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Our ability to pilot a car or airplane—or even to walk through city streets—has been completely transformed by the invention of the Global Positioning System (GPS). How did we navigate, though, before we had GPS? Recent work has shown that the mammalian brain uses an incredibly sophisticated GPS-like tracking system of its own to guide us from one location to the next.

Like the GPS in our phones and cars, our brain's system assesses where we are and where we are heading by integrating multiple signals relating to our position and the passage of time. The brain normally makes these calculations with minimal effort, so we are barely conscious of them. It is only when we get lost or when our navigation skills are compromised by injury or a neurodegenerative disease that we get a glimpse of how critical this mapping-and-navigation system is to our existence.

The ability to figure out where we are and where we need to go is key to survival. Without it, we, like all animals, would be

unable to find food or reproduce. Individuals—and, in fact, the entire species—would perish.

The sophistication of the mammalian system becomes particularly clear when contrasted to those of other animals. The simple roundworm *Caenorhabditis elegans*, which has just 302 neurons, navigates almost solely in response to olfactory signals, following the path of an increasing or decreasing odor gradient.

Animals with more sophisticated nervous systems, such as desert ants or honeybees, find their way with the help of additional strategies. One of these methods is called path integration, a GPS-like mechanism in which neurons calculate position based on constant monitoring of the animal's direction and speed of movement relative to a starting point—a task carried out without reference to external cues such as physical landmarks. In vertebrates, particularly in mammals, the repertoire of behaviors that enable an animal to locate itself in its environment has expanded still further.

More than any other class of animals, mammals rely on the capacity to form neural maps of the environment—patterns of electrical activity in the brain in which groups of nerve cells fire in a way that reflects the layout of the surrounding environment and an animal's position in it. The formation of such mental maps is mostly thought to occur in the cortex, the brain's wrinkled upper layers that developed quite late in evolution.

Over the past few decades researchers have gained a deep understanding of just how the brain forms and then revises

IN BRIEF

Determining where we are in relation to our surroundings—streets, trees or other landmarks around us—remains an essential skill without which our own survival, or even that of our species, would rapidly be endangered.

Networks of cells lodged deep within the brain work together to assemble an internal mental map of our environment that enables us to find our way seamlessly from place to place, as if these cells equated to a biological Global Positioning System.

Regions of the brain involved with pathfinding are also intimately connected to the formation of new memories. When these neural tracts malfunction, they can produce the severe disorientation experienced by a patient with Alzheimer's disease.

The Nervous System's Incredible Pathfinding Skills

Survival for any species requires an ability to take into account the surrounding environment and to make a calculation, even a crude one, of where an animal has been, where it is and where it is going. On higher rungs of the evolutionary chain, many species have developed "path integration" systems that allow them to perform this task without the need to locate where they are by referencing external landmarks. Mammals have found an even more elaborate solution that uses internalized mental maps.

A NEUROSCIENCE OF SPACE

THE STUDY of the brain's spatial maps began with Edward C. Tolman, a psychology professor at the University of California, Berkeley, from 1918 to 1954. Before Tolman's work, laboratory experiments in rats seemed to suggest that animals find their way around by responding to—and memorizing—successive stimuli along the path they move. In learning to run a maze, for instance, they were thought to recall sequences of turns they made from the maze's start to its end. This idea, however, did not take into account that the animals might visualize an overall picture of the entire maze to be able to plan the best route.

Tolman broke radically with prevailing views. He had observed rats take shortcuts or make detours, behaviors that would not be expected if they had learned only one long sequence of behaviors. Based on his observations, he proposed that animals form mental maps of the environment that mirror the spatial geometry of the outer world. These cognitive maps did more than help animals to find their way; they also appeared to record information about the events that the animals experienced at specific locales.

Tolman's ideas, proposed for the first time around 1930, remained controversial for decades. Acceptance came slowly, in part because they were based entirely on observing the behavior of experimental animals, which could be interpreted in many ways. Tolman did not have the concepts or tools to test whether an internal map of the environment actually existed in an animal's brain.

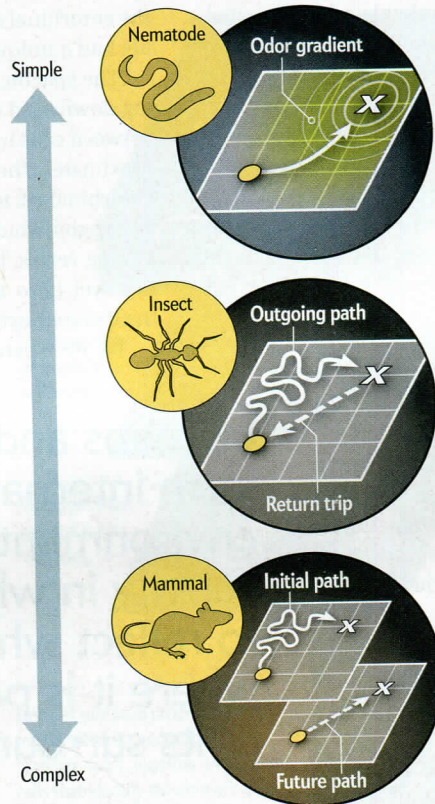
It took about 40 years before direct evidence for such a map appeared in studies of neural activity. In the 1950s progress in the development of microelectrodes made it possible to monitor electrical activity from individual neurons in awake animals. These very thin electrodes enabled researchers to identify the firing of single neurons as the animals went about their business. A cell "fires" when it triggers an action potential—a short-lasting change in the voltage across the neuronal cell membrane. Action potentials cause neurons to release neurotransmitter molecules that convey signals from one neuron to another.

John O'Keefe of University College London used microelec-

trodes to monitor action potentials in rats in the hippocampus, an area of the brain known for decades to be important for memory functions. In 1971 he reported that neurons there fired when a rat in a box spent time at a certain location—thus, he called them place cells. O'Keefe observed that different place cells fired at different locations in the box and that the firing pattern of the cells collectively formed a map of locations in the box. The combined activity of multiple place cells could be read out from the electrodes to identify the animal's precise location at any given time. In 1978 O'Keefe and his colleague Lynn Nadel, now at the University of Arizona, suggested that place cells were, in fact, an integral part of the cognitive map Tolman had envisaged.

A CORTICAL MAP

THE DISCOVERY of place cells opened a window into the deepest parts of the cortex, in areas farthest away from the sensory cor-



Tracing a Smell

The simple roundworm *Caenorhabditis elegans* exhibits perhaps the most basic animal navigation system. The worm world is organized according to smell. Equipped with a mere 302 neurons, it pushes itself straight ahead toward a food source by sensing ever increasing levels of an odor.

Internal GPS

Evolution has equipped even some insects and other arthropods with elaborate path-integration capabilities. They can monitor internally their speed and direction relative to a starting point. This allows them to find more efficient means of traveling a given route—a direct return instead of the zigs and zags traversed on an outbound journey.

Mental Maps

Mammals have evolved still more intricate orienteering skills in which neurons fire in their brain in sequences that mirror the routes they travel. These networks of neurons make up mental maps of the physical world. Animals store memories of past journeys and use them for the planning of future trips.

tices (those that receive inputs from the senses) and from the motor cortex (which emits the signals that initiate or control movement). At the end of the 1960s, when O'Keefe started his work, knowledge about when neurons switched on and off was largely restricted to areas called the primary sensory cortices, where neural activity was controlled directly by such sensory inputs as light, sound and touch.

Neuroscientists of that era speculated that the hippocampus was too far removed from the sensory organs to process their inputs in any manner that could easily be understood from a microelectrode recording. The discovery of cells in the hippocampus that created a map of an animal's immediate environment dashed that speculation.

Even though the finding was remarkable and suggested a role for place cells in navigation, no one knew what that role might be for decades after their discovery. Place cells were in an area of the hippocampus, called CA1, that was the end point in a signaling chain originating elsewhere in the hippocampus. It was hypothesized that place cells received many of the critical navigation-related computations from other hippocampal regions. In the early 2000s the two of us decided to explore this idea further in the new lab we had set up at the Norwegian University of Science and Technology in Trondheim. This pursuit ultimately led to a major discovery.

In collaboration with Menno Witter, now at our institute, and a set of highly creative students, we began by using microelectrodes to monitor the activity of place cells in the rat hippocampus after we had disrupted part of a neuronal circuit there known to feed information to these cells. We expected the work to confirm that this circuit was important to the proper functioning of the place cells. To our surprise, the neurons at the end of that circuit, in CA1, still fired when the animals arrived at specific locations.

Our team's inescapable conclusion was that place cells did not depend on this hippocampal circuit to gauge an animal's bearings. Our attention then turned to the only neural pathway that had been spared by our intervention: the direct connections to CA1 from the entorhinal cortex, an adjoining area that provides an interface to the rest of the cortex.

In 2002 we inserted microelectrodes in the entorhinal cortex, still in a collaboration with Witter, and began recording as the animals performed tasks that were similar to the ones we had used for our place cell studies. We guided electrodes into an area of the entorhinal cortex having direct connections to the parts of hippocampus where place cells had been recorded in almost every study before ours. Many cells in the entorhinal cortex turned out to fire when an animal was at a particular spot in the enclosure, much like the place cells in the hippocampus do. But unlike a place cell, a single cell in the entorhinal cortex fired, not only at one location visited by a rodent but at many.

The most striking property of these cells, though, was the way they fired. Their pattern of activity became obvious to us only when, in 2005, we increased the size of the enclosure in which we were recording. After expanding it to a certain size, we found that the multiple locations at which an entorhinal cell fired formed the vertices of a hexagon. At each vertex, the cell, which we called a grid cell, fired when the animal passed over it.

The hexagons, which covered the entire enclosure, appeared to form the individual units of a grid—similar to the squares formed by the coordinate lines on a road map. The firing pattern raised the possibility that grid cells, unlike place cells, provide information about distance and direction, helping an animal to track its trajectory based on internal cues from the body's motions without relying on inputs from the environment.

Several aspects of the grid also changed as we examined the activity of cells in different parts of the entorhinal cortex. At the dorsal part, near the top of this structure, the cells generated a grid of the enclosure that consisted of tightly spaced hexagons. The size of the hexagons increased in a series of steps—or modules—as one moved toward the lower, or ventral, part of the entorhinal cortex. The hexagonal grid elements in each module had a unique spacing.

The spacing of the grid cells in each successive module moving downward could be determined by multiplying the distance between cells in the previous module by a factor of about 1.4, approximately the square root of 2. In the module at the top of the entorhinal cortex, a rat that activated a grid cell at one vertex of a hexagon would have to travel 30 to 35 centimeters to an adjoining vertex. In the next module down, the animal would have to travel 42 to 49 centimeters, and so on. In the lowest module, the distance extended up to several meters in length.

We were extremely excited by the grid cells and their tidy or-

Humans and other mammals form internal maps of the environment—patterns of neural activity in which brain cells fire to reflect where an animal is and where it is positioned in relation to its surroundings.

ganization. In most parts of the cortex, the neurons have firing patterns that appear chaotic and inaccessible, but here, deep in the cortex, there was a system of cells that fired in a predictable and orderly pattern. We were eager to investigate. But these cells and place cells were not the only ones involved in mapping the mammal's world—other surprises also awaited us.

Back in the mid-1980s and early 1990s, James B. Ranck of SUNY Downstate Medical Center and Jeffrey S. Taube, now at Dartmouth College, had described cells that fired when a rodent faced a particular direction. Ranck and Taube had discovered such head-direction cells in the presubiculum, another region of the cortex adjacent to the hippocampus.

Our studies found that these cells were also present in the entorhinal cortex, intermingled among grid cells. Many head-direction cells in the entorhinal cortex also functioned as grid cells: the locations in the enclosure where they fired also formed a grid, but the cells became active at those locales only when the rat was facing a certain direction. These cells appeared to provide a compass for the animal; by monitoring the cells, one

could read out the direction the animal was facing at any given time relative to the surrounding environment.

A few years later, in 2008, we made a discovery in the entorhinal cortex of another cell type. These border cells fired whenever the animal approached a wall or an edge of the enclosure or some other divide. These cells appeared to calculate how far the animal was from a boundary. This information could then be used by grid cells to estimate how far the animal had traveled from the wall, and it could also be established as a reference point to remind the rat of the wall's whereabouts at a later time.

Finally, in 2015, yet a fourth kind of cell entered the scene. It responded specifically to the running speed, regardless of the animal's location or direction. The firing rates of these neurons increased in proportion to the speed of movement. Indeed, we could ascertain how fast an animal was moving at a given moment by looking at the firing rates of just a handful of speed cells. In conjunction with head-direction cells, speed cells may serve the role of providing grid cells continually updated information about the animal's movement—its speed, direction and the distance from where it started.

FROM GRID TO PLACE CELLS

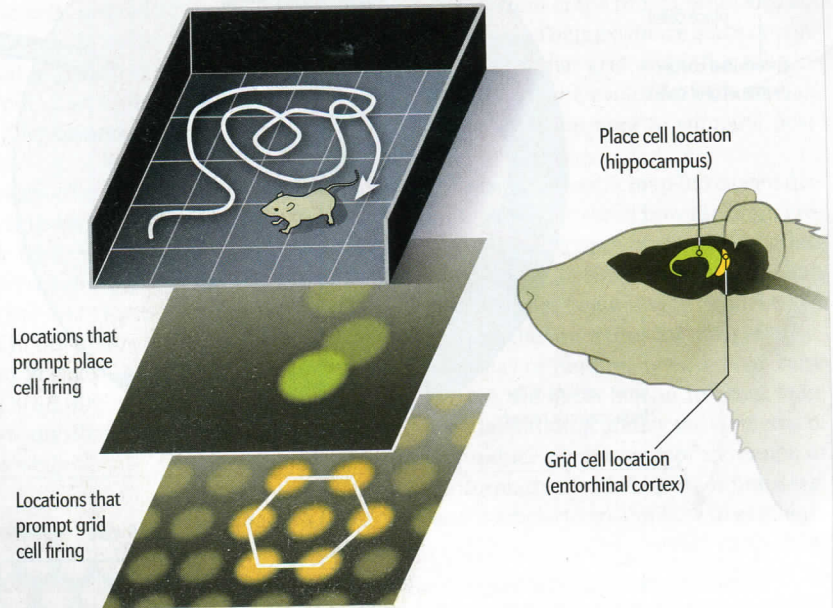
OUR DISCOVERY of grid cells grew out of our desire to uncover the inputs that allow place cells to give mammals an internal picture of their environment. We now understand that place cells integrate the signals from various types of cells in the entorhinal cortex as the brain attempts to track the route an animal has traveled and where it is going in its environment. Yet even these processes do not tell the whole story of how mammals navigate.

Our initial work focused on the medial (inner) entorhinal cortex. Place cells may also receive signals from the lateral entorhinal cortex, which relays processed input from a number of sensory systems, including information about odor and identity of objects. By integrating inputs from the medial and lateral parts of the entorhinal cortex, place cells interpret signals from throughout the brain. The complex interaction of messages arriving in the hippocampus and the formation of location-specific memories that this enables are still being investigated by our lab and others, and this research will undoubtedly continue for many years to come.

One way to begin to understand how the spatial maps of the medial entorhinal cortex and the hippocampus combine to aid navigation is to ask how the maps differ. John Kubie and the late

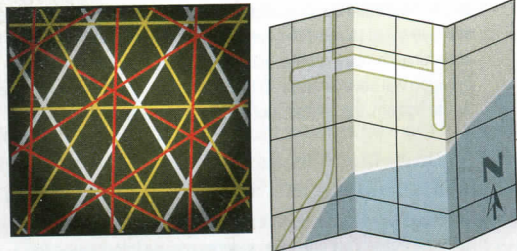
How the Brain Takes Its Bearings

The idea that the brains of mammals make a mental map that mirrors the spatial geometry of the outer world first emerged around 1930. Neuroscientists have subsequently identified cells that work together to create such maps. A key development came in 1971, when an American-British researcher found that place cells in the rat hippocampus fire at particular locations on the willy-nilly path an animal travels. In 2005 the authors discovered grid cells that let an animal measure its location in its environment—say, in relation to the walls of an enclosure. As the animal moves about, each grid cell fires at multiple locations that correspond to the vertices of a hexagon.



A Cognitive Map Emerges

Firing of grid cells produces a map (right), akin to a geographical map (far right). Together with place cells that identify the animal's location in a particular environment, grid cells enable the animal to build a mental picture of its surroundings.

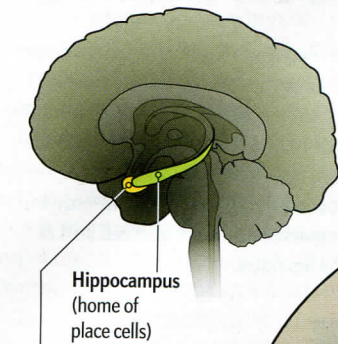


Robert U. Muller, both at SUNY Downstate Medical Center, showed in the 1980s that maps in the hippocampus made up of place cells may change entirely when an animal moves to a new environment—even to a different colored enclosure at the same location in the same room.

Experiments performed in our own lab, with rats foraging in up to 11 enclosures in a series of different rooms, have shown that each room, in fact, rapidly gives rise to its own independent map, further supporting the idea that the hippocampus forms spatial maps tailored to specific environments.

In contrast, the maps in the medial entorhinal cortex are universal. Grid cells—and head-direction and border cells—that fire together at a particular set of locations on the grid map for one environment also fire at analogous positions on the map for another

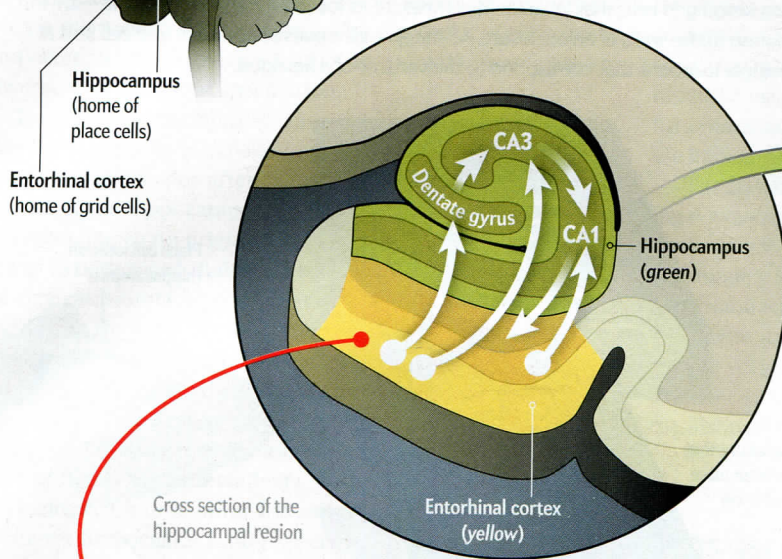
Inside the Brain's GPS



Hippocampus
(home of
place cells)

Entorhinal cortex
(home of grid cells)

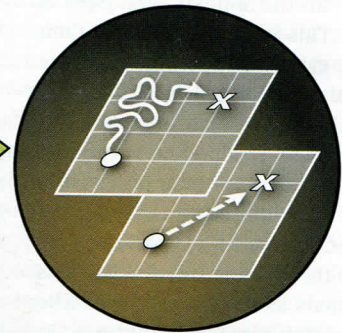
The neural navigation system of the human brain resides deep within a region known as the medial temporal lobe. Two areas of the medial temporal lobe—the entorhinal cortex and the hippocampus—act as key components of the brain's GPS. Networks of specialized cell types in the entorhinal cortex contribute to the complexity in the mammalian brain's pathfinding system.



Cross section of the
hippocampal region

Entorhinal cortex
(yellow)

Hippocampus
(green)

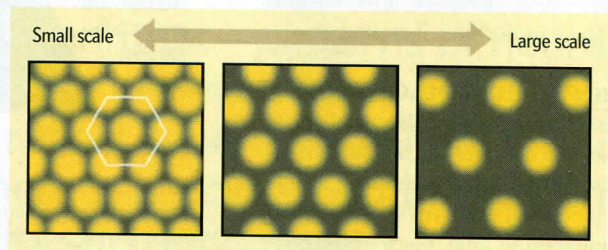


Messaging the Hippocampus

The entorhinal cortex transmits information from grid cells about direction and distance traveled. It does so by sending signals along several pathways to subregions of the hippocampus (the dentate gyrus, CA3 and CA1) that produce a mental map optimized for planning future journeys (inset).

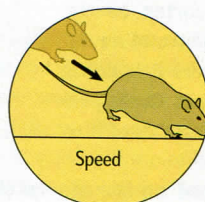
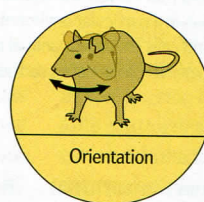
A Close Look at Grid Cell Organization ...

... reveals that the spacing of the hexagonal elements that aid in creating a spatial map change when moving from top to bottom in the entorhinal cortex. The broader spacings correspond to larger distances the rat needs to travel to activate a vertex on the grid. At the top of the entorhinal cortex, a rat that activates a grid cell at one vertex of a hexagon will have to move 30 to 35 centimeters to an adjoining vertex. At the bottom, the animal needs to go as far as several meters.



Other Specialized Cells Recently Discovered ...

... in the entorhinal cortex of rodents convey information to the hippocampus about the orientation of an individual's head, its speed of movement, and the distance to walls and other obstacles encountered. The output of these cells is combined to help create a composite map of the animal's environs.



environment—as if latitude and longitude lines from the first map were imposed on the new setting. The sequence of cells that fire as the animal moves northeast in one room of the cage repeats when the rat goes in that same direction in the other room. The pattern of signaling among these cells in the entorhinal cortex is what the brain uses for navigating through its surroundings.

These codes are then transmitted from the entorhinal cortex to the hippocampus, where they are used to form maps specific to a particular place. From the standpoint of evolution, two sets of maps that integrate their information to guide animals ap-

pear to be an efficient solution for a system used by animals for spatial navigation. The grids formed in the medial entorhinal cortex that measure distance and direction do not change from one room to the next. In contrast, the place cells of the hippocampus form individual maps for every single room.

LOCAL MAPS

UNDERSTANDING of the neural navigation system remains a work in progress. Almost all our knowledge of place and grid cells has been obtained in experiments in which electrical activity

from neurons is recorded when rats or mice walk about randomly in highly artificial environments—boxes with flat bottoms and no internal structures to serve as landmarks.

A lab differs substantially from natural environments, which change constantly and are full of three-dimensional objects. The reductionism of the studies raises questions about whether place cells and grid cells fire in the same way when animals find themselves outside the lab.

Experiments in complex mazes that try to mimic animals' natural habitat provide a few clues to what might be going on. In 2009 we recorded grid cells as animals moved through an intricate maze in which they encountered a hairpin turn at the end of each alley that marked the beginning of the next passageway. The study showed that, as expected, grid cells formed patterns of hexagons to map out distances for the rats in individual alleys of the maze. But each time an animal turned from one alley to the next, an abrupt transition occurred. A separate grid pattern was then superimposed on the new alley, almost as if the rat were entering an entirely different room.

Later work in our lab has shown that grid maps also fragment into smaller maps in open environments if these spaces are large enough. We are now researching how these smaller maps merge to form an integrated map of a given area. Even these experiments are oversimplified because the enclosures are flat and horizontal. Experiments performed in other labs—observing flying bats and rats that climb around in cages—are beginning to provide some clues: place cells and head-direction cells seem to fire in specific places throughout any three-dimensional space, and most likely grid cells do as well.

SPACE AND MEMORY

THE NAVIGATIONAL SYSTEM in the hippocampus does more than help animals get from point A to point B. Beyond receiving information about position, distance and direction from the medial entorhinal cortex, the hippocampus makes a record of what is located in a particular place—whether a car or a flagpole—as well as the events that take place there. The map of space created by place cells thus contains not only information about an animal's whereabouts but also details about the animal's experiences, similar to Tolman's conception of a cognitive map.

Some of this added information appears to come from neurons in the lateral part of the entorhinal cortex. Particulars about objects and events fuse with an animal's coordinates and are laid down as a memory. When the memory is later retrieved, both the event and the position are called to mind.

This coupling of place with memory recalls a strategy for memorization invented by ancient Greeks and Romans. The "method of loci" lets a person memorize a list of items by imagining putting each item at a position along a well-known path through a place, say, a landscape or a building—an arrangement often called a memory palace. Participants in memory contests still use the technique to recall long lists of numbers, letters or playing cards.

Sadly, the entorhinal cortex is among the first areas to fail in people with Alzheimer's disease. The illness causes brain cells there to die, and a reduction in its size is considered a reliable measure for identifying at-risk individuals. The tendency to wander and get lost is also among the earliest indicators of the disorder. In the later stages of Alzheimer's, cells die in the hip-

poampus, producing an inability to recall experiences or remember concepts such as the names of colors. In fact, a recent study has provided evidence that young individuals with a gene that places them at an elevated risk for Alzheimer's may have deficiencies in the functioning of their grid cell networks—a finding that may lead to new ways of diagnosing the disease.

A RICH REPERTOIRE

TODAY, MORE THAN 80 YEARS since Tolman first proposed the existence of a mental map of our surroundings, it is clear that place cells are just one component of an intricate representation the brain makes of its spatial environment to calculate location, distance, speed and direction. The multiple cell types that have been found in the navigation system of the rodent brain also occur in bats, monkeys and humans. Their existence across mammalian taxonomic orders suggests that grid and other cells involved in navigation arose early in the evolution of mammals and that similar neural algorithms are used to compute position across species.

Many of the building blocks of Tolman's map have been discovered, and we are beginning to understand how the brain creates and deploys them. The spatial representation system has become one of the best-understood circuits of the mammalian cortex, and the algorithms it uses are beginning to be identified to help unlock the neural codes the brain uses for navigation.

As with so many other areas of inquiry, new findings raise new questions. We know that the brain has an internal map, but we still need a better understanding of how the elements of the map work together to produce a cohesive representation of positioning and how the information is read by other brain systems to make decisions about where to go and how to get there.

Other questions abound. Is the spatial network of the hippocampus and the entorhinal cortex limited to navigation of local space? In rodents, we examine areas that have radii of only a few meters. Are place and grid cells also used for long-distance navigation, such as when bats migrate hundreds or thousands of kilometers?

Finally, we wonder how grid cells originate, whether there is a critical formative period for them in an animal's development and whether place and grid cells can be found in other vertebrates or invertebrates. If invertebrates use them, the finding would imply that evolution has used this spatial-mapping system for hundreds of millions of years. The brain's GPS will continue to provide a rich trove of leads for new research that will occupy generations of scientists in the decades ahead. ■

MORE TO EXPLORE

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