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A Straw Can Break a Neural Network's Back and Lead to Seizures—But Only When Delivered at the Right Time

Loss of Neuronal Network Resilience Precedes Seizures and Determines the Ictogenic Nature of Interictal Synaptic Perturbations

Chang WC, Kudlacek J, Hlinka J, et al. *Nat Neurosci*. 2018; 21(12):1742-1752. doi:10.1038/s41593-018-0278-y. PMID: 30482946.

The mechanism of seizure emergence and the role of brief interictal epileptiform discharges (IEDs) in seizure generation are 2 of the most important unresolved issues in modern epilepsy research. We found that the transition to seizure is not a sudden phenomenon, but is instead a slow process that is characterized by the progressive loss of neuronal network resilience. From a dynamical perspective, the slow transition is governed by the principles of critical slowing, a robust natural phenomenon that is observable in systems characterized by transitions between dynamical regimes. In epilepsy, this process is modulated by synchronous synaptic input from IEDs. The IEDs are external perturbations that produce phasic changes in the slow transition process and exert opposing effects on the dynamics of a seizure-generating network, causing either antiseizure or proseizure effects. We found that the multifaceted nature of IEDs is defined by the dynamical state of the network at the moment of the discharge occurrence.

Commentary

Seizure prediction is, for good reason, one of the holy grails of epilepsy research. See a seizure coming, and you can give a patient an early warning sign, or initiate a closed-loop intervention. To predict a seizure, you first need a good theory that might provide clues about what kinds of changes might precede the start of a seizure. With a good theory in hand, you then need to record a useful brain signal that might be decoded to reveal some of the early warning signs your theory tells you to look for. With a good signal being reliably recorded, you then need a smart deciphering algorithm that truly offers predictive power. Finally, once you know a seizure is coming, you can ask how internal events (such as interictal spikes) or external interventions (such as electrical stimulation) could either promote or delay the start of the upcoming seizure, offering insights into mechanisms and hopefully suggesting strategies for closed-loop seizure prevention. A recent study by Chang et al in *Nature Neuroscience* combines aspects of each of these steps to come to the conclusion that neural networks lose their "resilience" well before a seizure starts, making it far easier for a previously harmless interictal spike to now trigger a full-fledged seizure.

Let's start with the theory. Neural networks behave nonlinearly: their overall behavior is not easily predictable from the activity of their underlying ion channels, neurons, and synapses. Dynamical systems theory offers a powerful geometric and analytical framework for thinking about the behavior of such nonlinear systems and has been extensively used to model what causes the dramatic transitions between normal and epileptic brain states.[1-3] These models are characterized by the so-called stable and unstable fixed points, regimes of the system that are either attracting or repelling, respectively. When a neural network is in a stable healthy regime, perturbations (inputs) such as sensory or electrical stimulation, or even interictal spikes,[4,5] cannot easily switch this system into an epileptic state—the network absorbs the hit; it shakes, but remains resilient and quickly returns to its stable fixed point in the normal regime. All is well and the healthy regime is still standing strong. However, as a key parameter of the network—its overall excitability—slowly increases, the network becomes less resilient to perturbations. Exactly the same input as before, be it an interictal spike or electrical stimulation, can now severely rattle this excitable network and lead to catastrophic changes (for the aficionados: a fold bifurcation best describes this whole process). The healthy regime now falls dramatically and suddenly, replaced by an epileptic regime. The battle has been lost. The apparent culprit: the interictal spike or electrical stimulation. The real, hidden culprit: that mysterious, slowly changing excitability parameter.

Now for the prediction bit. Is there a warning sign for this progressive network instability, for this slow loss of resilience? In dynamical systems theory, the process leading to the tipping

point is often characterized by "critical slowing" (not to be confused with the slowing seen in some electroencephalogram signals during and after seizures). Critical slowing refers to the fact that as a network starts to lose its resilience, it is much slower to recover from any perturbations. This suggests a possible way to probe a neural network to see if it is starting to lose its resilience: weakly stimulate it at different times and see how long it takes to return to baseline. When the network starts to take a very long time to recover, then there might be a seizure around the corner. This is exactly what Chang et al demonstrated. First, using a high potassium hippocampal slice model, they showed that during the ~60 second interictal period seen in their prep, high frequency activity was not constant but tended to ramp-up well before the start of the next seizure. The same was true of other spontaneous metrics assessing the spatiotemporal spread of network activity, with the autocorrelation and spatial correlation of the local field potential (LFP) signals also increasing during the interictal period and the direct current potential showing progressively negative shifts. Most importantly in terms of consistency with the critical slowing theory, they showed that stimulation of inputs to CA1 (analogous to small perturbations) led to progressively longer lasting responses, with line length of the response peaking before the start of the next seizure. Thus, the high potassium slice seizure model clearly showed some of the hallmarks suggested by the critical slowing theory, consistent with a loss of network resilience.[2,6]

Do these predictions regarding network resilience hold in vivo? Chang et al looked for signs of critical slowing in a preclinical tetanus toxin model of hippocampal seizures, as well as in long-term recordings from patients with epilepsy.[7] Some evidence of early warning signs was seen in each, albeit with important caveats. Not all of the spatiotemporal metrics that were significant in the slice were also significant in the tetanus toxin model, with the autocorrelation and variance not changing significantly in between seizure clusters. These 2 metrics would have been expected to increase based on the critical slowing theory. Similarly, in the human data, only 4 of the 12 patients examined showed increases in the autocorrelation in the 30 minutes before the seizure. In another 4 patients, the autocorrelation significantly decreased over the same preseizure time frame, and was not significant in the remaining 4. Even if the critical slowing principle applied to a particular seizure, it is not trivial to find consistent early warning signs of a lack of resilience in fully intact circuits in vivo. There are several reasons for this. The mysterious, slowly changing excitability parameter is likely to correspond to a variety of underlying biological variables (altered potassium or chloride levels, impaired inhibition, synaptic failure, among many others), and each of these might lead to important differences in how the loss of network resilience manifests itself. Large-scale single unit recordings may have provided more insight than the LFP-only signals recorded by the authors in their chronic seizure model. Furthermore, the precise positioning of electrodes with respect to the seizure focus is obviously of immense importance in being able to record signals that capture appropriate early warning signs. This can be especially difficult when it comes to human epilepsy, where precise targeting of the seizure focus is not trivial, and seizures can start due to a tremendous range of etiologies, corresponding to a wide variety of biological excitability parameters.

Why might this be clinically important? In particular, can we use this information to somehow delay or prevent seizures? In their slice model, Chang et al compared the effects of electrical stimulation delivered at different times on the duration of the interictal period. As expected, moderate to strong electrical stimulation late in the interictal period was enough to start the next seizure (since the network had already lost its resilience). However, stimulation early in the interictal period (soon after the previous seizure) actually appeared to extend the interictal period, delaying the expected time to the next seizure. This might have important implications. Devices such as the Responsive Neurostimulator[8] try to decrease seizure frequency by delivering electrical stimulation in response to subtle changes in the LFP. Such devices might be able to further improve their efficacy by only stimulating when no early warning signs of a critical slowing are visible, potentially helping to reinforce the network while it is still resilient. However, the most difficult aspect of this will be to prove that reliable early warning signs can indeed be observed in the vast majority of patients with different kinds of seizures.[7] Despite the challenges ahead, the work by Chang et al represents an insightful, integrative step in combining theory, experiment, and analysis of both preclinical and clinical data to move our understanding of seizure initiation mechanisms forward.

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