Epilepsy & Behavior 26 (2013) 212–228

Contents lists available at SciVerse ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Review

The epilepsies: Complex challenges needing complex solutions

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ARTICLE INFO

Article history:
Accepted 16 September 2012
Available online 10 November 2012

Keywords:
Complex systems
Emergent properties
Epileptogenesis
Epileptogenic circuits
Semiology
Graph theory
Computational models

ABSTRACT

It is widely accepted that epilepsies are complex syndromes due to their multi-factorial origins and manifestations. Different mathematical and computational descriptions use appropriate methods to address nonlinear relationships, chaotic behaviors and emergent properties. These theoretical approaches can be divided into two major categories: descriptive, such as flowcharts, graphs and other statistical analyses, and explicative, which include both realistic and abstract models. Although these modeling tools have brought great advances, a common framework to guide their design, implementation and evaluation, with the goal of future integration, is still needed. In the current review, we discuss two examples of complexity analysis that can be performed with epilepsy data: behavioral sequences of temporal lobe seizures and alterations in an experimental cellular model. We also highlight the importance of the creation of model repositories for the epileptology field and encourage the development of mathematical descriptions of complex systems, together with more accurate simulation techniques.

This article is part of a Special Issue entitled "The Future of Translational Epilepsy Research".

1. Introduction

Epilepsies are chronic neurological syndromes defined by the occurrence of paroxysmal and self-limited convulsive or non-convulsive seizures [1–3]. Recurrent and spontaneous seizures are a common aspect of all epilepsies and are characterized by synchronous high-frequency discharges of neuronal populations in the brain [1,3]. This pathological excessive synchronization of neuronal networks typically produces complex behavioral patterns [2–11]. The search for the mechanisms underlying seizure activity is currently one of the major goals of epilepsy research. It is believed that over 65 million people around the world suffer from some form of epileptic seizures or syndrome, making epilepsy the second most common neurological disorder after stroke and a major burden for public health systems [12,13].

The International League Against Epilepsy (ILAE)'s classifications of seizures [14] and epileptic syndromes [15] are based on concepts that have arisen and developed over the previous decades. Since then, several advances in molecular cell biology, genetics, structural and functional neuroimaging, neurophysiology techniques and computational neuroscience provided valuable information on the nature of epilepsy [16]. Although the ILAE's classifications of seizures and epileptic syndromes are well known and convenient, they do not incorporate this vast amount of knowledge in an appropriate and clear way. For these reasons, the Commission on Classification and Terminology of the ILAE has recently proposed new, alternative concepts and terminology [17]. These proposals are still under discussion, and new data will be incorporated as they become available [18]. For example, the concepts of generalized and focal seizures are now meant to describe networks more than localized structures. Generalized seizures originate at some point within a bilateral network that can include cortical or subcortical structures, but not necessarily the entire cortex. Focal seizures are limited to a network localized in only one cerebral hemisphere and may also include subcortical structures. Therefore, the evidence of focal origin [19] in primary generalized seizures gives support to the recently proposed concept of "systems epilepsy", which describes epileptogenic circuits and their semiological outcome as complex systems [20].

Additionally, terms such as idiopathic, symptomatic, benign and cryptogenic, among others, have been inappropriately applied and have been associated with inaccurate prognoses, such as "good" and "bad" outcomes (see details in [18]). The conflicts and discussions regarding these concepts, terminologies and classifications are extremely helpful and note the natural need to accept the advances in neuroscience and to incorporate them into basic and clinical epilepsy research [16]. This has not been an easy task, given that more than 30 years have passed since the publication of the consensus on seizure classification [14] and as more than 25 years have passed since the consensus on epileptic syndromes [15].

In a more philosophical and conceptual arena, we believe that the current disagreements in the field of epilepsy research are telltale signs of a Kuhnian paradigm crisis [9,21], in which the products of

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http://dx.doi.org/10.1016/j.yebeh.2012.09.029

normal scientific progress can no longer respond to the challenges and desires of the scientific community. This conflict is evident in the current challenge of analyzing the ever-growing body of evidence produced by epilepsy investigators and converting these massive amounts of data into concise phenomenological explanations.

2. Definitions of complexity, complex systems and emergent properties

There are a multitude of reasons to consider epilepsies as a complex systems problem, given the known variety of pathological conditions associated with their origins. Additionally, different behavioral patterns are associated with various forms with specific pathogenic insults; however, similar pathogenic insults may induce different patterns of a seizure expression. These descriptions, despite usually being qualitative, contain the basis of a complex theory problem, as one of the most intuitive definitions of a "Complex System" (CS) relates to the length of its description [22]. A CS is characterized by the presence of a specific pattern of relationships between its elements. This pattern can vary from utter randomness on one end to complete regularity on the other. On both sides, there are conditions that can be considered so simple that they can be described by short expressions. For example, when we say "this pattern is random" or "this pattern is regular," those statements are shorter than "the network presents a pattern with a cluster of units connected with other clusters by certain shortcuts" or, in other words, "a small world network pattern" [23]. Different descriptions of epilepsy satisfy this condition: they are complex in the sense of the length of their description.

It is also possible to consider epilepsies as emergent properties of epileptogenic circuits [9,22,24], as a seizure is the final result of the interaction of several mechanisms that are impossible to describe based solely on their individual properties (see sections: "Behavior in epileptic seizures as source of complexity: examples from TLE semiology" and "Sources of complexity at the cellular and molecular levels"). One of the most important properties of a CS is the capacity to produce complex emergent behaviors that cannot be reduced to the sum of the elements that constitute the system. Therefore, the emergent properties of the epilepsies are another link between the diseases and CS theory.

3. Mathematical modeling of complexity in the epilepsies

The recognition that epilepsies behave like a CS allows us to approach the problem with a set of methods prepared to address nonlinear relationships, chaotic behaviors and emergent properties [25–27]. However, to use these methods, it is necessary to describe the phenomena mathematically. Two different approaches have been used to mathematically model epilepsies [28]. The first approach attempts to fit experimental data into an intelligible distribution to build a stochastic (probabilistic) model. This approach is analogous to choosing a specific distribution, *e.g.* a Gaussian function, to synthesize parameters such as the mean and standard deviation and thus describe the behavior of a given data set. The second method tries to build a mathematical model that is able to reproduce a specific behavior, similar to the way that the Hodgkin–Huxley model simulates membrane dynamics.

The two methods address complexity in different ways. The stochastic method, with its top-down approach, models a given problem without much attention to the underlying details. In contrast, the deterministic method, with its bottom-up approach, provides a detailed mathematical/computational description of a system based on certain hypotheses in an attempt to reproduce a specific behavior of the system.

Deterministic models of CSs employ nonlinear equations that, in addition to their sensitivity to small changes, show predictable trajectories that describe the evolution of the variable's state across time. This property of exhibiting predictable trajectories allows for different nonlinear systems to converge in a similar behavior, even when using different approximations. This opens the possibility of using different levels of analysis to study a phenomenon. In this sense, we may consider that neural networks behave like nonlinear systems. This assumption allows us to include or exclude certain elements without significantly affecting the overall behavior of the network. In some cases, the simulation may include equations that describe, for example, the overall ionic diffusion across the membrane, while in other cases, each ionic current may be represented by a unique equation, but both systems can reproduce a similar system trajectory. However, these trajectories cannot be considered to represent fixed behaviors, as they can be affected by changes in the model's parameters. In this manner, small alterations in the initial settings of the model can lead to completely different simulated trajectories for a given system. In the field of systems dynamics, these qualitative changes in the behavior of the CS are called bifurcations (in mathematical terms) or phase transitions (in physical terms) [27,29], and the study of these changes is increasing our understanding of a variety of phenomena related to normal and pathological states. See Fig. 1 for a schematic view of different modeling approaches.

4. Reviewing complexity data from clinical and experimental protocols

We will discuss how the behavioral and cellular nature of epilepsy demands the development of novel methods for descriptive (stochastic) and explicative (deterministic) modeling. We also highlight the need for a common computational framework for these models to increase the efficiency of interpreting and sharing of novel data. This review begins with a discussion of sophisticated techniques used to measure the more apparent phenomena associated with seizure semiology, briefly discusses electroencephalography (EEG), functional imaging and circuit characterization and ends with a detailed description of cellular and molecular mechanisms. All of these analytical levels are sources of complexity; the end-point is a sum of these intermixed phenomena that gives rise to emergent properties, *i.e.*, those that are dependent on previous levels, but which are not explainable only by the summation of each of the components. A previous analytical model of epileptogenic circuits as sources of complexity has been proposed based on experimental models [9,30]. In addition to suggesting several sources of complexity, these reviews noted the need to develop computational neuroscience tools in order to propose solutions to experimental problems, which is the domain of the field known as neuroinformatics [9,31]. These computational solutions will be updated and discussed at the end of the current review.

5. Multifactorial origin of complexity in epilepsies

In patients with epilepsy, seizure is the final common pathway of the ictal pattern. Underneath the exuberant behavioral and electroencephalographic expression of epileptic seizures, there are several molecular, metabolic, cellular and functional changes in brain activity that strongly affect the patient's brain function. Moreover, there are other variables influencing patients with epilepsy, such as developmental disorders and limitations caused by their psychological deficits, memory impairments, mood disturbances, antiepileptic drug (AED) treatment and its side effects, the decline in the quality of life caused mainly by the repetitive seizures, and the social stigma associated with the disease. The techniques applied to evaluate patients with epilepsy and their seizures, such as medical history, seizure semiology, genetic studies, scalp and invasive video-EEG, brain stimulation and neuroimaging, and neuropsychological, social and psychiatric evaluations are fundamental strategies for finding the origin(s) of the seizures and to assess the cognitive and social consequences of epilepsy. At the same time, a diverse spectrum of treatment options are discussed and, depending on the case, different combinations are implemented in an attempt to prevent or reduce the frequency of seizures. Treatment strategies include different pharmacological compounds [32], dietary restrictions [33–36], vagal nerve or deep brain electrical stimulations