EPILEPSY CURRENTS

Current Literature
In Clinical Science

Long-Term Patterns of Seizure Recurrence: Estimating Risk From Ambulatory Intracranial EEG Recordings

Multi-Day Rhythms Modulate Seizure Risk in Epilepsy.

Baud MO, Kleen JK, Mirro EA, Andrechak JC, King-Stephens D, Chang EF, Rao VR. *Nat Commun* 2018;9:88.

Epilepsy is defined by the seemingly random occurrence of spontaneous seizures. The ability to anticipate seizures would enable preventative treatment strategies. A central but unresolved question concerns the relationship of seizure timing to fluctuating rates of interictal epileptiform discharges (here termed interictal epileptiform activity, IEA), a marker of brain irritability observed between seizures by electroencephalography (EEG). Here, in 37 subjects with an implanted brain stimulation device that detects IEA and seizures over years, we find that IEA oscillates with circadian and subject-specific multidien (multi-day) periods. Multidien periodicities, most commonly 20–30 days in duration, are robust and relatively stable for up to 10 years in men and women. We show that seizures occur preferentially during the rising phase of multidien IEA rhythms. Combining phase information from circadian and multidien IEA rhythms provides a novel biomarker for determining relative seizure risk with a large effect size in most subjects.

Commentary

It is probably the unpredictability of seizures that is the single most disabling feature of epilepsy for our patients. Individual seizures, even when associated with loss of awareness and motor control, are usually brief and self limited. The risk of physical injury (or worse) that accompanies seizures can be mitigated when the patient is in a safe position and environment and attended to by others. Even among patients with quite refractory forms of epilepsy (multiple seizures per day), most likely spend only a very small temporal fraction of their lives actually in the middle of a seizure or postictal state. The fact that we cannot predict that small fraction of time during which a patient may be dangerously impaired, however, makes all the difference. If we knew with certainty the timing of upcoming ictal events, then even patients with frequent seizures could plan ahead, take measures to ensure their safety, suffer less anxiety regarding the uncertainty of their next seizure, and might very well be allowed to drive and partake in other restricted activities at appropriate times.

While we are not yet at the stage of being able to predict the timing of seizures with the necessary degree of reliability in most patients, it has been quite clear for some time that seizures are not, in any sense of the word, random. Even decades ago the tendency of seizures to occur at certain times of day or at recurring intervals of days or weeks was clearly recognized in particular individuals (1). In the current era, however, we have a tool that has not previously been available, one that may revolutionize our understanding of rhythms of epileptic activity over long timescales: ambulatory intracranial EEG recording, such as with the responsive neurostimulator (RNS) (2).

Baud et al. studied 37 subjects with implanted responsive neurostimulation devices (NeuroPace, Inc., Mountain View, CA), which allow for access to long-term intracranial EEG data acquired in patients' natural environments. By examining the periodicity with which the interictal epileptiform activity (IEA) and ictal events occurred in these patients, who had recording durations ranging from approximately 3 months to nearly 10 years, the investigators were able to look for evidence of both circadian and multiday rhythms that influence the underlying risk of epileptic brain activity.

There are several notable findings from this work:

1. Although the exact periodicity of multiday rhythms in IEA differs from subject to subject, within each individual these periods are quite stable over many years, with the most common multiday pattern having a periodicity of 20 to 30 days.

2. Seizures are most likely to occur not necessarily when IEA are at their highest occurrence, but rather on the rising phase of the IEA multiday rhythms. As the authors note, this result can potentially serve to reconcile some prior conflicting data about the rate of interictal discharges and the likelihood of seizure occurrence.

3. Combining the influence of circadian and multiday rhythms to estimate the risk of a seizure occurring at a particular

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time can lead to some fairly large effect sizes in some patients, raising the tantalizing possibility of more reliable predictive algorithms in the future.

4. Perhaps nonintuitively, the power of these circadian and multiday rhythms in identifying seizure risk seems to be higher in those who have a relatively low seizure frequency, and lower in those who have a relatively high seizure frequency.

As the authors acknowledge, we must exercise some caution in our interpretation of these otherwise exciting and novel results. Their subjects were epilepsy patients refractory enough to consider neurosurgical intervention and yet not amenable to focal resection, usually because of multiple foci (mostly mesial temporal), so they represent a fairly narrow segment of the broader epilepsy population. Raw EEG data are generally not available for review in the RNS system due to data storage limitations, so most of these analyses are based on the device's counts of IEA and ictal events (which depend on programmed parameters that are optimized by treating clinicians over time). The reliability of detecting actual ictal events by the RNS is indeed imperfect (though the authors take pains to minimize the chance of including "false-positive" seizure detections).

The results of this study and other work in recent years that has also taken advantage of data from long-term ambulatory intracranial EEG recording systems (3, 4) have both long- and short-term implications for clinical care. On the longer time horizon, these findings contribute to our growing knowledge of the underlying biological rhythms that may contribute to clinically discernible patterns of seizure occurrence and may ultimately lead to more robust prediction algorithms. In the short term, though, I for one am much less likely now to say to patients that seizure occurrence is "random" or that perceived patterns in their seizures are misperceptions of purely stochastic events. Even though it appears that for most subjects in this study, the periodicity of their seizure risk was not actually clinically apparent, as a field we are learning that underlying oscillations in seizure tendency are robust and generally stable over time, and thus form an attractive target for prognostic and therapeutic advances.

by Bernard S. Chang, MD

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