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Ripple While You Walk, and You May Get Lost: Pathological High-Frequency Activity Can Alter Spatial Navigation Circuits

The Impact of Pathological High-frequency Oscillations on Hippocampal Network Activity in Rats With Chronic Epilepsy.

Ewell LA, Fischer KB, Leibold C, Leutgeb S, Leutgeb JK. *eLIFE*. 2019;8:pii: e42148. doi:10.7554/eLife.42148. PMID: 30794155

In epilepsy, brain networks generate pathological high-frequency oscillations (pHFOs) during interictal periods. To understand how pHFOs differ from normal oscillations in overlapping frequency bands and potentially perturb hippocampal processing, we performed high-density single unit and local field potential recordings from hippocampi of behaving rats with and without chronic epilepsy. In epileptic animals, we observed 2 types of co-occurring fast oscillations that by comparison to control animals could be classified as "ripple-like" or "pHFO." We compared their spectral characteristics, brain state dependence, and cellular participants. Strikingly, pHFO occurred irrespective of brain state, were associated with interictal spikes, engaged distinct subnetworks of principal neurons compared to ripple-like events, increased the sparsity of network activity, and initiated both general and immediate disruptions in spatial information coding. Taken together, our findings suggest that events that result in pHFOs have an immediate impact on memory processes, corroborating the need for proper classification of pHFOs to facilitate therapeutic interventions that selectively target pathological activity.

Commentary

The hippocampus is located in the temporal lobe and is critical for learning, memory, and successful spatial navigation. Consequently, many patients with temporal lobe epilepsy (TLE) report problems with their memory, with deficits becoming more pronounced over time.[1] How does TLE alter hippocampal circuits to not only cause seizures but also impair memory? To answer this question, we ideally need to be able to record from, and compare, neuronal activity in both healthy and epileptic brains. Such invasive recordings are, appropriately, rare in healthy humans, necessitating animal models to fill part of the void. A recent article by Ewell et al investigates this question in a rodent TLE model by focusing on how pathological high-frequency activity (pHFA) in epileptic animals alters hippocampal cells and circuits when compared to healthy controls. As discussed below, the article presents a number of key results, but perhaps the most important observation is that pHFA also occurs during movement, negatively impacting how well hippocampal neurons can encode spatial information and suggesting a neural correlate of impaired spatial memory in TLE.

While hippocampal ripples and pathological fast ripples are both well-studied phenomena in healthy[2,3] and epileptic[4-6] brains, respectively, direct comparisons and analyses of the two across healthy versus epileptic subjects in the same study are rare. Ewell et al recorded from the CA1 of the hippocampus in 4 control and 4 TLE[7,8] rats during both resting and foraging conditions. The authors were able to show that epileptic brains were capable of generating two distinct types of high-frequency events: One was a "ripple-like" high-frequency oscillation (HFO) whose frequency ($\sim$180 Hz) was similar to ripples seen in healthy controls, while the other was a fast ripple event, likely indicative of pathological HFA. Pathological HFA had higher frequencies (220-260 Hz) and larger amplitude low-frequency envelopes than both healthy (control) ripples and TLE ripple-like events. Inhibitory neurons typically set the frequency of healthy ripples, but since inhibitory neurons were not analyzed in this study, it is difficult to say whether the pHFA observed here was also partially paced by inhibition or simply represented pseudo-synchronous activation of neurons.[9] Given the relatively circumscribed frequency range of this pHFA, at least some involvement of inhibition is possible. Despite this, as discussed in a recent commentary,[10] we prefer to use the all-encompassing term HFA, as opposed to HFO, when referring to pathological high-frequency events, unless it is clear that such events are truly rhythmic and paced by inhibition. It should also be noted that pHFA in patients with epilepsy usually has a broader frequency range[4-6] than that observed in these epileptic rodents, possibly reflecting differing degrees of inhibitory

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failure. Regardless, these observations showed that TLE rats can generate both types of high-frequency events (ripples and fast ripples) at the same hippocampal electrode location.

The authors next looked at the likelihood of each type of high-frequency event occurring during the foraging epochs. During movement, the healthy hippocampus generates 6-12 Hz theta oscillations, and these active states are typically devoid of any ripples.[2] This is exactly what Ewell et al observed in their control animals. Similarly, ripple-like events in TLE rats also occurred during immobility and were less likely to occur during faster movements. However, pHFA was consistently seen during movement and, in fact, had the same rate of occurrence independent of brain state (resting vs moving at different speeds). Most importantly, pHFA led to transient disruptions in theta rhythms during movement. Given the importance of hippocampal theta in coordinating spatial learning and memory,[11] this critical observation suggests that pHFA may impair hippocampal network coordination and sequence learning during active movement.

How are hippocampal neurons modulated by healthy ripples, ripple-like events, and pHFA? As expected, Ewell et al found that healthy ripples in control animals recruited the vast majority of hippocampal CA1 principal, likely excitatory, neurons (91% of CA1 neurons recorded). If ripple-like events in TLE rats were indeed identical to healthy ripples in control rats, then they too should recruit a similar proportion of neurons. This was not the case. Ripple-like events only modulated 46% of the principal neurons isolated in this condition. Pathological HFA recruited even fewer, with only 21% of neurons being modulated. Thus, although the local field potential activity during ripple-like events in TLE animals looks very similar to that during healthy ripples, the neurons are not responding in the same way. For pHFA, although these events are accompanied by larger low-frequency envelopes than ripples (indicative of stronger excitatory drive), fewer neurons are recruited. Why could this be? This is a crucial question, but it requires the recording and analysis of inhibitory fast-spiking neurons in CA1 as well as neurons in upstream brain regions that provide inputs to CA1 during ripple-like or pHFA events. While both increased and decreased rates of inhibition have been posited as possible explanations, the more probable scenario has to do with the precise temporal coordination of inhibitory and excitatory inputs which is likely to be disrupted in epilepsy.[12]

Ewell et al next asked what proportion of neurons were active during foraging, and whether their activity was directly impacted by pHFA during movement. In healthy animals, hippocampal CA1 pyramidal cells fire in restricted regions of space and are hence called place cells. In typical healthy animals, not all CA1 cells fire in a given environment, and these cells are called silent cells.[13,14] In their study, Ewell et al report a surprisingly large proportion of CA1 cells in healthy controls as being active during foraging, although this may be related to the relatively low threshold of 2 Hz for defining a cell as active. Nonetheless, with the same threshold, the proportion of active cells in TLE rats (41%) was much lower than that in control rats (86%). This property of having few cells in a population encode a given environment has been referred to as population sparseness.[14] It should be noted that increased population sparseness is not always a bad thing for neural codes—as Thompson and Best said when they described silent hippocampal cells, in spatial information processing "neural silence may be as important a signal as neural activity."[13] In addition to the population effects, the cells that were active in TLE rats had diffuse, not-so-sparse place fields (compared to healthy place fields that were restricted to smaller regions of space). Thus, there was less single-cell sparseness[14] for the cells that were firing during active behavior. The spatial information content of these active TLE cells was lower due to the diffuse firing, indicating that their activity patterns are not very informative about where the rat is at any given moment in time. Thus, TLE leads to increased population sparseness as well as impaired spatial information coding by individual active cells. Pathological HFA contributed to the impaired spatial coding abilities of active cells. After removing the spikes associated with pHFA during foraging, the spatial information content was partially increased although not to the levels of cells in control rats. Pathological HFA thus impacts spatial coding in two ways, by leading to spurious, uninformative action potentials during foraging and by transiently disrupting theta rhythms.

These findings reproduce and extend several related observations in humans. Intracranial recordings in patients have shown that the occurrence of interictal spikes is correlated with impaired performance on cognitive and memory tasks.[15,16] Similarly, interictal spikes also suppress theta rhythms in the human hippocampus.[17] Interictal spikes often (but not always) co-occur with pHFA.[10] Thus, it is likely that pHFA in humans is also disrupting theta rhythms and impairing performance on memory tasks. Ewell et al show that this pHFA is likely to have a significant impact on the hippocampal spatial code by altering the firing patterns of hippocampal neurons that are important for spatial memory. This study also emphasizes why it is so important to record single neuron activity together with interictal spikes, ripples, and fast ripples: even though the "ripple-like" activity in TLE animals looked almost identical to ripples in healthy animals, neuronal responses during these events were very different, potentially reflecting altered inhibitory dynamics. The same is likely to be true in patients, highlighting the continued need for rare single neuron recordings in humans. While Ewell et al expertly looked at excitatory neurons in the hippocampus, perhaps the only weakness of the study is that it did not report the activity of fast-spiking inhibitory neurons. Future work will ideally be able to reveal how precise epilepsy-induced alterations in inhibitory neuronal rate and temporal codes mechanistically shape the observations presented in this fascinating study.

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