gest that grid cells help the hippocampus generate place cells during memory formation.

How the brain encodes the when of memories has received far less attention, notes Andy Lee, a cognitive neuroscientist at the University of Toronto. “Space is something we see, it’s easy to manipulate... It’s somewhat easier for us to grasp intuitively,” he says. “Time is much harder to study.”

Despite the thinness of the subject, researchers have established in the last decade or so “that the brain has multiple ways to tell time,” says Dean Buonomano, a behavioral neuroscientist at the University of California, Los Angeles, and author of the 2017 book Your Brain is a Time Machine. Time is integral to many biological phenomena, from circadian rhythms to speech perception to motor control or any other task involving prediction, Buonomano adds.

One of the biggest breakthroughs in understanding time as it relates to episodic memory came a few years after Tsao completed his thesis. Howard and his postdoc Karthik Shankar had been developing a mathematical model of the brain’s perception of time, and between individual episodic memories. For Marc Howard, long fascinated by questions about the physical nature of time and the brain’s perception of it, the puzzle was a captivating one.

In the years leading up to Eichenbaum’s paper, Howard and his colleagues had begun to develop a mathematical model of the brain’s temporal context neurons. These neurons, called temporal context cells, become active at the beginning of an experience—to mark the passage of time, Howard says. But the first piece of the puzzle was still missing. No one had identified the gradually evolving set of temporal context neurons needed to produce the time signal in the first place, Howard says.

The findings, which are beginning to be extended to humans, are helping to create a proxy for the passage of time using a population of “temporal context cells” that gradually changes its activity. According to this model, all neurons in this population become active following some input (a sensory stimulus, for example), and then relax, one by one, creating a gradually decaying signal that is unique from moment to moment. Then, during memory formation, the brain converts this signal into a series of sequentially firing “timing cells,” which log moments within a memory. The same framework could also work to tag entire episodes according to the order in which they took place.

The specific mathematical details of the model—in particular, the use of an operation called a Laplace transform to describe how temporal context cells compute time, and the inversion of that transform to describe the behavior of the hypothesized timing cells—nicely recapitulated several known features of episodic memory, such as the fact that it’s easier to remember things that happened more recently than things that happened a long time ago. And after hippocampal timing cells, with their sequential firing patterns, were described in 2011, Howard, by then at Boston University, was gratified to see that they seemed to possess many of the properties he and Shankar had predicted for their so-called timing cells.

But the first piece of the puzzle was still missing. No one had identified the gradually evolving set of temporal context neurons needed to produce the time signal in the first place, Howard says.

Finding a signal
After graduating from Harvey Mudd in 2009, Tiao returned to the Kavli Institute for a PhD. Although he mostly worked on other projects, by the end of his program he’d convinced himself, and the Moszers, that the rat experiments from his summer internship were worth another look. Tiao was “an exceptional student,” May-Britt Moser says, and the Kavli team trusted that his data were correct, “but we didn’t know what we were seeing.” The neurons in the LEC seemed to be behaving so unpredictably.

Digging back into his old work after he graduated from his PhD program, Tiao began thinking about better ways to analyze the data. “We had always looked at activity at the level of individual neurons,” he says, “At some point, we decided to look at it at the entire population level.” In doing so, Tiao revealed that LEC activity was, in fact, changing—gradually, within and between trials.

Data from further experiments, carried out by Kavli researchers after Tiao moved to Stanford University for a postdoc in 2015, showed that a whole cluster of cells within the LEC became active at specific timepoints during behavioral tasks: a rat trained to associate a stimulus with a subsequent reward would have one hippocampal neuron that peaked in activity a couple hundred milliseconds after the stimulus was presented, another that peaked in activity a few hundred milliseconds after that, and so on—as if the hippocampus were somehow marking the passage of time.

The findings, which are beginning to be extended to humans, thanks to work by Lee and a separate team at the University of Texas Southwestern, among others, generated interest in the representation of time alongside space in episodic memories. Yet it was unclear what was telling these cells when to fire, or what rule, if any, they played in the representation of time passing within and between individual episodic memories. For Marc Howard, long fascinated by questions about the physical nature of time and the brain’s perception of it, the puzzle was a captivating one.

In the years leading up to Eichenbaum’s paper, Howard and his postdoc Karthik Shankar had been developing a mathematical model of the brain’s perception of its environment, which generates time cells. These time cells become active sequentially at specific moments during an experience to mark the passage of time.