

INTERICTAL SPIKES: MEMORIES FORSAKEN

Hippocampal Interictal Spikes Disrupt Cognition in Rats. Kleen JK, Scott RC, Holmes GL, Lenck-Santini PP. *Ann Neurol* 2010;67(2):250–257. **OBJECTIVE:** Cognitive impairment is common in epilepsy, particularly in memory function. Interictal spikes (IISs) are thought to disrupt cognition, but it is difficult to delineate their contribution from general impairments in memory produced by etiology and seizures. We investigated the transient impact of focal IISs on the hippocampus, a structure crucial for learning and memory and yet highly prone to IISs in temporal lobe epilepsy (TLE). **METHODS:** Bilateral hippocampal depth electrodes were implanted into 14 Sprague-Dawley rats, followed by intrahippocampal pilocarpine or saline infusion unilaterally. Rats that developed chronic spikes were trained in a hippocampal-dependent operant behavior task, delayed-match-to-sample. Depth-electroencephalogram (EEG) was recorded during 5,562 trials among five rats, and within-subject analyses evaluated the impact of hippocampal spikes on short-term memory operations. **RESULTS:** Hippocampal spikes that occurred during memory retrieval strongly impaired performance ($p < 0.001$). However, spikes that occurred during memory encoding or memory maintenance did not affect performance in those trials. Hippocampal spikes also affected response latency, adding approximately 0.48 seconds to the time taken to respond ($p < 0.001$). **INTERPRETATION:** We found that focal IIS-related interference in cognition extends to structures in the limbic system, which required intrahippocampal recordings. Hippocampal spikes seem most harmful if they occur when hippocampal function is critical, extending human studies showing that cortical spikes are most disruptive during active cortical functioning. The cumulative effects of spikes could therefore impact general cognitive functioning. These results strengthen the argument that suppression of IISs may improve memory and cognitive performance in patients with epilepsy.

COMMENTARY

Even in 2010, the epilepsy community is debating the fundamental definition of a seizure—witness the recent point-counterpoint articles in the pages of this journal (1,2). At issue is the duration of electrographic discharges that constitutes a clinical seizure, which speaks to the uncertainty of where the divide between interictal and ictal begins. Clearly, if very brief discharges can be shown to be associated with a clinical alteration in motor activity, responsiveness, memory function, or other classic features of a seizure, it would support the case that such a discharge comprises a clinical seizure. Whether considered ictal or interictal, brief spikes that cause transient cognitive dysfunction deserve serious attention and respect in clinical practice to avert intellectual deficits.

This debate is not new: there is a long history of attempts to define the duration of an interictal discharge that causes an interruption of consciousness. In clinical practice, such a determination is fraught with difficulties, including identifying the site of origin of the interictal discharges, ascertaining whether the spikes are focal versus generalized, and establishing whether a particular number or frequency of discharges is required to produce a measurable alteration in cognition. What is the optimum testing paradigm (e.g., motor vs cognitive, which cognitive test should be used)? How can a test be administered rapidly enough to determine whether the spikes will affect outcome? Do interictal discharges in various regions or depths of the brain or those stemming from different epilepsy syndromes

cause discrete kinds of cognitive impairment? It is crucial to address these questions, because they verify whether or not interictal discharges warrant aggressive anticonvulsant treatment (3).

One approach to addressing these questions is to use an animal model. As occurs with other issues in epilepsy research, animal models do not exactly mimic the human situation, but do allow the investigator to study aspects that cannot be examined in humans. For instance, depth electrodes can be used in animals, whereas this technique is impractical or unethical in patients. In addition, a variety of seizure-induction methods can be used to create various areas of neuronal damage or mimic epilepsy syndromes, and the animals can be subject to multiple testing procedures, if appropriate. Electrophysiological and histopathological studies can test hypotheses about the localization of interictal spikes and their distribution as well as identify the type of cellular dysfunction. The challenge is to design a test that has relevance to the cognitive processes of humans.

In this context, Kleen and colleagues devised a clever experimental protocol to test the effects of interictal spikes on cognition in adult rats. Pilocarpine was injected into one hippocampus, producing a syndrome of limbic seizures akin to human temporal lobe epilepsy. After a period of status epilepticus, interictal discharges appeared in both hippocampi, as measured by depth electrodes implanted into each hippocampus. Once a baseline frequency of interictal spikes was established, the investigators could employ a behavioral test specifically chosen to assess memory function. They could then assess whether the occurrence of interictal spikes affected short-term memory.

The investigators used the delayed-match-to-sample (DMTS) test, which is a test of hippocampal integrity. In this test, a rat is briefly presented a lever, which suddenly appears on one wall of the apparatus, to one side of a pellet dispenser. The rat is then trained to poke its snout into a hole on the opposite wall of the chamber. Then, after a variable and controllable delay, two levers are shown—the original one plus a second lever on the other side of the dispenser. The rat must remember which of the two levers appeared first and then depress it to receive a food reward. The unique advantage of the DMTS test is that three phases of memory function can be assessed separately: 1) encoding (related to initial sample presentation), 2) maintenance (correlated with delay time), and 3) retrieval (determined by pressing the correct lever). Furthermore, once both levers appear, the delay in response to lever pressing can be measured; variation in this latency is an additional indicator of an effect of interictal spikes. A further advantage of the paradigm is that each rat serves as its own control, as memory functions can be compared during periods of interictal spiking and periods without interictal spikes in the same animal.

The results provide an intriguing conclusion. Analysis of over 5,000 trials showed that interictal spikes diminished only the retrieval phase of memory function, leaving encoding and maintenance unscathed. In addition, interictal spikes were associated with significantly longer response latencies, adding more than half a second to the response latency in trials without interictal spikes. The investigators controlled for potential confounding factors, such as the rat's state of vigilance or attention as well as effects resulting from spontaneous seizures, ensuring that the experimental results correlated best with the occurrence of interictal spikes.

These findings provide new fodder for the debate as to whether interictal spikes affect cognition. Interictal spikes not only impair memory but also selectively alter the subcomponent of memory function responsible for retrieval of information, that is, the laying down of new memories and encoding them. The concern immediately arises whether cumulative effects of interictal spikes over long periods of time lead to long-lasting rather than just transient cognitive disruption. To the extent that the results can be extrapolated to patients, the obvious question is whether aggressive treatment to reduce

interictal spikes might improve selective aspects of cognition, in this case, memory retrieval. Those experiments remain to be performed in rodents. Another caveat is that not all interictal spikes are created equal. Rolandic spikes are frequent, yet cognitive changes are usually subtle in rolandic epilepsy (4). In contrast, the slow spike waves of Lennox-Gastaut syndrome are considered a biomarker for profound mental impairment. Therefore, the brain region supporting interictal spikes and their pathological context are critical determinants of cognitive disruption. Whether or not interictal spike reduction would lead to cognitive enhancement or a better quality of life in patients also remains unresolved. Finally, anticonvulsants themselves are associated with deficits of cognition and alertness, so they do not constitute a panacea—not to mention the fact that anticonvulsant drugs are more effective at suppressing seizures than at getting rid of interictal spikes (5).

The major significance of the results by Kleen et al. is that they establish that interictal spikes can disrupt specific cognitive functions and that this impairment can be studied in the laboratory using carefully designed procedures. A fascinating, unresolved issue is determining the mechanism of how interictal spikes undermine memory retrieval. The challenge is now to decide how to use this kind of information in the clinical setting. It looks as if the debate will go on, if memory serves!

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References

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