Pathologic brain network activity

Memory impairment in epilepsy

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Our thinking, memory and cognition in general, relies upon precisely timed interactions among neurons forming brain networks that support cognitive processes. The surgical evaluation of drug-resistant epilepsy using intracranial electrodes provides a unique opportunity to record directly from human brain and to investigate the coordinated activity of cognitive networks. In this issue of *Neurology*®, Kleen and colleagues[1] implicate pathologic hippocampal network activity during specific memory processes in the occurrence of errors in patients' performance on a short-term memory task.

Epilepsy is characterized by pathologic brain electrical activity, which is evident not only during seizures (ictal) but also between them (interictal) in the form of brief interictal epileptiform discharges (IEDs). The importance of IEDs has long been debated with regard to epileptogenesis and seizure generation, but they have always played an important role in clinical practice for assisting in diagnosis and for localization of epileptic foci. Their possible role in affecting memory and cognition is debated but considered marginal despite early demonstration of IED-associated "transitory cognitive impairment"[2] and prolonged reaction times and misperception of visual stimuli.[3] In at least one situation, apparently silent epileptic discharges can have a dramatic effect on cognition: in patients with electrical status epilepticus during sleep.[4] In addition, cognitive deficits and IEDs often precede the onset of epilepsy, and may even predict its outcome.[5] Therefore, elucidating the relationship between the memory impairments so frequent in patients with temporal lobe epilepsy and the frequent IEDs found in mesial temporal lobe structures has potentially important diagnostic and therapeutic clinical applications.

Kleen and coauthors have translated their previous animal studies to humans and investigated the effect of IEDs on memory. Previously they reported impaired short-term memory performance in rats that developed chronic IED as a result of intrahippocampal infusion of pilocarpine.[6] The main finding was that hippocampal IEDs impaired the retrieval of spatial memory in rats but not the encoding or maintenance of such memories: retrieval was impaired when it occurred time-locked to an IED.

Those findings led the authors to explore the effect of distinct types of hippocampal IEDs on human memory, during specific phases of a short-term memory task and occurring in either brain hemisphere relative to the identified seizure onset zone. In agreement with the animal work, IEDs in the hippocampus contralateral to the seizure focus were associated with impairment during the retrieval phase of the task. Patients' performance was also impaired during memory maintenance but only when IEDs occurred in both hippocampi. Finally, these effects occurred only for repetitive IEDs or spatially diffuse IEDs, but not for single focal interictal spikes.

The results are consistent with the hypothesis that IEDs interfere with specific network operations underlying memory maintenance and retrieval in the hippocampus. In order to affect a particular neuronal network supporting memory processing in this task, an IED had to spread far enough in time or space within the task-dominant hemisphere, thus explaining why a single epileptiform spike was less likely to disrupt that network process. These findings do not prove a causal relationship between IEDs and disrupted memory processing, but it is difficult to imagine an experiment that could provide stronger evidence. The results emphasize the importance of brain network synchrony and coordination in supporting memory. One would like to see how different IEDs affect the network oscillations underlying memory maintenance and retrieval in the task, e.g., in the theta or gamma bands, but it is a fair assumption that all IEDs affect these networks and activities, albeit at different degrees, some of which may be difficult to demonstrate. One important question remains: it is not clear to what extent the impairments related to IEDs contribute to the overall memory impairment of the patients and whether patients are actually impaired in the task itself due to lack of an adequate control group in the study. Other paradigms will need to be used to assess what type of memory (i.e., verbal or

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spatial, short or long term) is primarily affected by IEDs occurring in specific brain regions involved in particular memory processes.

IEDs are not limited to spikes and sharp waves. The latter are often associated with bursts of high-frequency oscillations, which have been linked to pathologic network activity,[7] at the same time playing vital roles in memory processing.[8] Ultimately, our understanding of cognitive deficits, IEDs, seizure generation, and epilepsy will require elucidating their brain mechanisms on the level of individual neuronal activity and interactions among functionally connected networks across brain structures. Recent evidence implicates brain network activity underlying memory processing in suppression of the IEDs,[9] which even raises the possibility of cognitive therapy as an unexplored epilepsy treatment.

Knowledge gained from translating basic science discoveries into clinical research, as exemplified in the elegant approach of Kleen and colleagues, may lead to development of novel antiepileptic medications targeted at the mechanisms of IEDs and guide the ongoing clinical trials using deep brain stimulation. IEDs may be more than the marker that epileptologists have usually considered them to be. They may also be significant pathologic events on their own.

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DISCLOSURE

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