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Summary

Epileptic seizures are the hallmark of epilepsies. Though many facts are known about molecular and cellular changes during seizures, only slow progress is made in better understanding large-scale ictal dynamics and their possible feed-back on local processes. Recent studies have therefore made use of methods and concepts from the fascinating but often quite abstract field of complex systems. Here it is discussed, how this novel approach may help to shed new light onto long-known observations and thus promote a deeper understanding of epileptic seizures. The hope and goal of such systems-inspired research remain that unraveling the dynamics of epileptic seizures on and between multiple spatial scales will lead to improved diagnostic and therapeutic approaches.

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Key words: Quantitative EEG, nonlinear dynamics, critical transitions

Epileptische Anfälle und Systeme

Epileptische Anfälle sind das definierende Phänomen der Epilepsien. Während sehr viel über die molekularen und zellulären Veränderungen während epileptischer Anfälle bekannt ist, werden die dynamischen iktalen Vorgänge auf grösseren räumlichen Skalen und ihre möglichen Rückwirkungen auf lokale Prozesse erst langsam besser verstanden. Neuere Studien verwenden deshalb zunehmend Methoden und Konzepte aus dem faszinierenden aber häufig auch abstrakten Gebiet komplexer Systeme. Hier soll gezeigt werden, wie diese Herangehensweise helfen kann, bekannte Beobachtungen in neuem Licht zu sehen und dadurch zu einem tieferen Verständnis epileptischer Anfälle zu gelangen. Letztlich sind Hoffnung und Ziel, dass ein tieferes Verständnis epileptischer Anfälle auch den Weg zu verbesserten diagnostischen und therapeutischen Möglichkeiten öffnet.

Schlüsselwörter: Quantitatives EEG, nicht lineare Dynamik, kritische Übergänge

Les crises et le système de l’épilepsie

Les crises d’épilepsie constituent la marque distinctive de l’épilepsie. On dispose de beaucoup d’informations sur les modifications moléculaires et cellulaires qui se produisent pendant les crises d’épilepsie, mais les processus ictiaux dynamiques à large échelle et leurs possibles répercussions sur les processus au niveau local ne sont que lentement de mieux en mieux compris. De nouvelles études utilisent à cet égard de plus en plus de méthodes et de concepts issus du domaine fascinant mais bien abstrait de systèmes complexes. On montre ici comment cette approche peut aider à voir sous un jour nouveau des observations connues et aboutir ainsi à une compréhension plus importante des crises d’épilepsie. En fin de compte, on espère et pose comme objectif qu’une compréhension plus approfondie des crises d’épilepsie ouvre aussi la voie à une amélioration des possibilités diagnostiques et thérapeutiques.

Mots clés : EEG quantitatif, dynamique non linéaire, passages critiques

Two observations about epilepsy are intriguing and challenging at the same time. First, despite many new “antiepileptic” drugs, the percentage of epilepsy patients who are rendered seizure free by current pharmacological treatment has not significantly increased over recent years. Second, despite most intensive transdisciplinary efforts, it is still not possible to predict epileptic seizures with a specificity that would allow for relevant improvements of clinical management. Both of these unpleasant facts may at least partially be due to our still far from complete understanding of epileptic seizures, which are the hallmark of epilepsy. It is rationale to assume that we first have to deepen our knowledge about seizure dynamics, i.e. how seizures initiate, propagate and terminate, before we will be able to better control this type of transient but extreme dys-coordination of neuro-glial activity. In particular, the intuitive concept of seizures as monolithic states of “hypersynchrony” has turned out to be too simplistic [1] and may even become misleading when developing new therapeutic approaches like trying to rationally design molecules or electric stimulation paradigms. Evidence has been accumulating that one way to advance our understanding of epileptic seizures might be to invoke modern concepts from systems [2, 3] and network theory [4 - 7].

What is a system?

The famous notion that "the whole is more than the sum of its parts" is attributed to Aristotle. This quote leads to the obvious question about what exactly is "more" or "additional" if one compares a "whole" to the plain "sum of its parts". Within the context of systems theory a straightforward answer is that "interactions" are what is the "more", interactions may constitute the crucial difference between a mere sum of parts and a "whole". **Figure 1** illustrates that there are (at least) two forms of interactions. First there are interactions between elements potentially giving rise to a functional whole ("bottom-up", smaller-scale to larger-scale effects) [3]. Then, there may be "top-down" (larger-scale to smaller-scale) interactions between "the whole" and its parts. Typical examples where this type of "circular causality" may occur are some of the most beautiful natural phenomena like flocks of birds, schools of fish or the synchronized collective signaling of fireflies. Importantly, all of these phenomena do not have a central coordinator, but are emergent from self-organizing interacting elements or agents. Another example of a self-organizing system where bottom-up and top-down influences become relevant is the stock market. Stock exchange is particularly interesting, because it is quantitative by its very nature. The fluctuating price of a stock is an immediate global measure of all the pairwise interactions between buyers and sellers. At the same time, the price of a stock is observed by the brokers and influences their decisions. Thus, stock exchange is another example of a complex system where circular causality reigns. In regard to cortical neurophysiology it has recently been demonstrated that endogenous electric fields that are generated by physiological neuronal activity should be strong enough to influence action potential firing of the very neurons that gave rise to these fields in the first place [8]. This finding might turn out to be particularly important for pathological neuronal activity, which probably generates even stronger endogenous electric fields that might then coordinate neuronal activity and play a role in seizure termination for example by promoting large-scale synchronization [9, 10].

Critical transitions

The large-scale patterns, the "functional whole", which may emerge in complex systems can undergo qualitative changes. If these changes happen abruptly, they have been referred to as so-called "critical transitions" [11, 12]. Typical instances of such critical transitions are crashes at the stock market, the occurrence of earth quakes, outbreaks of pathogens or climatic shifts. Of course, dramatic changes may be brought about by shock-like external influences like the extinction of the dinosaurs, which in one popular theory is attributed to the impact of an asteroid into our planet at the end of the cretaceous period approximately 65 million years ago [13]. However, the term "critical transition" typically refers to situations, when only small – external or internal – changes have dramatic consequences onto the dynamics of a system. One possibility for how small causes may have progressively larger effects is, if a system is brought to a so-called tipping point, i.e. from a stable to a less stable, then marginally stable and finally unstable state. A ball in a trough may serve as an intuitive example for this process. In **Figure 2A** the ball is placed into a relatively deep trough. If it is exposed to

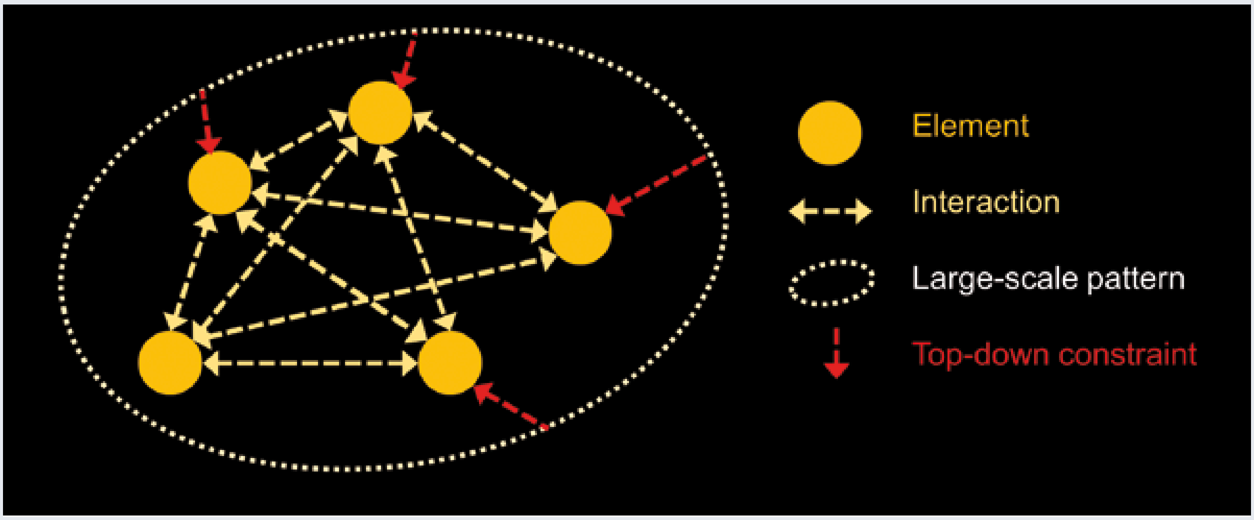

Figure 1. Abstract representation of a system. Displayed are elements, their interactions, the emerging large-scale pattern or "functional whole" and its top-down constraints on the elements.

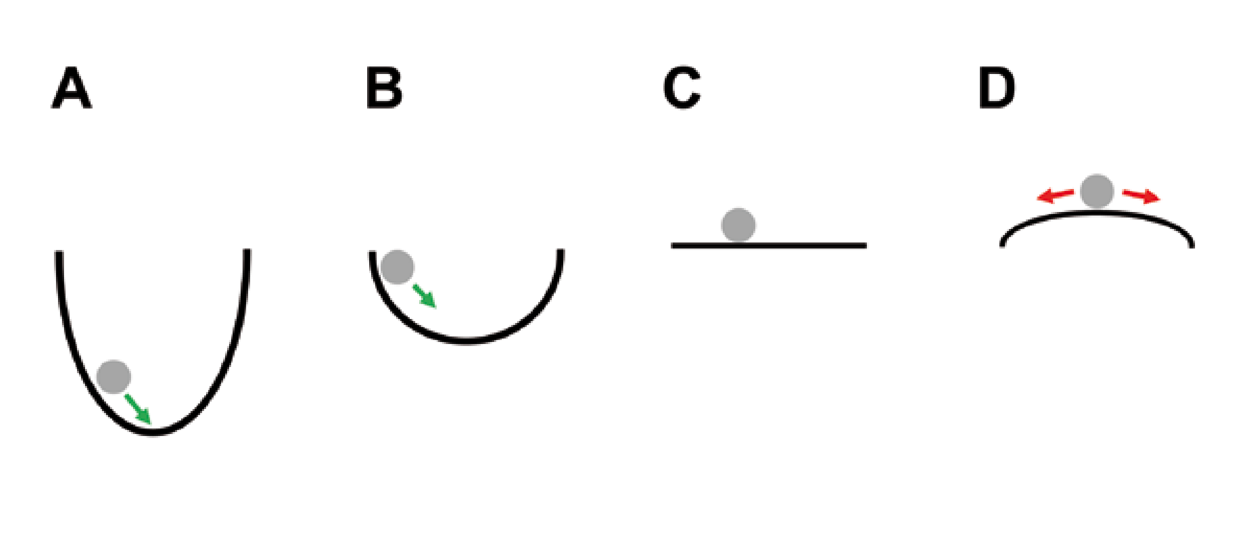

Figure 2. A ball exposed to random perturbations and located in different surroundings – from a trough to a bulge – is an illustrative mechanical example of a system that changes from a stable (A) to a less stable (B), then marginally (C) and finally unstable state (D).

some perturbations, it will be driven back towards the stable equilibrium at the bottom of the trough. If the trough becomes shallower, then the restoring forces diminish (**Figure 2B**). Importantly, if the ball is exposed to a similar perturbation as before, it will be pushed away further from the bottom of the trough and it will take longer to return. In the case of a completely even plane (**Figure 2C**), the ball will never return back to where it was pushed away from. Finally, if the surface starts to bulge it will lift the ball into an unstable equilibrium. In this situation, even tiny perturbations will have large effects and the ball will be driven away from the top of the bulge (**Figure 2D**). In other words, the system is at a "tipping point". This simplified mechanical example demonstrates two pre-cursors of critical transitions that have been observed in many other, much more complicated systems, namely "critical" slowing down and increasing variance [14]. Other typical dynamical signatures heralding dramatic changes of system behavior are increasing spatio-temporal correlations and so-called flickering. The latter refers to the phenomenon that a system may jump between different co-existing stable states that are separated by unstable ones.

Seizure termination as a critical transition

In an important and highly original recent paper, Kramer et al. [15] pointed out that the EEG signals recorded during an epileptic seizure have many of the characteristics observed during critical transitions in other systems. In particular – as is illustrated in **Figure 3A** for the intracranial EEG (iEEG) recorded during a temporal lobe seizure of one of our patients undergoing presurgical evaluation for pharmaco-resistant epilepsy – towards seizure termination EEG signals become slower, their variance increases and synchronization (here measured as the total correlation strength [16]) strongly increases (**Figure 3c**). Furthermore, towards the end of the seizure, there are "bursts" of activity, i.e. short and large amplitude signals separated by brief periods of flattening, which may be interpreted as flickering, assuming that the ictal and post-ictal dynamics are represented by two stable and coexisting states. In **Figure 4** this situation is illustrated using again the simplified mechanical model of a ball exposed to random perturbations and moving in or between troughs. The two troughs shown in **Figure 4A** represent the ictal and the post-ictal state, which are thought to co-exist towards the end of the seizure. The ictal state becomes less and less stable (i.e. the trough levels out), while the post-ictal state gains stability. In a simulation study, Kramer et al. [15] identified changes of excitatory synaptic strength as a possible parameter for controlling the stability of the large-scale dynamical states. Both states co-existing, brain dynamics will jump between ictal dynamics characterized by large-amplitude EEG signals and the post-ictal state with low amplitude EEG signals. At the moment, when the ictal state loses its stability the high-amplitude EEG signals will stop immediately and to speak in terms of the figurative mechanical model the ball will drop into the only deep trough that remains.

Interestingly, in their landmark paper, Kramer et al. [15] found most of the pre-cursors of critical transitions on larger spatial scales and not on the single-unit level, which is consistent with the concept that global dynamics may constrain local processes, i.e. that the "top-down" (larger-scale to smaller-scale) constraints become stronger towards the end of the seizure and in the post-ictal time period.

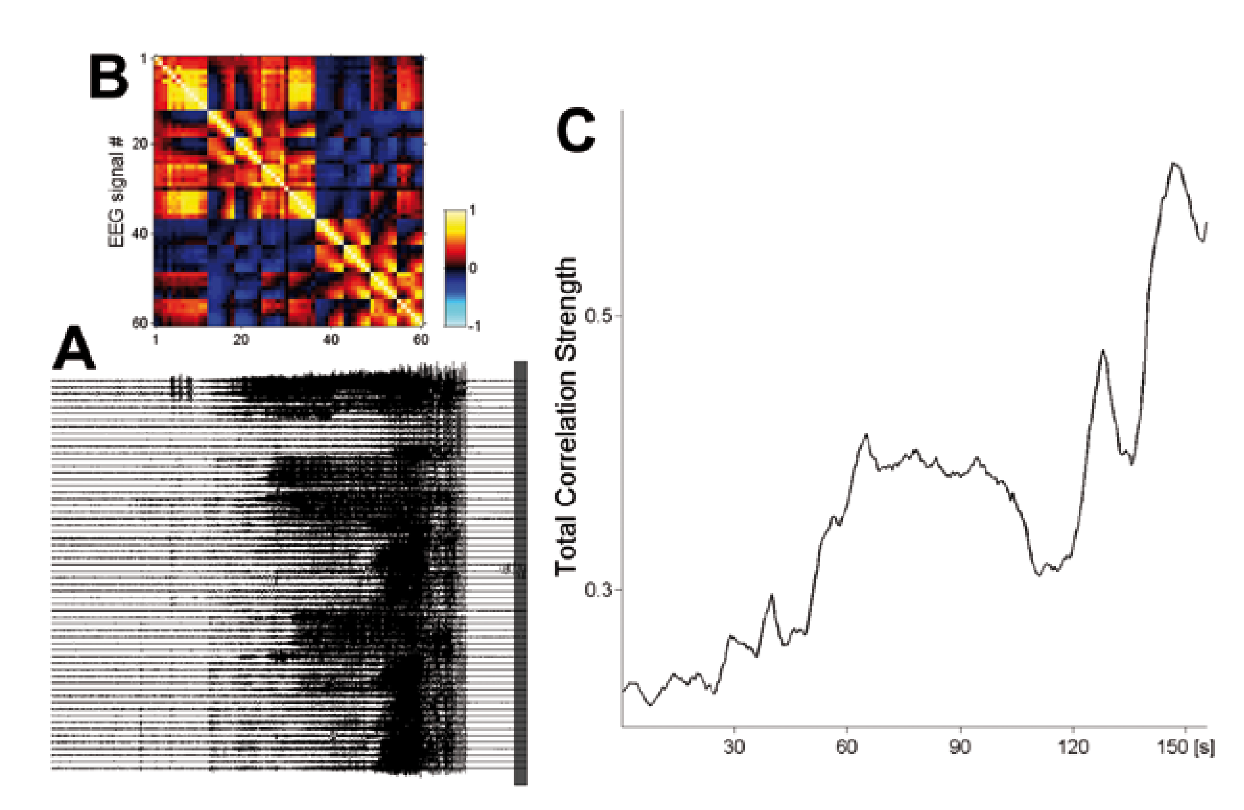

Figure 3. Ictal intracranial EEG changes recorded during a temporal lobe seizure and consistent with a critical transition. A. Note how the signals become slower, their amplitudes increase towards the end of the seizure and how the seizure abruptly stops after the occurrence of a series of bursts, i.e. generalized high-amplitude EEG signals of short duration and separated by periods of flattening. These signal changes may be interpreted as critical slowing down, increasing variance and flickering between two stable states. The shaded rectangle at the end represents the moving window with a duration of 4s, which was shifted along the recording in steps of 1s. For each time step the slope cross correlation matrix [2] (B) and the total correlation strength [16] as a large-scale measure of synchronization (C) have been computed for the EEG signals contained within the moving window. Clearly, synchronization during the seizure reveals a complicated increasing and decreasing time course. Importantly, towards seizure end and in the post-ictal state synchronization is significantly larger than before the seizure (C).

Summary, caveat and outlook

The key point of this article is that modern concepts of systems theory may help to better understand epileptic seizures by promoting new interpretations of long known observations. In particular, changes of EEG signal characteristics before, during and after seizure termination are consistent with a so-called critical transition.

Here, it is important to stress that systems-inspired approaches to seizure dynamics are not a form of naive "anti-reductionism". Specific characteristics of the elements and their interactions remain crucial for any practical application, even if the large-scale dynamics reveal patterns that may also be observed in systems consisting of completely different elements. Or, put more bluntly: the brain is neither a school of fish nor a flock of birds, and applying a "one size fits all" approach – though often intellectually seductive – was not successful in many other fields and also won't work for epileptology [17]. However, if one takes this caveat seriously and does not lose sight of the particularities of a specific system under study, the concepts described in this article have definitely the potential to advance our understanding of seizure dynamics. Maybe they will even help to pursue therapeutic concepts that might otherwise seem completely irrational. For example if seizure termination corresponds to a critical transition that is promoted by strong synchrony, then one might test drugs that increase the propensity for neurons to increase and synchronize their activity. Substances that increase the excitability of dendrites [18] and thus render neurons more sensitive for distal synaptic inputs might then turn out to have seizure terminating effects. If one follows classical concepts of ictogenesis, which state that seizures are solely due to "excessive" and "hypersynchronous" neuronal output, then one would focus – as is generally done – on drugs that have contrary effects like hyperpolarizing neuronal membranes by either enhancing outward or blocking inward ion currents.

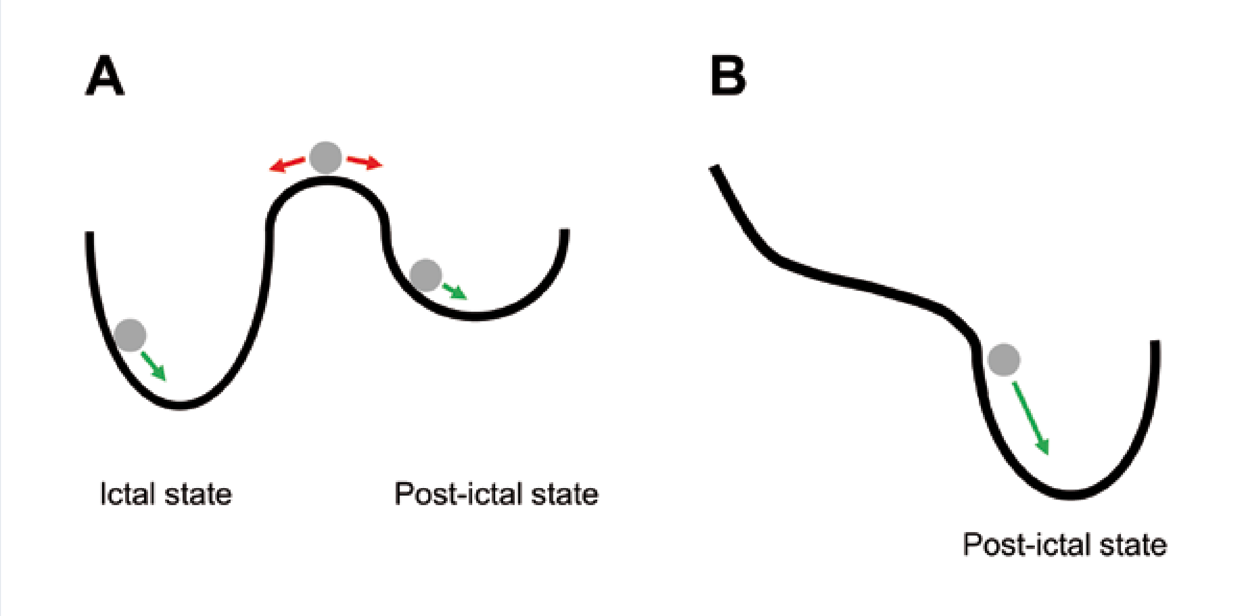

Figure 4. Vanishing bistability of states as a model for a critical transition. A. Towards the end of the seizure there may exist two stable and one unstable state. The system – represented by the ball exposed to perturbations – will spend most time in the most stable state, i.e. in the deepest trough. B. Seizures may then terminate suddenly when the ictal state loses its stability and – to use the figurative example – the ball falls into the only remaining deep trough, which represents the post-ictal state. In a computational study of seizure termination Kramer et al. [15] identified the strength of excitatory synapses as a parameter that controls the stability of large-scale dynamic states, i.e. the "force" that shapes the landscapes of troughs and bulges.

One of the possible reasons why the notions of complex systems theory and networks have not yet become part of standard medical training (and textbooks) is that they are often presented in an unnecessarily formal and distinctly mathematical way. While there is no doubt, that in the longer run one has to work through at least some mathematics to attain a deeper level of understanding, some truly brilliant authors have been able to explain clearly the main points of the theory of complex systems in a non- or at least less technical way. Below I list – in order of increasing mathematical content – four of these gems of "popular" (in the best sense of the word) scientific writing that I would highly recommend to anyone interested in a more profound but still readable introduction to the fascinating field of complex systems. Personally I am convinced that the theory of complex systems and its associated set of powerful analysis tools will open the door to a better understanding of epileptic seizures and thus ultimately help us to improve our diagnostic and therapeutic methods.

Non- or less technical introductory books about complex systems

- Steven H. Strogatz. Sync: How Order Emerges from Chaos in the Universe, Nature, and Daily Life. Hyperion, 2004: ISBN-10: 0786887214

- Malcolm Gladwell. The Tipping Point: How Little Things Can Make a Big Difference. Back Bay Books, 2002: ISBN-10: 9780316346627

- Albert-Laszlo Barabasi. Linked: How Everything Is Connected to Everything Else and What It Means for Business, Science and Everyday Life. Plume, 2003: ISBN-10: 0452284392

- Marten Scheffer. Critical Transitions in Nature and Society. Princeton Studies in Complexity, 2009: ISBN-10:0691122040

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