This Week in The Journal

Hippocampal Neurons Encode Temporal Sequences

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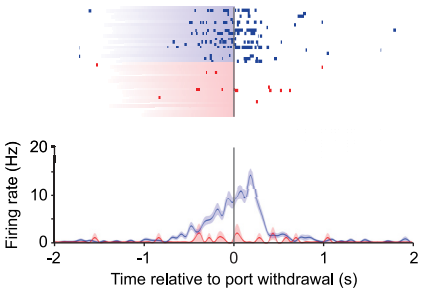
(see pages 1547–1563)

The critical role of the hippocampus in episodic memory has long been recognized. In particular, the hippocampus is thought to encode spatial, temporal, and semantic relationships among objects and events (Eichenbaum and Cohen, 2014, Neuron 83:764). Numerous human and rodent studies have provided support for this hypothesis. First, the discovery of place cells, which exhibit changes in firing rate as animals move through an environment, provided evidence that the rodent hippocampus represents spatial sequences. More recently, cells that appear to encode the passage of time have been identified. Now Allen et al. present evidence that hippocampal neurons encode temporal relationships between nonspatial stimuli.

Rats were trained to recognize a sequence of five odors, after which they had to determine whether odors were presented in or out of order to earn a reward. Neuronal activity was recorded in CA1 as rats performed this task. The firing rate of ~26% of recorded neurons (many more than would be expected by chance) differed depending on whether the odor being sniffed was in the learned sequence. Some neurons responded when the present odor was in the learned sequence—regardless of the odor's identity—and others responded whenever an odor was experienced out of order. Some neurons responded only when a particular odor was presented in the correct position, and still others responded only when a particular odor was presented out of order. Finally, some neurons responded when any wrong odor was presented at a particular temporal position. Overall, the analyses suggested that the firing of individual neurons contained sufficient information to distinguish whether an odor was in or out of sequence, and that neuronal ensemble activity reflected whether items were in the learned sequence on a trial-by-trial basis.

In these experiments, the location and overt behavior of rats were unchanged across trials, minimizing the likelihood that differences in neuronal firing were attributable to such confounds. Moreover, the proportion of cells that showed sequence-dependent changes in firing rate was correlated with accuracy on the task. Therefore, the results strongly suggest that hippocampal neurons encode temporal relationships between events—a central feature of episodic memories—and that this information is used to guide behavior.



A neuron that responded more to in-sequence odors (blue) than to out-of-sequence odors (red). Rasters (top) show spikes and odor sampling periods (shading) on individual trials. Perievent time histograms (bottom) show mean firing rates across all trials. See Allen et al. for details.

Astrocytic NFAT Slows Synaptic Recovery after Injury

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(see pages 1502–1515)

Nuclear factor of activated T cells (NFAT) is a transcription factor that resides in the cytoplasm under baseline conditions. When intracellular calcium levels rise, the calcium/calmodulin-dependent phosphatase calcineurin dephosphorylates NFAT, unmasking a nuclear translocation signal. Consequently, NFAT enters the nucleus where it regulates expression of various genes, most notably those involved in lymphocyte activation during immune responses. Calcineurin-dependent activation of NFAT also occurs during activation of astrocytes and microglia, and it is thus thought to contribute to neuroinflammation after brain injury and in neurodegenerative diseases. Consistent with this hypothesis, astrocytic NFAT expression was elevated in a mouse model of Alzheimer's disease (AD), and inhibiting NFAT activation selectively in astrocytes—by expressing the inhibitory peptide VIVIT—reduced astrocytic hypertrophy, plaque formation, synaptic deficits, and cognitive impairment (Furman et al., 2012, J Neurosci 32:16129).

Following these promising results, Furman et al. asked whether astrocytic NFAT activation also contributes to synaptic disruption after traumatic brain injury in rats. Previous work showed that unilateral controlled cortical impact (CCI) causes loss of synaptic inputs from hippocampal CA3 to CA1. Although synapses re-emerge within a week, they remain weak, and long-term depression (LTD) is easier to induce in the injured hippocampus than in the contralateral hippocampus. When VIVIT was expressed in hippocampal astrocytes beginning ~8 weeks before injury, however, synaptic strength and the ability to induce LTD were similar in CCI-treated and uninjured rats. Furthermore, VIVIT expression attenuated CCI-induced loss of the scaffolding protein PSD-95 and an AMPA receptor subunit, and it enhanced astrocytic production of the synapse-promoting protein hevin. Surprisingly, however, VIVIT did not reduce expression of glial fibrillary acidic protein (GFAP)—a marker of astrocyte activation—after CCI, as it did in AD-model mice.

These data suggest that NFAT-dependent transcriptional regulation in astrocytes contributes to synaptic impairment after CCI injury independently of astrocyte activation (or at least independently of GFAP expression). They also indicate that different transcriptional programs underlie astrocyte activation in AD mice, in which NFAT is required, and after traumatic injury in rats, in which NFAT is dispensable. Finally, they suggest that preventing activation of NFAT may promote recovery of brain function after traumatic injury while sparing protective functions of activated astrocytes.

This Week in The Journal is written by Teresa Esch, Ph.D.