

Time Finds Its Place in the Hippocampus

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<http://dx.doi.org/10.1016/j.neuron.2013.05.039>

In this issue of *Neuron*, Kraus et al. (2013) show that a population of “time cells” in the hippocampus responds to the passage of time rather than simply reflecting path integration. This study advances our understanding of how time is represented in the hippocampus.

The hippocampus is required for creating new episodic memories, memories of specific experiences along with when and where those experiences occurred. Recalling when events occurred in our past is such an effortless task for us that we can take it for granted, but until a relatively recent study by Clayton and Dickinson (1998), it was unclear whether animals had a similar ability. In their study, Clayton and Dickinson took advantage of a natural food caching behavior of scrub jays to show that these birds can remember how long ago they cached a perishable food item and use this information to determine whether the food has spoiled. This elegant experiment firmly established that animals could store information about how long ago an event occurred, but exactly how the hippocampus (and its homologous structure in birds) encodes time in its representations of episodic information remains a mystery. It has been known for several years that relative time in the form of sequential activity of place cells is stored in the hippocampal network. For example, experienced sequences of active place cells are compressed by the theta oscillation (Skaggs et al., 1996) and can be “replayed” during various stages of sleep and during sharp-wave ripples in awake animals (O’Neill et al., 2010). Recently, it has been shown that some cells in the hippocampus represent not only sequences but also elapsed time (Pastalkova et al., 2008). These cells have later been termed “time cells” (MacDonald et al., 2011). In a typical experiment, a rat performs a working memory task with one important characteristic: during the delay portion of the task, the rat must stay in one place for several seconds before making its choice, effectively keeping the rat’s location constant. If the cells act as pure place cells,

then they should be active during the entire delay period. Remarkably, many cells are active only during brief intervals of time, and the preferred interval of the cell is constant from trial to trial. Pastalkova and colleagues (2008) suggested that time is represented by the fact that cells fire in a self-organized sequence. After an initial kick, a set of recurrently connected cells begins a pattern of activation that spreads from one cell to another. In this way, the elapsed time could be read out by the state of the network, rather than in the activity of a single pacemaker or clock.

A critical question remains unresolved in all prior studies of time cells: can the time cell phenomenon be explained by simpler mechanisms, such as continuous changes in sensory stimulation or behavior, including path integration? In the earlier studies, the rat was either running in a running wheel or free to move on a small platform, leaving many variables uncontrolled. In this issue, Kraus et al. (2013) use a new behavioral paradigm to examine whether the time cells are influenced by path integration. In Kraus et al. (2013)’s experimental design, a rat ran through a modified version of the classic alternating T-maze. In the stem part of the maze, where the rat must hold in working memory whether to go right or left, the rat was required to run on a treadmill. In some trials, the rats ran for a prescribed amount of time (“time-fixed”), while in others they ran for a prescribed distance (“distance-fixed”). Because the treadmill could be run at different speeds every trial, Kraus et al. (2013) were then able to consider whether the cells more tightly locked to time or distance (Figure 1). Time and distance are inherently linked (the farther you run, the longer it will take), but the paradigm

provides enough of a dissociation between them to provide a useful test. Kraus et al. (2013) found that firing of most of the cells on the treadmill were best explained by a combination of time and distance, but critically, a modest number of cells (8% of the cells that were active on the treadmill) responded exclusively to time and not distance. These data suggest that at least a subset of time cells may in fact represent time objectively, independently of distance traveled.

We still have much to learn about time cells. One fundamental issue is whether time cells are always time cells or if they can change to place cells in other contexts. Here Kraus et al. (2013) provide a tantalizing hint. Their main analyses focused on the period in which the rat ran on the treadmill, but they also examined the activity of those cells on other portions of the maze. Some pure time cells in the treadmill running also had what looked like pure place fields in other parts of the maze, suggesting that time cells are not predetermined to always be time cells and can even switch to another cell type within the same session. More detailed analyses are required, but based on these results, it seems that time cells, like many odor cells (Wood et al., 1999) or goal cells (Fyhn et al., 2002), might be place cells that adapt to the specific requirements of the task or environment. If time cells can switch to place cells over the course of a single session, then it is not clear how a downstream cell might know when the cell is signaling time or place. One scheme would be to represent time and distance information on distinct phases or cycles of an oscillation. Jezek and colleagues (2011) suggested that the theta cycle is the fundamental unit for segregating competing information.

To address this issue, Kraus et al. (2013) analyzed whether the spiking of time cells occurs on distinct theta cycles from distance cells. Surprisingly, they found that both time cells and distance cells fired on the same theta cycles, leaving this question unresolved.

It is also not known whether time cells appear in a wide range of tasks or whether they specialize in working memory. To date, time cells in hippocampus have only been observed in short delay periods in a working memory task and have been proposed mainly as a way to bridge small gaps in discontinuous events (MacDonald et al., 2011), similar to the way that activity during the trace interval is believed to associate the conditioned stimulus with the unconditioned stimulus during trace conditioning (Solomon et al., 1986). If time cells are an essential component of episodic memory, then they should also exist over multiple time domains, from milliseconds to hours. One intriguing possibility is that the representation of time is topographically graded in the hippocampus in the same way as the representation of space (Kjelstrup et al., 2008), such that cells in the dorsal portion respond to short intervals of time while cells in the ventral portion respond to much longer intervals (Pilly and Grossberg, 2012). Such a topographic organization would also strongly support the hypothesis that the representations of time and place emerge from common mechanisms. An alternative, though not mutually exclusive, mechanism is that the hippocampus may represent the experiences separated by hours through firing rate changes and partial reorganization of firing fields in CA1 (Mankin et al., 2012). It is worth noting that both of these proposed timing mech-



Figure 1. Dissociation between Elapsed Time and Path Integration in the Hippocampus

During the delay period of a working memory task, Kraus et al. (2013) required the rat to run on a treadmill for either a fixed amount of time or a fixed distance. This allowed Kraus et al. (2013) to evaluate whether “time cells” of the hippocampus respond best to the amount of time or distance traveled. Their main finding is that some cells responded to time independent of distance, indicating that pure time cells exist in the hippocampus. Drawing by H. Fyhn.

anisms, like the responses to odors, goals, and objects, occur against the backdrop of a stable map and may exploit the same neural algorithms used for the representation of space (Buzsáki and Moser, 2013). In this view, the representations of time may be a mere modification of the hippocampal representation of space, rather than being coded through entirely distinct mechanisms.

The brain contains multiple clocks operating across a wide range of time-scales, from the millisecond precision of sensory and motor systems to daily fluctuations of circadian rhythms (Mauk and Buonomano, 2004). Within this spectrum, the time cells of the hippocampus occupy an important middle ground, representing time on the order of seconds and perhaps longer. The precise mechanisms behind the generation of time fields and whether other structures organize according to the time kept in the hippocampus remain to be seen, but Kraus et al. (2013) make

it clear that time and place coexist in the hippocampus.

ACKNOWLEDGMENTS

D.C.R. is supported by the Marie Curie Foundation (GA-2011-301674). M.B.M. is supported by the Kavli Foundation and a Centre of Excellence grant from the Norwegian Research Council.

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