

## EPILEPSY AND FORGETFULNESS: ONE IMPAIRMENT, MULTIPLE MECHANISMS

### **Impaired Single Cell Firing and Long-term Potentiation Parallels Memory Impairment Following Recurrent Seizures.**

Zhou JL, Shatskikh TN, Liu X, Holmes GL. *Eur J Neurosci* 2007;25(12):3667-3677. Patients with epilepsy are at substantial risk for memory impairment. Animal studies have paralleled these clinical observations, demonstrating impaired hippocampal function as measured by spatial memory in rodents subjected to seizures. However, the mechanism of seizure-induced hippocampal impairment is unclear. Here we investigated the effects of recurrent seizures on water-maze performance, a behavioural measure of learning and memory, long-term potentiation (LTP; considered a test of synaptic plasticity and memory) and place-cell firing patterns, a single-cell indicator of spatial memory. LTP and CA1 place-cell activity were examined in separate groups of freely moving rats, before and after 10 flurothyl-induced seizures. Water maze performance was examined in a third group of rats, five with previously induced seizures and five controls. Recurrent flurothyl seizures were associated with marked impairment in LTP and a reduction in the frequency of the peak theta power. Compared to baseline recordings, place-cell firing patterns following recurrent seizures were significantly less precise, had lower firing rates and were less stable. Impaired place-cell firing was seen as early as after two seizures and persisted at least 72h after the last seizure. Water-maze performance was also significantly impaired in animals that underwent recurrent seizures. No cell loss or synaptic reorganization was observed in the hippocampus or in several other cortical areas that are vulnerable to seizures. These results demonstrate that relatively brief excitatory events, not producing visible cell damage, can nevertheless cause long-lasting changes in hippocampal physiology, observable as impairments in place-cell function, LTP and spatial memory.

### COMMENTARY

Impairments of learning and memory in patients with epilepsy represent a significant burden under conditions of an already debilitating disease. While the phenomenon of deficient learning, memory, and cognition in epilepsy has been well established, its place in the pathophysiology of epilepsy continues to be a subject of debates. A number of mechanisms may contribute to the disruption of memory function in epilepsy patients. One commonly cited reason for memory function impairment is hippocampal neuronal cell loss that is due both to the precipitating insult (e.g., status epilepticus or brain trauma) and recurrent seizures. Furthermore, frequent recurrent seizures, even in the absence of neuronal injury, may lead to the decline of learning and memory. It is also possible that chronic, persistent dysfunction of limbic circuits, which is characteristic of epilepsy, may impair memory even in the absence of neuronal injury and seizures. A less frequently contemplated scenario is that memory disorders may develop as a result of other comorbidities of epilepsy (e.g., depression), rather than from major hallmarks of the disease, such as neurodegeneration and seizures. Needless to say, understanding the nature of memory deficits associated with epilepsy is important, because it would define therapeutic approaches to their treatment. Meanwhile, experimental and clinical evidence accumulated to date, although abundant, provides little mechanistic clarification.

Impairments of learning and memory have been documented in animal models of limbic epilepsy triggered by status epilepticus. However, data obtained from poststatus epilepticus models are difficult to analyze, since these models are characterized both by extensive neurodegeneration and by spontaneous seizures, with respective contributions of each of the two factors in memory deficits being hard to interpret. Liu et al. reported that the extent of both memory deterioration and hippocampal place cell activity positively correlated with the severity of hippocampal neuronal injury and mossy fiber sprouting after pilocarpine status epilepticus (1). However, no correlation between hippocampal pathology and memory deficits with frequency of spontaneous seizures was performed; therefore, it was still possible that memory deficits in poststatus epilepticus animals resulted from frequent seizures, which in turn occurred because of severe hippocampal pathology. Stafstrom et al. found that memory deficits were observed after kainic acid status epilepticus induced in rats at postnatal day 20 or later, but not in 5- or 10-day-old pups (2). At these younger ages, animals apparently developed neither hippocampal injury nor spontaneous recurrent seizures; hence, causative relationship between each of the two factors and memory impairment was hard to establish. In clinical observations, the extent of cognitive and memory disorders is more pronounced in patients with a longer history of the disease. Again, however, this finding might reflect a longer history of seizures, progressing neuropathology, or both.

One possible way to address the role of spontaneous seizures and hippocampal neuronal injury in memory deterioration is to examine how either neuroprotection or elimination of spontaneous seizures by anticonvulsant treatment would affect memory performance. Such studies are complicated

because neuroprotective and anticonvulsant interventions are often hard to dissociate from one another. Furthermore, post-status epilepticus spontaneous seizures exhibit remarkable resistance to antiepileptic medications, and complete eradication has never been achieved.

In their study Zhou and colleagues employed a model of repetitive seizures in the absence of gross hippocampal pathology. Such an approach allowed the authors to show that brief, recurrent seizures themselves may induce impairment of memory and cognition. Furthermore, observed behavioral alterations paralleled several key correlates of learning and memory, such as long-term potentiation and the activity of hippocampal place cells.

Kindling is a model of epilepsy that affords examining the chronic epileptic state, particularly the sustained increase of excitability and seizure susceptibility in the absence of both extensive neurodegeneration and spontaneous seizures. Interestingly, there appears to be a consensus that the kindling state per se, does not affect memory and learning. Such deficits, when observed in kindled animals, most likely result from kindled seizures rather than from tonic changes in the excitability of limbic circuits (3).

The possibility that cognitive disorders are secondary to other comorbidities of epilepsy has received little attention. For example, depression, a very common comorbidity in epilepsy patients, also is known to have significant impact on cognitive and memory performance. Thus, under conditions of an experimental model of depression, animals developed deficits in spatial memory tasks; these deficits were successfully corrected by the antidepressant fluoxetine (4). In contrast, a recent clinical study failed to reveal any correlation between depression and cognitive deficits in epilepsy patients (5). More studies are necessary to definitively address this issue. If memory disorders in epilepsy patients are indeed related to depression, it is possible that the correction of cognitive and memory deficits paradoxically might be achieved through antidepressant medication.

In this regard, the kindling state, which as discussed, does not lead to memory impairments, is characterized by persistent anxiety, fear, altered emotional tone, and depression (6,7). Such dissociation between memory and mood impairments in kindled animals by itself is interesting, as it outlines two different

patterns of epilepsy comorbidities: those that are associated with discrete epileptic events (such as seizures) and those that depend on tonic dysfunction of limbic neuronal network. Furthermore, even if one comorbid state, for example depression, does not directly disrupt memory function, it may still exacerbate it.

Given the complexity of memory and cognition mechanisms, as well as the diversity of underlying neuronal processes, it is unlikely that impaired memory and cognition in epilepsy can be explained by a single mechanism. Indeed, a variety of factors (e.g., neuronal cell loss, recurrent seizures, interictal perturbations, and sustained tonic dysfunction of limbic circuits) likely contribute to the impairments of learning and memory. However, in spite of accumulated data, the question still remains to be answered: do learning and memory impairments require special dedicated treatment or would merely getting rid of the epileptic foci or seizures be sufficient?

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## References

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