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How Epileptic Spikes Impair Memory

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EEG spikes, memory impairment, ripples

Spatiotemporal Dynamics Between Interictal Epileptiform Discharges and Ripples During Associative Memory Processing

Henin S, Shankar A, Borges H, et al. (2021). Spatiotemporal dynamics between interictal epileptiform discharges and ripples during associative memory processing. *Brain*;*144*(5):1590-1602. doi:10.1093/brain/awab044

We describe the spatiotemporal course of cortical high-gamma activity, hippocampal ripple activity and interictal epileptiform discharges during an associative memory task in 15 epilepsy patients undergoing invasive EEG. Successful encoding trials manifested significantly greater high-gamma activity in hippocampus and frontal regions. Successful cued recall trials manifested sustained high-gamma activity in hippocampus compared to failed responses. Hippocampal ripple rates were greater during successful encoding and retrieval trials. Interictal epileptiform discharges during encoding were associated with 15% decreased odds of remembering in hippocampus (95% confidence interval 6-23%). Hippocampal interictal epileptiform discharges during retrieval predicted 25% decreased odds of remembering (15-33%). Odds of remembering were reduced by 25-52% if interictal epileptiform discharges occurred during the 500-2000 ms window of encoding or by 41% during retrieval. During encoding and retrieval, hippocampal interictal epileptiform discharges were followed by a transient decrease in ripple rate. We hypothesize that interictal epileptiform discharges impair associative memory in a regionally and temporally specific manner by decreasing physiological hippocampal ripples necessary for effective encoding and recall. Because dynamic memory impairment arises from pathological interictal epileptiform discharge events competing with physiological ripples, interictal epileptiform discharges represent a promising therapeutic target for memory remediation in patients with epilepsy.

Commentary

It was established in many studies, starting with that of Aarts et al[1] that interictal epileptic discharges (IEDs) result in a transient functional impairment of the region in which they occur. This is not surprising given that at the time of an IED a large pool of neurons is involved in generating an abnormal synchronous discharge and is obviously not available for performing its normal functions. If IEDs occur once per hour, the 100 or 200 msec impairment is most likely of little practical significance. In the scalp EEG, most adult patients show sporadic IEDs that look like they would be in this group of little practical significance. If they occur every 2 or 3 seconds, as is often seen in intracranial recordings, their consequences may become noticeable. Mesial Temporal Lobe Epilepsy (MTLE) is the most common and most studied type of focal epilepsy. It has been long established that patients with MTLE have memory impairments. We also know that when electrodes are implanted in mesial temporal structures in these patients, IEDs are very frequent. One can then wonder whether these IEDs play a role in memory impairment and by what mechanism this occurs.

The recent study of Henin et al[2] sheds a new light on these questions. Earlier studies, such as those of Krauss et al[3] and Kleen et al[4] documented a decrease in memory performance particularly when IEDs occurred at the time of memory retrieval, although Kleen et al also found that IEDs occurring during the maintenance period (between encoding and retrieval) also affected memory. Results depended of course on the type of memory task (verbal, non-verbal) and the localization of the IEDs.

Before discussing the study of Henin et al, I will make a short aside to avoid confusion. The epilepsy literature has separated High Frequency Oscillations (HFOs) into ripples (80-250 Hz) and fast ripples (250-500 Hz). The community that has studied the role of hippocampal oscillations in memory and learning, principally in rodents[5] but also in humans[6,7] has used the word "ripple" with a different meaning: also termed "sharp-wave ripples" these oscillations occur in the hippocampus and other structures of healthy individuals and their roles in the processes

of memory encoding and retrieval have been clearly established in elegant experiments in patients with intracerebral electrodes; they are usually defined as having a frequency of 80 to 120 Hz. The paper of Henin et al uses "ripples" with the latter definition.

Henin et al studied 15 patients with relatively widespread subdural electrode coverage as well as intracerebral electrodes in mesial temporal structures. Subjects performed a memory task that involved verbal and non-verbal aspects: they learned to associate a face with the name of a profession; at retrieval, they were shown the face and asked to recall the associated profession. The authors analyzed the EEG at the time of encoding and at the time of retrieval (the time following the face presentation, and the time immediately before the voiced response). They analyzed High Gamma Activity (HGA, 60 to 170 Hz), which has been associated with cognitive processing, and hippocampal ripples (brief oscillations between 80 and 120 Hz which have been clearly associated temporally with memory function) during encoding and retrieval. Analyzing only trials without IEDs to avoid the possible confound of pathological HFO often present with IEDs, and analyzing only channels outside the seizure onset zone to avoid potentially pathological regions, they found that successful encoding trials resulted in increased HGA in frontal regions and in the hippocampus, and successful retrieval trials resulted in increased hippocampal HGA. Results were similar for hippocampal ripples. They thus established the importance of HGA and hippocampal ripples for the successful performance of the memory task.

In a second part of the study, they looked at the influence of IEDs on memory performance and of IEDs on the occurrence of HGA and of ripples. When IEDs occurred during the encoding period, odds of remembering were decreased by 15%. When IEDs occurred during retrieval, odds of remembering were decreased by 25%. Ripples, which were shown in the first experiment to be important for encoding and retrieval, were decreased in the periods immediately following IEDs, a phenomenon which may contribute to the memory impairment experienced by patients with MTLE. The authors concluded that it may be interesting to consider treatments that could suppress IEDs, assuming this would result in improved memory function.

This carefully performed study confirms, with a few differences, what had been demonstrated before, i.e. that IEDs occurring during memory tasks disrupt memory performance. In addition to earlier studies, they quantified the degree of memory impairment related to the occurrence of IEDs during a memory task and their experiment proposes a possible mechanism responsible for impaired memory function: the high frequency activity (high gamma and ripples) that seems necessary for the normal performance of memory function is disrupted during IEDs and immediately following them, a possible cause of impaired function.

Interictal epileptic discharges, wherever they occur in the brain, are likely to result in diminished function of the affected region and it seems reasonable to attempt to suppress them. If this can be done without significant side effects, it would most likely result in improved function, in this case, in improved memory. A major question remains however: in MTLE, there is usually hippocampal atrophy or another structural lesion. Frequent IEDs are also observed in regions of focal cortical dysplasia. What is the relative importance of the structural lesion and of the IEDs in reducing function? In this study, the authors found that memory performance was reduced by approximately 20% when IEDs occurred at the time of encoding or retrieval. In everyday life, how often is it that IEDs actually interfere with memory function? If it occurred every time the memory function was in operation, there would be a 20% decrease in function according to this study. If it occurred half the time, memory would be impaired 10% of the time. It is very difficult to separate the contributions of structural abnormalities and that of functional abnormalities such as IEDs (and there may also be other functional abnormalities).

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