Seizure Prediction and its Applications

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KEYWORDS

- Spatiotemporal dynamical analysis of EEG • Ictogenesis
- Seizure prediction • Closed-loop seizure control

Epilepsy is considered a window to the brain's function and is therefore an increasingly active, interdisciplinary field of research.[1,2] The sacred or divine disease is among the most common disorders of the nervous system, second only to stroke and Alzheimer disease, and affects 1% to 2% of the world's population.[3,4] Although epilepsy occurs in all age groups, the highest incidences occur in infants and in the elderly.[5–7] This high incidence of epilepsy stems from it having a large number of causes, including genetic abnormalities, developmental anomalies, and febrile convulsions, as well as brain insults such as craniofacial trauma, central nervous system infections, hypoxia, ischemia, and tumors.

The hallmarks of epilepsy are recurrent seizures and epileptic spikes. If seizures cannot be controlled, the patient experiences major limitations in family, social, educational, and vocational activities. These limitations have profound effects on the patient's quality of life.[8] Epileptic seizures and spikes are caused by the sudden development of pathologic, synchronous neuronal firing in the cerebrum and can be recorded by scalp, subdural, and intracranial electrodes. Seizures may begin locally in portions of the cerebral hemispheres (partial/focal seizures) with a single or multiple foci, or simultaneously in both cerebral hemispheres (generalized seizures). After a seizure's onset, partial seizures may remain localized and cause mild cognitive, psychic, sensory, motor, or autonomic symptoms, or may spread (secondarily generalized) to cause altered consciousness, complex automatic behaviors, or bilateral tonic-clonic convulsions. Even though seizures typically run their course (seconds to minutes) and the brain subsequently recovers by itself, there are cases in which recovery is accomplished only through external intervention (ie, high doses of antiepileptic drugs), as in status epilepticus (SE), a life-threatening condition.[9,10] The brain also does not recover by itself in the event of sudden unexplained death in epilepsy (SUDEP). SUDEP is a less common condition than SE, is seemingly unpredictable, and hence extremely difficult to monitor and provide for external intervention.[11,12]

One of the most debilitating aspects of epilepsy is that seizures seem to occur without warning. Until recently, the general belief in the medical community was that epileptic seizures could not be anticipated. Seizures were assumed to occur abruptly and randomly over time. However, hypotheses on the mechanisms of ictogenesis and predictability of seizures had been postulated in the past based on reports from clinical practice (eg, existence of auras) and scientific intuition (eg, theory of reservoir).[13,14] In the 1970s, attempts to show that seizures are predictable had also been undertaken via computer analysis of the electroencephalogram (EEG).[15] Despite those early attempts, the results were not encouraging. Systematic and robust detection of a preictal period across seizures in the same patient, as

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Neurosurg Clin N Am 22 (2011) 489–506
doi:10.1016/j.nec.2011.07.004
1042-3680/11/$ – see front matter

well as across patients, remained elusive. The essential features of the brain's transition to epileptic seizures were not captured, and a theoretic framework for seizure development that could lead to definition and subsequent detection of such preictal features was missing.[16,17]

It was in the 1980s that new signal processing methodologies emerged, based on the mathematical theory of nonlinear dynamics and chaos for the study of spontaneous formation of organized spatial, temporal, or spatiotemporal patterns in physical, chemical, and biologic systems.[18–29] These methodologies quantified the complexity and randomness of the signal from the perspective of invariants of nonlinear dynamics and represented a drastic departure from the signal processing techniques based on linear systems analysis (eg, Fourier analysis). Because the brain is inherently a nonlinear system, the general concept at that time was that seizures represented transitions of the epileptic brain from its normal, less ordered (chaotic) state to an abnormal, more ordered state and back to a normal state along the lines of chaos-to-order-to-chaos transitions.[30] How this concept, when applied to the EEG in epilepsy, eventually changed some long-held beliefs about seizures and their dynamical causes is discussed later. Within this framework, systematic mathematical analysis of long-term EEG recordings that included seizures started in the mid-1980s at the University of Michigan (U of M), creating, at the time, the largest worldwide database of digitally stored peri-ictal EEG recordings with seizures. The existence of long-term preictal periods (order of minutes) was shown in 1988 by nonlinear dynamical analysis of EEGs recorded by subdural arrays from patients undergoing phase II monitoring of their seizures at the U of M Hospital's Epilepsy Monitoring Unit (EMU).[31]

EXISTENCE OF A PREICTAL PERIOD: SEIZURE PREDICTABILITY

Among the important measures of the dynamics a linear or nonlinear system exhibits are the Lyapunov exponents that measure the average information flow (bits per second) the system produces along local eigendirections in its state space.[32,33] Positive Lyapunov exponents denote generation of information, whereas negative exponents denote destruction of information. A chaotic nonlinear system possesses at least 1 positive Lyapunov exponent, and it is because of this feature that its behavior seems random, even if it is deterministic in nature. Methods for calculating these measures of dynamics from experimental data have been published.[34]

The brain, being nonstationary, is never in a steady state in the strictly dynamical sense, at any location. We have shown that, in the case of a nonstationary system with transients like epileptic spikes, the use of the short-term maximum Lyapunov exponent (STL_{max}) constitutes a more accurate characterization of the rate of the average information flow[35] than the traditional maximum Lyapunov (L_{max}) exponent.[36] STL_{max} is estimated from sequential EEG segments of 10 seconds in duration per recording site to create a set of STL_{max} profiles with time. Analysis of scalp, subdural, or depth EEG from patients with focal (temporal and frontal lobe) epilepsy at the U of M, and subsequently at the University of Florida and Arizona State University, showed that the STL_{max} profiles at brain sites systematically and progressively converge to similar values tens of minutes before a seizure and remain entrained up to the onset of the seizure.[37–48] We have called this phenomenon preictal dynamical entrainment (convergence of measures of EEG dynamics long before a seizure onset), the involved brain sites critical sites, and the corresponding pairs of sites that interact in this dynamical sense critical pairs. The focal sites are typically part of the set of critical sites. Therefore, the following hypothesis was formed that directly relates to mechanisms of ictogenesis: the epileptic brain is dynamically entrained by the focal sites long before a seizure's occurrence.

It was further hypothesized that the brain starts malfunctioning because of this loss of relative independence of processing of information at normal brain sites long before a seizure develops. Such a preictal entrainment is illustrated in **Fig. 1** for a patient with focal epilepsy and EEG recorded by intracranial electrodes (see **Fig. 1**A, B). The STL_{max} profiles of critical sites with time are shown in **Fig. 1**C. The convergence of STL_{max} profiles of a pair of sites is quantified by the T-index, a statistical measure of the distance between the mean values of the respective time series. Small values of T-index denote small distances between the corresponding STL_{max} profiles, and hence entrainment of dynamics. T-index values with time are estimated within a running window of 10 minutes in duration (60 STL_{max} values) for a pair of STL_{max} profiles. Pairs of sites that are dynamically entrained in the 10-minute period before a seizure are characterized as critical pairs. The average T-index profile illustrated in **Fig. 1**D represents the average of all T-indices over time across the thus selected critical pairs of sites. From **Fig. 1**D, it is clear that, if critical pairs of sites are selected (retrospectively) from the immediate preictal period of a seizure, a seizure is predictable. For example, in the seizure depicted in **Fig. 1**B, a warning