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Disrupted Spatial Maps in Epilepsy Highlight the Importance of Timing in Neural Codes

Breakdown of Spatial Coding and Interneuron Synchronization in Epileptic Mice

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Temporal lobe epilepsy causes severe cognitive deficits, but the circuit mechanisms remain unknown. Interneuron death and reorganization during epileptogenesis may disrupt the synchrony of hippocampal inhibition. To test this, we simultaneously recorded from the CA1 and dentate gyrus in pilocarpine-treated epileptic mice with silicon probes during head-fixed virtual navigation. We found desynchronized interneuron firing between the CA1 and dentate gyrus in epileptic mice. Since hippocampal interneurons control information processing, we tested whether CA1 spatial coding was altered in this desynchronized circuit, using a novel wire-free miniscope. We found that CA1 place cells in epileptic mice were unstable and completely remapped across a week. This spatial instability emerged around 6 weeks after status epilepticus, well after the onset of chronic seizures and interneuron death. Finally, CA1 network modeling showed that desynchronized inputs can impair the precision and stability of CA1 place cells. Together, these results demonstrate that temporally precise intrahippocampal communication is critical for spatial processing.

Commentary

Memory impairment is a pervasive comorbidity of temporal lobe epilepsy (TLE), and therefore, it is important to gain mechanistic understanding of how memory processes are dysfunctional in epilepsy. Pathological signatures of epilepsy such as seizures and interictal spikes emerge at the network level—and thus a prevalent idea in the field is that mechanistic understanding of ictal and interictal activity requires network-level observation and analysis. Parallel efforts to understand memory deficits in epilepsy are similarly adopting system-level approaches to determine coding deficits that would confer memory impairment. The study by Shuman, Ahoaroni, Cai et al is one such study. A tour de force, employing high-density electrophysiology, chronic wireless one-photon calcium imaging in freely moving animals, electroencephalogram, computational modeling, and behavior, their study confirms several observations from other laboratories, adds unprecedented time line data about the evolution of functional disruption during disease progression, and puts forth an "input timing" hypothesis for memory deficits.[1]

Neurons within the rodent hippocampus have tuning curves that reflect the spatial position of the animal, so called "place cells." Place cells are thus active when animals are at specific locations in a maze. This neural code is thus commonly studied as a proxy for the integrity of spatial memory, and furthermore, it is postulated that degradations in codes for place would confer memory impairment. Several labs have found deficits in place coding in animal models of TLE. Especially in this era of "crisis of reproducibility in biological sciences,"[2] it is essential to highlight when findings are robust across laboratories—and in this case, across animal models for TLE. Including this study, several laboratories have now reported that in chronic epilepsy, the spatial tuning curves of place cells broaden and are less stable over time and furthermore that the proportion of active cells that encode place is decreased in TLE.[3,4] The study by Shuman et al stands out from past research in 2 big ways. First, by employing wireless one-photon imaging, they have recorded from an enormous population of neurons and are able to record during behaviors that are hindered when animals are tethered. Second—and very importantly—their method allows longitudinal recording. This allowed for them to track place cells over days and show that instability in the code is massive when looking at larger timescales. Furthermore, they were able to determine *when* in course of epilepsy the deficits in place coding emerged. They found that place cell deterioration happened well after animals developed chronic behavioral seizures. Thus, they were able to rule out that place cell deterioration is mediated directly by interneuron death (which occurs early in epileptogenesis) or directly by the emergence of seizures—because seizures emerged several weeks before changes in place coding.

Instead, they propose that place cell deterioration occurs because of mistimed inputs arriving to CA1. With silicon probe recordings, they found that interneurons in the dentate gyrus lose their temporal coordination with theta rhythm at the population level. Theta rhythm is a voltage oscillation that dominates hippocampal local field potential when animals are running. Typically, interneurons fire synchronously at specific phases of theta rhythm. Here, it was observed that individual neurons are still theta rhythmic, but they fire at different phases of CA1 theta with respect to one another. This results in a mismatch between population activity in CA1 and dentate gyrus. They modeled improper interneuron coordination within the dentate gyrus by perturbing the timing of inputs to CA1 (CA3 and entorhinal cortex). This was done because their model was confined to CA1. They show that such mistimed input to CA1 is capable of conferring place field deficits consistent with what they observe experimentally. Using the same logic as used for ruling out other mechanisms, it will be important to determine *when* the temporal discoordination emerges during the course of epilepsy—in other words, does temporal discoordination precede place cell deterioration. If the timing is right (pun intended), it is exciting to consider how such timing deficits emerge and could be rescued.

Along those lines, it is striking how the physiology described here overlaps with hippocampal physiology after lesions of the medial entorhinal cortex. After such lesions, place fields enlarge and become less stable.[5] Furthermore, there are problems with fine scale spike timing. Unlike interneurons which are theta phase locked, place cells fire at different phases of theta depending on the position of the animal within the place field—a process called theta phase precession.[6] Phase precession is proposed to be important for organizing population codes in the hippocampus to allow for encoding of sequential experiences. After lesion of medial entorhinal cortex, pyramidal cells in CA1 no longer exhibit theta phase precession.[7] Again—a parallel with TLE, where it has also been observed that phase precession is compromised.[8] Thus, perhaps improper timing within the hippocampus points to upstream problems in the entorhinal cortex, indicating that it would be worth expanding our view to consider larger interacting networks. Indeed, the authors also perturbed entorhinal inputs in their computational model, but it is unclear whether changes in entorhinal cortex could actually drive the interneuron coordination deficits observed. Finally, how might timing in diseased networks be restored? Interestingly, one study found that rodents with malformations (often associated with epilepsy) showed improvement in temporal coding features after animals experienced environmental enrichment after weaning.[9] Mechanistically, it is not clear how such experience would confer such changes, but it hints at a relationship between temporal precision of codes and plasticity mechanisms—however, such rescue may only occur during specific developmental windows. Looking forward, it would be interesting to test whether such "behavioral" interventions would also rescue temporal codes such as interneuron coordination and phase precession in TLE in adults.

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