Catch the Rhythm!

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Thalamic Deep Brain Stimulation Modulates Cycles of Seizure Risk in Epilepsy

Gregg NM, Sladky V, Nejedly P, et al. *Sci Rep.* 2021;11:24250. doi:10.1101/2021.08.25.21262616.

Chronic brain recordings suggest that seizure risk is not uniform, but rather varies systematically relative to daily (circadian) and multiday (multidien) cycles. Here, one human and seven dogs with naturally occurring epilepsy had continuous intracranial EEG (median 298 days) using novel implantable sensing and stimulation devices. Two pet dogs and the human subject received concurrent thalamic deep brain stimulation (DBS) over multiple months. All subjects had circadian and multiday cycles in the rate of interictal epileptiform spikes (IES). There was seizure phase locking to circadian and multiday IES cycles in five and seven out of eight subjects, respectively. Thalamic DBS modified circadian (all 3 subjects) and multiday (analysis limited to the human participant) IES cycles. DBS modified seizure clustering and circadian phase locking in the human subject. Multiscale cycles in brain excitability and seizure risk are features of human and canine epilepsy and are modifiable by thalamic DBS.

Commentary

Over 30 antiseizure medications have been approved for human use; however, they are not always effective, and many patients with epilepsy live in constant fear of when their next seizure will occur. Even when medications control seizures, they sometimes have serious side effects that limit their use. More effective and less toxic antiseizure interventions are therefore needed, and a better understanding of seizure triggering mechanisms is expected to speed the development of such therapies.

Although our insight into seizure triggering mechanisms remains limited, there is increasing evidence that chronobiological factors are involved. Sir William Gowers was the first to report daily (circadian) patterns of seizure vulnerability in patients with epilepsy.[1] (Note, that circadian is used synonymously with daily in this commentary, although some authors restrict the use of circadian to daily rhythms that are driven by an endogenous circadian clock). Later studies confirmed and extended Gowers' findings. For example, in an intracranial EEG study of 131 adult humans with focal epilepsies, Durazzo et al. found that the region of seizure onset was an important determinant for the time of seizure risk during the circadian cycle.[2] Occipital and parietal lobe seizures occurred in strong Gaussian-like distributions, 180 degrees out of phase with each other, and frontal and mesial temporal lobe seizures also exhibited unique seizure risk profiles. A more recent study using long-term recordings of brain activity from 37

patients with an implanted responsive neurostimulation device (RNS, NeuroPace), has shown that the rate of interictal epileptiform activity (IEA)–a marker of brain irritability–not only exhibits distinct circadian patterns, but also intriguing multidien (multi-day) patterns.[3] The authors demonstrated that seizures occurred preferentially during the rising phase of multidien IEA cycles, suggesting the presence of a second rhythm which underpins seizure risk and a possible link between interictal activity and seizures. These observations have since been extended, and multidien IEA rhythms have been reported in data acquired with other implantable devices including in naturally occurring canine epilepsy and in mouse models of epilepsy, indicating that these are robust and reproducible features of epilepsy across multiple species.[4-8]

It is not known, however, whether these circadian and multidien rhythms can be modulated to prevent seizures more effectively and with fewer side effects than the current standard of care. As a first step towards addressing this issue, Gregg et al used two novel brain implantable investigational devices (NeuroVista Seizure Advisory System (NeuroVista) and Summit RC + S (Medtronic)) to record interictal epileptiform spikes (IES) and EEG activity. Nineteen dogs and one human with naturally occurring epilepsy were each implanted with one of these devices. Eight of the subjects–one

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human and seven dogs–met the inclusion criteria for the current study. Three of the subjects, one human and two dogs, had the RC + S device with electrodes placed bilaterally in the anterior thalamic nuclei and the hippocampus. The other subjects had either the NeuroVista device placed with subdural strip electrodes or were converted from the NeuroVista device to the RC + S device, but with subdural strip electrodes. The subjects had a median recording duration of 298 days, during which a median of 45 seizures were recorded. All subjects had circadian IES cycles. Some of the animals had ultradian cycles, with the most pronounced cycle occurring every 12-hour in the two dogs implanted with the RC + S device and electrodes placed bilaterally in the thalamus and hippocampus. Many of the subjects had multidien cycles, and seizures were locked to circadian and multidien IES cycles in five and seven of the eight subjects, respectively.

The one human and two dogs with the RC + S device and bilateral thalamic and hippocampal electrodes received continuous, deep brain stimulation (DBS) to the thalamus over several months. The stimulation modified circadian (all three subjects) and multidien (analysis limited to the human participant) IES rhythms. Although some findings were evident in the two dogs which received DBS, limited adherence to the monitoring protocol precluded a full assessment of the effects of stimulation on IES cycles in the dogs. The authors showed that low-frequency thalamic stimulation modulated IES cycles by reducing the amplitude of circadian IES cycles in the human subject. High frequency stimulation had the opposite effect on multidien (13–21-day) IES cycles in the human subject, enhancing the amplitude of this cycle. Moreover, the authors found that thalamic stimulation had a significant impact on the burden of clustered seizures (seizures that occur within 24 h of a preceding seizure) in the human subject. High-frequency stimulation increased the burden of clustered seizures relative to baseline and low frequency stimulation, while low-frequency stimulation did not have an effect. The increased seizure burden of *clustered* seizures after high-frequency stimulation is unexpected. However, the data should be interpreted with caution because it is based on a single human with epilepsy and therefore may not be generalizable to the larger patient population.

The study by Gregg et al. is the first evidence that DBS can be used to modulate circadian and multidien cycles of IES. Deep brain stimulation is approved by the US Food and Drug Administration (FDA) to treat Parkinson's disease, essential tremor, dystonia, refractory obsessive-compulsive disease, and severe epilepsy. RNS and DBS devices have been approved for epilepsy treatment by the FDA, and additional devices are being evaluated in laboratory or clinical trials. As with the RNS and RC + S devices, the main features of newer devices are that they are closed loop feedback control devices which continuously monitor brain activity and stimulate when a programmable detection criterion is met. With each successive generation the devices can be expected to have a larger number of channels to monitor network locations more comprehensively, more powerful customizable feature

detectors, and more memory to store EEG and feature detections for review. The strength of the present study is that it uses clinically relevant technologies to monitor and modulate circadian and multidien IES cycles in subjects with naturally occurring epilepsy. While this places the study on the path towards possible clinical use, additional issues remain to be resolved such as the efficacy of the approach and potential side effects.

While the modulatory effects of thalamic stimulation on circadian and multidien rhythms are intriguing, several gaps in knowledge remain. First, the unexpected increase in IES cycle amplitude and seizure clustering burden after high-frequency stimulation suggest further studies of the impact of stimulation on these aspects in conjunction with studies of the impact of stimulation on total seizure count. Second, the roles of different stimulation parameters (e.g., continuous vs duty cycle, and the frequency of stimulation) on IES cycles and seizure clustering remain to be established in larger patient populations. Third, it is possible that inter-individual differences in the location of the seizure onset area explains the lack of group level phase preference of seizure timing relative to the circadian spike rate cycle, as shown in other studies.[2,9] The authors targeted the thalamus using two different stimulation parameters, and it remains an open question whether stimulation of other brain regions using the same or different paradigms would be more effective in reducing the seizure clustering burden or in modulating the joint phase of the circadian and multidien rhythms which appears to maximally modulate seizure risk.

Although many of the molecular mechanisms of circadian rhythms have been established, very little is known about the underlying biology of multidien rhythms in epilepsy. A larger sample size with sufficiently long recording and stimulation sessions will be necessary to establish the reproducibility of the results. Studies of multidien cycles are challenging because of the protracted nature of these processes (weeks to months) making such studies laborious, costly, and slow to perform. The development of newer wearable and implantable technologies and their design for long-term use offer a possible avenue for improved traction for monitoring, understanding, and modulating circadian and multidien rhythms in epilepsy.

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