THE MATRIX IN YOUR HEAD

The discovery of place-tracking neurons called grid cells, our experts say, "changes everything"

By James J. Knierim

In the 2001 suspense thriller *Memento,* the lead character, Lenny, suffers a brain injury that makes him unable to remember events for longer than a minute or so. This type of amnesia, known as anterograde amnesia, is well known to neurologists and neuropsychologists. Like Lenny, sufferers remember events from their life histories that occurred before their injuries, but they cannot form lasting memories of anything that occurs afterward. As far as they recall, their personal histories ended shortly before the onset of their disorders.

The cause of Lenny's problem was probably damage to his hippocampus, a pair of small, deep-brain structures crucial to memory—and also important to some of today's most exciting and consequential neuroscience research. Decades of research have made clear that the hippocampus and surrounding cortex do more than just place our life events in time. The hippocampus, along with a newly discovered set of cells known as grid cells in the nearby cortex, traces our movement through space as well. And by doing so, it supplies a rich array of information that provides a context in which to place our life's events. The picture that is emerging is of historic importance and more than a little beauty.

Exactly how does the brain create and store autobiographical memories? Although that question has fascinated scientists, philosophers and writers for centuries, it was only 50 years ago that scientists identified a brain area clearly necessary for this task—the hippocampus. The structure's role was made clear in 1953, when William Scoville, a Hartford, Conn., surgeon seeking to relieve the epileptic seizures that were threatening to kill a patient known as H.M., removed most of H.M.'s hippocampus and discovered he had rendered him unable to form new, conscious memories. Since then, the case of H.M., along with extensive animal research, has firmly established that the hippocampus acts as a kind of encoding mechanism for memory, recording the timeline of our lives.

In the 1970s another discovery inspired the theory that the hippocampus also encodes our movement through space. In 1971 John O'Keefe and Jonathan Dostrovsky, both then at University College London, found that neurons in the hippocampus displayed place-specific firing. That is, given "place cells," as O'Keefe dubbed these hippocampal neurons, would briskly fire action potentials (the electrical impulses neurons use to communicate) whenever a rat occupied a specific location but would remain silent when the rat was elsewhere. Thus, each place cell fired for only one location, much as would a burglar alarm tied to a tile in a hallway. Similar findings have been reported subsequently in other species, including humans.

These remarkable findings led O'Keefe and Lynn Nadel, now at the University of Arizona, to propose that the hippocampus was the neural locus of a "cognitive map" of the environment. They argued that hippocampal place cells organize the various aspects of experience within the framework of the locations and contexts in which events occur and that this contextual framework encodes relations among an event's different aspects in a way that allows later retrieval from memory.

FAST FACTS

Finding Our Place

1>> Rats (and presumably humans) have thousands of specialized brain cells, called grid cells, that track an animal's location in the environment.

2>> Each grid cell projects a virtual latticework of triangles across its environment and fires whenever the rat is on any triangle's corner.

3>> Every time the rat moves, it announces its location on multiple grids; collectively, the grid cells thus track the rat's location and path.

4>> Grid cells populate cortical areas next to the hippocampus, long recognized as a center of memory. Many researchers believe the grid cells' spatial data enable the hippocampus to create the context needed to form and store autobiographical memories.

GREG PEASE *Getty Images (preceding pages)*

Each week in Mind Matters, www.sciammind.com's expert-written "blog seminar," researchers of mind and brain explain and discuss their disciplines' most notable recent findings. In the premiere installment, reproduced here, spatial cognition scientists James J. Knierim and A. David Redish ponder the discovery of grid cells—specialized neurons that encode in complex fashion an animal's location.

Mind Matters examines a new finding every week. Join the discussion at www.sciammind.com

This view has been hotly debated for years. Yet a consensus is emerging that the hippocampus does somehow provide a spatial context that is vital to episodic memory. When you remember a past event, you remember not only the people, objects and other discrete components of the event but also the spatiotemporal context in which the event occurred, allowing you to distinguish this event from similar episodes with similar components.

(When you remember a past event, you also remember the spatiotemporal context in which it occurred.)

But *How?*

Despite intensive study, however, the precise mechanisms by which the hippocampus creates this contextual representation of memory have eluded scientists. A primary impediment was that we knew little about the brain areas that feed the hippocampus its information. Early work suggested that the entorhinal cortex, an area of cortex next to and just in front of the hippocampus [*see box on next page*], might encode spatial information in a manner similar to that of the hippocampus, though with less precision.

This view has now been turned upside down with the amazing discovery of a system of grid cells in the medial entorhinal cortex, described in a series of recent papers by the Norwegian University of Science and Technology's Edvard Moser and May-Britt Moser and their colleagues. Unlike a place cell, which typically fires when a rat occupies a single, particular location, each grid cell will fire when the rat is in any one of many locations that are arranged in a stunningly uniform hexagonal grid—as if the cell were linked to a number of alarm tiles spaced at specific, regular distances. The locations that activate a given grid cell are arranged in a precise, repeating grid pattern composed of equilateral triangles that tessellate the floor of the environment [*see box on next page*].

Imagine arranging dozens of round dinner plates to cover a floor in their optimal packing density, such that every plate is surrounded by other, equidistant plates; this arrangement mimics the triggering pattern tied to any given grid cell. As the rat moves around the floor, a grid cell in its brain fires each time the rat steps near the center of a plate. Other grid cells, meanwhile, are associated with their own hexagonal gridworks, which overlap each other. Grids of neighboring cells are of similar dimensions but are slightly offset from one another.

These grid cells, conclude the Mosers and their co-workers, are likely to be key components of a brain mechanism that constantly updates the rat's sense of its location, even in the absence of external sensory input. And they almost certainly constitute the basic spatial input that the hippocampus uses to create the highly specific, context-dependent spatial firing of its place cells.

This discovery is one of the most remarkable findings in the history of single-unit recordings of brain activity. Reading the paper announcing

(The Author)

JAMES J. KNIERIM is associate professor of neurobiology and anatomy at the University of Texas Medical School at Houston, where he studies the role of the hippocampus and related brain structures in spatial learning and memory.

> It is one of the **most remarkable findings** in the history of single-unit recordings of brain activity.

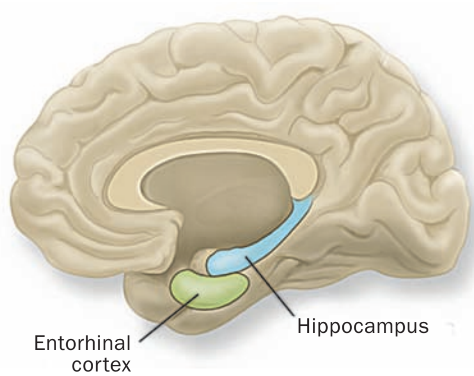
this discovery in my office for the first time, I realized immediately that I was reading a work of historic importance in neuroscience. No one had ever reported a neural response property that was so geometrically regular, so crystalline, so perfect. How could this even be possible? Yet the data were convincing. "This changes everything," I muttered.

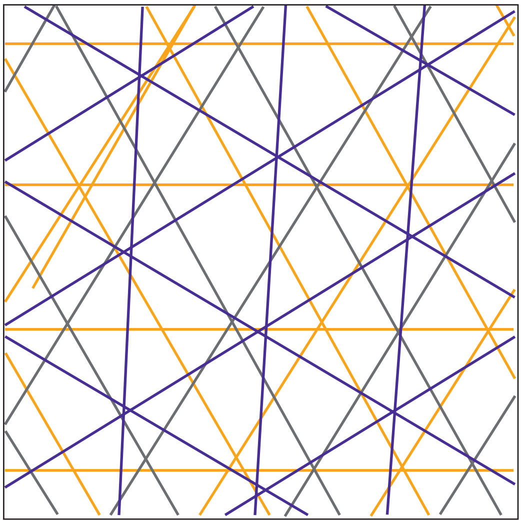
My excitement rose partly from the sheer beauty of the grid-cell response pattern. But it rose, too, from a belief that this was a major step in our quest to understand how the hippocampus might form the basis of episodic memory. Grid cells give us a firm handle on what kind of information is encoded in one of the major inputs into the hippocampus. From this foundation we can start to create more realistic models of what computations occur in the hippocampus to transform these grid representations into the more complex properties that have been discovered about place cells over the past three decades. For example, different subsets of place cells are active in different environments, whereas all grid cells appear to be active in all environments. How is the general spatial map encoded by grid cells turned into the environment-specific (or context-specific) maps encoded by place cells?

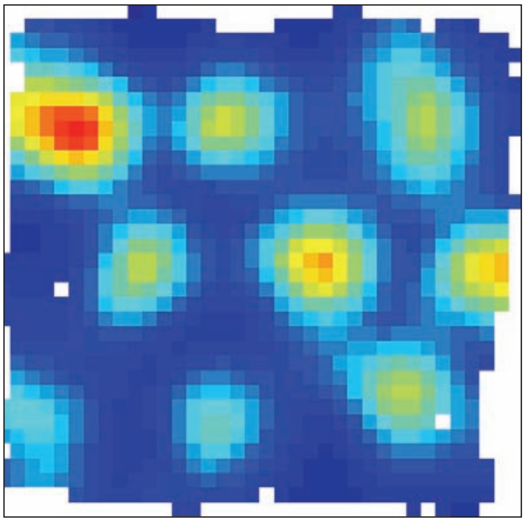
Moreover, the discovery of grid cells affirms emphatically that the hippocampus and medial temporal lobe are outstanding model systems for

The Brain's Tracking System

The "cognitive map" of the environment arises in the hippocampus—long known to be important for memory—and in grid cells in the entorhinal cortex. An individual grid cell projects across the environment a latticework of perfectly equilateral triangles (*bottom left*), the corners of which are sensitive to the rat's presence. Because the grids projected by the brain's thousands of grid cells overlap, the grid cell system fires whenever the rat moves (*bottom right*). The animal's location is thus constantly updated.







KATHERINE SUTLIFF, FROM "IN THE PLACE SPACE," BY D. K. BILKEY, IN *SCIENCE*, VOL. 305; AUGUST 27, 2004, REPRINTED WITH PERMISSION FROM AAAS (*brain*); FROM "NEUROSCIENCE: NEURONS AND NAVIGATION," BY GYÖRGY BUZSÁKI, IN *NATURE*, VOL. 436; AUGUST 11, 2005 (*triangular grids*); MAY-BRITT MOSER *Norwegian University of Science and Technology* (*grid cell activity*)

A Window into Cognition

By A. David Redish

Over the past 30 years, the place cell has become one of the most studied examples of a cellular correlate—that is, a neuron demonstrably connected to a particular behavior, sensation or mental activity—not driven by an immediate sensory or motor cue. As James J. Knierim notes in the main article, each hippocampal place cell fires action potentials only when the rat is in a specific location within an environment (the "place field" of the cell). Thus, if you know where each place cell's place field is, you can track an animal's path by observing the activity of its place cells. Systems neuroscientists call this process "reconstruction." When the animal is asleep, the population of place cells "replays" the animal's experience; using the reconstruction process, it is possible to follow the sequence being replayed and thus to know, in a sense, what the animal is thinking. Place cells provide a way to directly observe cognition, even in the rat.

The term "cognitive map" traces its origin back to Edward C. Tolman. In a classic 1948 paper, the University of California, Berkeley, psychologist proposed that somewhere in the brain existed a representation of the environment—constructed by the animal—which could be used to make plans and navigate the world. The key was that the map had to be "cognitive"—that is, constructed internally from a combination of cues and memory.

The 1971 discovery of hippocampal place cells by University College London neuroscientists John O'Keefe and Jonathan Dostrovsky seemed to put the cognitive map in the hippocampus. (A hippocampal place cell fires only when a rat occupies a specific location in a given environment.) But the cognitive map, asserted O'Keefe and his colleague Lynn Nadel, now at the University of Arizona, in their 1978 book *The Hippocampus as a Cognitive Map,* was still a cognitive construct. Place cells, properly understood, reflected not any specific environmental cue but rather the animal's perception of its place in the environment.

The question of what made a place cell fire when the rat was in its place field remained unanswered. Computational models suggested that place cells encoded some association between external and internal representations of space. But no one really knew what information

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the hippocampus was actually being fed to do these computations.

As Knierim observes, the discovery of grid cells seems to answer exactly that question—which is why cognitive scientists find grid cells intensely exciting. As soon as the paper was published, researchers started examining their earlier work on the entorhinal cortex to try to find the grid cells hidden in their data. Theorists immediately began to build computational models of how the grid is formed and how it might drive hippocampal activity.

Grid cells, like place cells, can provide a way for us to observe and trace cognition. And because the entorhinal grid cells project directly to the hippocampal place cells, we now have an access point to examine broader mechanisms of cognitive processing. Papers by the Norwegian University of Science and Technology's Edvard Moser and May-Britt Moser and other researchers have done exactly that.

One of the most interesting things about the grid cell discovery is that no one predicted it. Theories and models had envisioned that the entorhinal cortex would play an important role in the cognitive map and that entorhinal cells would show more stable intercellular relations across environments than place cells do. But no one imagined that the entorhinal cells would cover the environment with tessellating triangular grids—and anyone who had suggested such a thing would have been laughed out of town.

A. DAVID REDISH is associate professor of neuroscience at the University of Minnesota and author of Beyond the Cognitive Map *(MIT Press, 1999).*

Each grid cell fires when a rat is in any one of many locations that are arranged on a stunningly uniform hexagonal grid in the brain.

understanding the way in which the brain constructs cognitive representations of the world "out there" that are not explicitly tied to any sensory stimulation. There is no pattern of visual landmarks, auditory cues, somatosensory input or other sensations that could possibly cause a grid cell to fire in such a crystalline fashion across any environment. This firing pattern—which is similar regardless of whether the rat is in a familiar, lit room or in a strange location that is pitch-dark—must be a pure cognitive construct. Although grid cell firing patterns are updated and calibrated by sensory input from the vestibular, visual and other sensory systems, they do not depend on external sensory cues.

Some have argued that hippocampal place cells are similarly independent. But the known influence of external landmarks on place cells, and their tendency to fire in single locations, led others to argue that place cells are driven primarily by unique combinations of sensory landmarks that exist at particular locations. This argument cannot explain the firing patterns of grid cells.

The Road Ahead

So what does account for grid cell dynamics? One possibility is that these cells allow an animal to constantly update its physical location on its internal cognitive map by keeping track of its own movements. That information is in turn conveyed to the hippocampus, which combines this spatial representation with other data about an event to create specific, context-rich memories of unique experiences—the ability that *Memento*'s Lenny had lost.

The discovery of grid cells has generated a palpable sense of excitement. We can anticipate that further research into grid cells (along with the other major input to the hippocampus, the lateral entorhinal cortex) will reveal the neural mechanisms that let us remember our personal histories—a vital process that forms the very foundation of one's sense of identity. **M**

(Further Reading)

- **The Hippocampus as a Cognitive Map.** John O'Keefe and Lynn Nadel. 1978. Out of print. Available at **www.cognitivemap.net**
- **Beyond the Cognitive Map.** A. David Redish. MIT Press, 1999. Available at **www.mitpress.mit.edu**
- **Microstructure of a Spatial Map in the Entorhinal Cortex.** Torkel Hafting, Marianne Fyhn, Sturla Molden, May-Britt Moser and Edvard I. Moser in *Nature,* Vol. 436, pages 801–806; August 11, 2005.
- **Conjunctive Representation of Position, Direction, and Velocity in Entorhinal Cortex.** Francesca Sargolini, Marianne Fyhn, Torkel Hafting, Bruce L. McNaughton, Menno P. Witter, May-Britt Moser and Edvard I. Moser in *Science,* Vol. 312, pages 758–762; May 5, 2006.

We Get Comments...

Like most blogs, Mind Matters invites reader comments and questions. Unlike most blogs, reader comments and questions often get answered by leading researchers—the authors of the posts that provide reviews of recent papers, as well as some who visit the blog—and *Scientific American Mind* editors. The sampling below, from the installment on grid cells, includes posts from readers, James J. Knierim, who wrote the installment's lead piece, and Mind Matters editor David Dobbs.

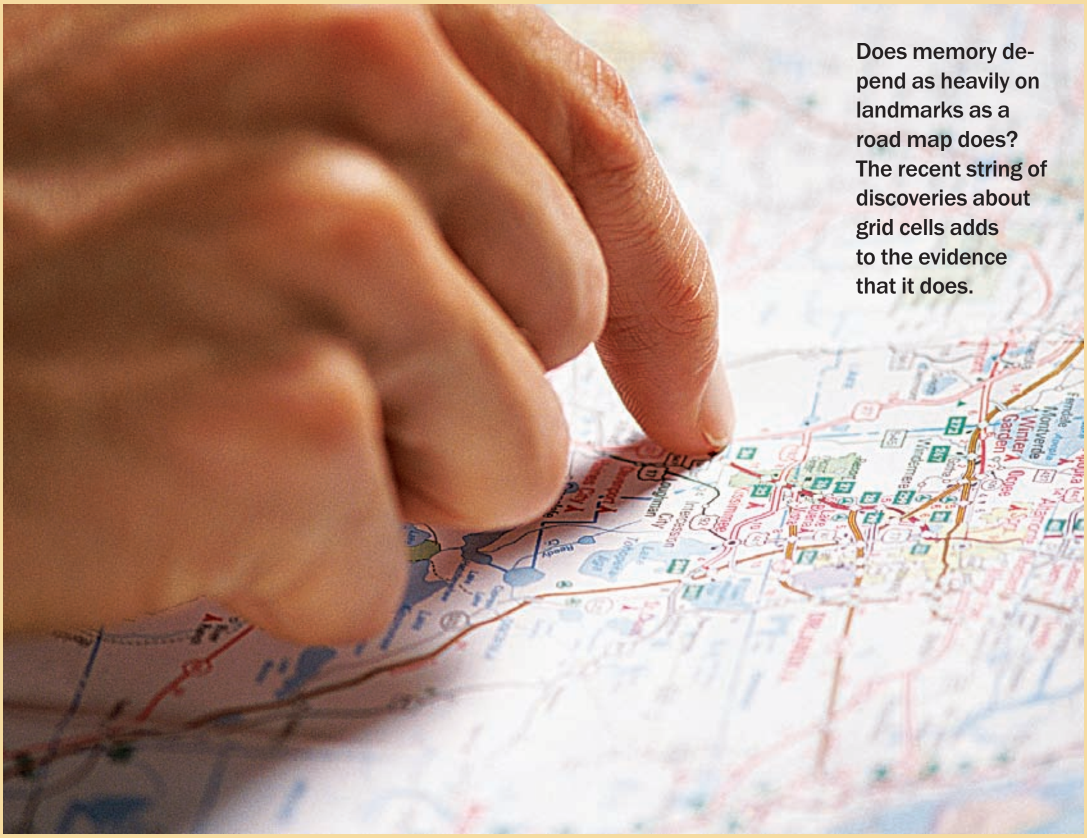
Do Grid Cells Map Dreams?

What are your thoughts on the stored memory of dreams/daydreams in relation to grid cell activity? Is dream space plotted in the same way as reality, and perhaps are those people who seem to never recall their dreams simply not accessing those portions of the spatial map while asleep? —Ian

KNIERIM REPLIES:
Good question, Ian. When a rat sleeps, the hippocampal place cells sometimes fire in the same order in which they fired during a short behavioral sequence when the rat was awake. This process is thought to be related to the formation of long-term memories, as the hippocampus "replays" the rat's recent experience to the neocortex for long-term storage. Grid cells are presumably also involved in this process, because they are a gateway between the hippocampus and the neocortex.

Mythical Mapping

I can't help but be impressed by a seeming relation between the apparent functions of these entorhinal and hippocampal structures and humankind's practice of projecting important mythical events onto features of physical landscapes. American Indians actually visit specific landscape features to recall specific events of their past. History, for us, is a matter of documentation, but before writing it was a



Does memory depend as heavily on landmarks as a road map does? The recent string of discoveries about grid cells adds to the evidence that it does.

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matter of memory—group memory. Tying this history to places might serve a societal function similar to that played by grid cells for individual memories. ***—Bill Crane***

KNIERIM REPLIES:
There may well be a relation between these cultural practices and how our brain is actually wired to remember events. Something about places, either real or imagined, helps us to remember events.

A well-known example is a mnemonic trick used by performers to memorize long lists of random items. As the audience calls out each item, the performer imagines the item as being placed in a particular location in a familiar room. When it is time to recall the list in order (forward or reverse), the performer mentally steps through the sequence of locations and is able to recall the items previously imagined there.

DOBBS ADDS:
The memory-aid method Jim describes (tying items to familiar locations) is called the method of loci, and it was used routinely by the Greeks and Romans to remember long speeches. I have a friend who can remember random strings of numbers or words. He associates the words or numbers to familiar spots along the 18 holes of his favorite golf course. A learned and lively book called *The Art of Memory,* by Frances A. Yates (University of Chicago Press, 1966), describes this method.

As to aboriginal wanderings: Bruce Chatwin's superb book *The Songlines* (Viking, 1987) concerns routes to which Australian aborigines tied narrative songs relating essential myths or stories. Lovely book.

There's a nice neurospatial-anthropology thesis waiting to be written here....

The Wow Factor

The computational power of the brain is astounding. A tiny color topographic plotter/position tracker in the brain is a great new understanding.
—Jim Arneson