population suffers from epilepsy. In about half of these patients focal seizures originate from functional and/or morphological lesions of the central nervous system. Antiepileptic drugs insufficiently control or even fail to manage epilepsy in 30 - 50 % of the cases. It can be assumed that 10 - 15 % of these cases would profit from epilepsy surgery. Successful surgical treatment of focal epilepsies requires exact *localization* of the epileptic focus and its *delineation* from functionally relevant areas. For this purpose different presurgical evaluation methodologies are currently in use (see [5] for an overview). Neurological and neuropsychological examinations are complemented by neuroimaging techniques that try to identify potential morphological correlates. Currently, the *gold standard* for an exact localization of the epileptic focus, however, is to record the patient's spontaneous habitual seizure using electroencephalography. Depending on the individual occurrence of seizures, this task requires long-lasting and continuous recording of the EEG. In case of ambiguous scalp EEG findings invasive recordings of the electrocorticogram (ECoG) or the stereo-EEG (SEEG) via implanted electrodes are indicated. This procedure, however, comprises a certain risk for the patient and, moreover, is time-consuming and expensive.

With the advent of the theory of nonlinear dynamics [6] new concepts and powerful algorithms were developed to analyze apparently irregular behavior, a distinctive feature of the EEG. During the last decade a variety of nonlinear time series analysis techniques nonlinear time series analysis (NTSA) [7] has been repeatedly applied to EEG recordings during physiological and pathological conditions. Nonlinear measures like dimensions, Lyapunov-exponents, entropies, or recent approaches that aim to characterize interdependencies, synchronization, or similarities were shown to offer new information about complex brain dynamics (see [8-11] for an overview). Today it is commonly accepted that the existence of a deterministic and even chaotic structure underlying neuronal dynamics is difficult or even impossible to prove. Nevertheless, nonlinear approaches to the analysis of brain systems generate new clinical measures as well as new ways of viewing brain electrical function, particularly with regard to epileptic brain states. Indeed, recent results provide converging evidence that NTSA allows to reliably characterize different states of brain function and dysfunction, provided limitations of analysis techniques are taken into consideration and, thus, results are interpreted with care (e.g., only relative measures with respect to recording time and recording site are assumed reliable).

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II. Localizing the epileptic focus

Several lines of evidence originating from studies of human epileptic brain tissue as well as of animal models of chronic seizure disorders indicate that the epileptic brain, even between seizures, is different from normal. Based on the fact that neurons involved in the epileptic process exhibit paroxysmal depolarization shifts that are scarcely modulated by physiological brain activity, we hypothesized that this highly synchronized neuronal behavior should be accompanied by an intermittent *loss of complexity* or an *increase of nonlinear deterministic structure* in the corresponding electrographic signal even during the seizure free interval (interictal state) [12]. In order to characterize the spatio-temporal dynamics of the epileptogenic process we have developed a variety of univariate and bivariate analysis techniques [12-16] and applied them to long-lasting interictal ECoG/SEEG recordings covering different states of normal behavior and vigilance as well as different extents of epileptiform activity. Analyses of EEG recordings from up to now more than 300 patients indicate that nonlinear EEG analysis techniques allow to reliably localize epileptic foci in different cerebral regions in more than 80 % of the cases. This holds true regardless of whether or not obvious epileptiform activity is present in the recordings.

These findings already indicate the potential relevance of nonlinear EEG analysis to improve understanding of intermittent dysfunctioning of the dynamical system brain in between seizures. Moreover, results also stress the high relevance of nonlinear EEG analyses in clinical practice since they provide potentially useful diagnostic information.

III. Can epileptic seizures be anticipated?

Anticipation of seizures is one of the most challenging aspects of epileptology. Although there are numerous studies exploring basic neuronal mechanisms that are likely to be associated with seizures, to date, no definite information is available as to the generation of seizures in humans. In this context the term “critical mass” might be misleading in the sense that it just implies an increasing *number of neurons* that are entrained into an abnormal discharging process. This *mass* phenomenon would be easily accessible for conventional EEG analyses which, however, failed to detect it. Autoregressive modeling of the EEG indicated that electroencephalographic changes characteristic for pre-ictal states may be detectable, at most, a few seconds before the actual seizure onset [17]. Coherence analyses pointed to an increase of inter- and intrahemispheric coupling that might occur minutes before a seizure [18]. The relevance of brief bursts of focal pathological neuronal activity leading to spikes in the EEG and occurring prior to seizure onset was investigated in several clinical studies, however with inconsistent results [19-21].

Recent studies indicate that the seizure initiating process should be regarded as an unfolding of an increasing number of critical, possibly nonlinear *dynamical interferences* between neurons within the focal area as well as with neurons surrounding this area. Indeed, there is converging evidence from different laboratories that nonlinear analysis is capable to characterize this collective behavior of neurons from the gross brain electrical activity and hence allows to define a critical transition state, at least for a high percentage of cases [14, 22-31].

IV. Future aspects

Results obtained so far are promising and emphasize the high value of nonlinear EEG analysis techniques for both clinical practice and basic science. However, up to now findings were mainly obtained from retrospective studies in well elaborated cases and using invasive recording techniques. Thus, on the one hand, evaluation of more complicated cases as well as prospective studies on a larger population of patients are necessary.

The possibility of defining a critical transition state can be regarded the most prominent contribution of nonlinear EEG analysis to advance knowledge about seizure generation in humans. This possibility has recently been expanded by studies indicating accessibility of critical pre-seizure changes from non-invasive EEG recordings [25, 28]. However, to achieve an unequivocal definition of a critical pre-seizure transition state from either invasive or non-invasive recordings, a variety of influencing factors have to be evaluated beforehand. Despite considerable effort in characterizing the spatio-temporal dynamics of the epileptogenic process, a variety of pathologically or physiologically induced dynamical interactions are nor yet fully understood. Among others, these include different sleep stages, different cognitive states, as well as daily activities that clearly vary from patient to patient. Along with these studies, nonlinear EEG analysis techniques have to be further improved. New techniques are needed that allow a better characterization of non-stationarity and high-dimensionality in brain dynamics, techniques disentangling even subtle dynamical interactions between pathological disturbances and surrounding brain tissue as well as refined artifact detection and elimination techniques. Since the techniques currently available allow a differentiated characterization of the epileptogenic process, the combined use of these techniques along with appropriate classification schemes [e.g. 32, 33] can be regarded a promising venture.

Once given an improved sensitivity and specificity of nonlinear EEG analysis techniques, broader clinical applications on a larger population of patients, either at home or in a clinical setting can be envisaged. As a future perspective one might also consider implantable seizure anticipation and prevention devices similar to devices already in use with Parkinsonean patients. Although optimization of algorithms underlying the computation of specific nonlinear measures [26, 34] already allows, at present, to continuously track the temporal behavior of nonlinear measures in real time, these applications still require the use of powerful computer systems, depending on the number of recording channels necessary to allow unequivocal characterization of the epileptogenic process. Thus, further optimization and development of a miniaturized analyzing system are definitely necessary. However, taking into account the technologies currently available realization of such systems can be expected within the next few years.

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