100 bats and a long, dark tunnel—a neuroscientist's quest to unlock the secrets of 3-D navigation

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Nachum Ulanovsky with one of his research bats. Credit: David Vaaknin for Nature

On a sun-parched patch of land in Rehovot, Israel, two neuroscientists peer into the darkness of a 200-metre-long tunnel of their own design. The fabric panels of the snaking structure shimmer in the heat, while, inside, a study subject is navigating its dim length. Finally, out of the blackness bursts a bat, which executes a mid-air backflip to land upside down, hanging at the tunnel's entrance.

Nachum Ulanovsky, the study leader, looks affectionately at the creature as his graduate student offers it a piece of banana—a reward for the valuable data it has just added to their latest study of how brains navigate.

The vast majority of experiments probing navigation in the brain have been done in the confines of labs, using earthbound rats and mice. Ulanovsky broke with the convention. He constructed the flight tunnel on a disused plot on the grounds of the Weizmann Institute of Science—the first of several planned arenas—because he wanted to find out how a mammalian brain navigates a more natural environment. In particular, he wanted to know how brains deal with a third dimension.

The tunnel, which Ulanovsky built in 2016, has already proved its scientific value. So have the bats. They have helped Ulanovsky to discover new aspects of the complex encoding of navigation—a fundamental brain function essential for survival. He has found a new cell type responsible for the bats' 3-D compass, and other cells that keep track of where other bats are in the environment. It is a hot area of study—navigation researchers won the 2014 Nobel Prize in Physiology or Medicine and the field is an increasingly prominent fixture at every big neuroscience conference.

"Nachum's boldness is impressive," says Edvard Moser of the Kavli Institute for Systems Neuroscience in Trondheim, Norway, one of the 2014 Nobel laureates. "And it's paid off—his approach is allowing important new questions to be addressed."

And for brain scientists hitting the limits of what they can learn from highly simplified behaviour in the lab, Ulanovsky is a pioneer of 'natural neuroscience'. Over the years, his arenas and tunnels have been getting larger, more sophisticated and less like an artificial lab environment. Up next is a giant maze that will allow his team to ask even more advanced questions about how the brain copes with making decisions—such as which way to turn—on the wing. "If we want to really understand how the brain works, we need to study animals doing more natural tasks," says Dora Angelaki, a neuroscientist at Baylor College of Medicine in Houston, Texas. "More of us are finally starting to realize this."

Armed for science

When Ulanovsky opened his lab at the Weizmann Institute in 2007, he was completing a circular flight path of his own. His family emigrated from Moscow to Israel in 1973, when he was just four months old, and settled in Rehovot. As a child, Ulanovsky played in the Weizmann's subtropical gardens and attended science events for local children and young people.

Nachum Ulanovsky takes a walk in the flight tunnel. Credit: Weizmann Institute of Science

Once they turn 18, most physically fit Israelis enter compulsory military service. But Ulanovsky didn't want to lose academic momentum when he graduated from high school at 16, so he enrolled in a three-year physics course at Tel Aviv University—even though that meant starting his military service late and, as a result, serving for a longer period.

His service proved productive. In addition to getting general military training, he was put in a research and development division because of his physics background. Over five years, he learnt technical skills such as designing high-tech instruments and programming that would later prove invaluable in designing arenas and sensors for his bats. The army allowed him time off to take courses that supported his growing interest in biology. He left the army intent on becoming a neuroscientist, and launched into a Ph.D. at the Hebrew University in Jerusalem, studying how the cat brain processes auditory signals.

He discovered that auditory neurons have their own type of memory, and promptly immersed himself in the voluminous memory literature, where he discovered the overlapping field of navigation (animals have to remember where they have been to navigate, and it is not by chance that memory and navigation are processed in the same brain area). The field was dominated by studies in ground-based rats and mice, whose navigational experience is relatively easy to measure as they scuttle around small boxes in labs. But the question of how different animals perceive the world as they move vertically—swimming, climbing trees or flying—had not been seriously addressed. Ulanovsky decided that to study the brain's complex navigational code more holistically, he needed a mammal whose route-finding experience is mostly 3-D, which led him to the only flying mammal: the bat.

He joined a bat lab at the University of Maryland in College Park to learn more about the creatures. He found several similarities to rodent models of navigation, discovering that bats, too, use special cells to get around1. By 2007, Ulanovsky had his own bat lab and a tenure-track position at the Weizmann.

Ulanovsky is a composed person, but his equanimity can wobble when he talks about bats. His voice gets louder by a few decibels, and his face lights up. "In the West, people are frightened by creatures of the night—in Hollywood movies, when the heroine goes into a dark building and bats come rushing out, you know something bad is going to happen." The fear is misplaced, he says. "In China, bats are considered a good omen."

Space odyssey

Neuroscientists have been mesmerized by how the brain encodes its spatial environment ever since the 1970s, when John O'Keefe at University College London found that the rat brain had a neat way to know where the animal is2. When he placed electrodes in a region of the brain called the hippocampus, O'Keefe found neurons that fired only when a rat was in a particular location in its enclosure, creating a sort of cognitive map. He called them 'place cells'.

Nearly three decades later, Edvard Moser and May-Britt Moser, also at the Kavli Institute, discovered another type of way-finding cell in the nearby entorhinal cortex: grid cells, which fire not just at a single place in the enclosure, but at multiple points arranged in a hexagon3. These cells make up a brain code that allows the animal to keep track of its relative position in space, much like a tiny Global Positioning System (GPS). The Mosers shared the 2014 Nobel prize with O'Keefe; they and other scientists have also discovered other types of navigation cell in the hippocampal area, including those that fire in response to head direction4, or to a border such as a cage wall5.

Almost all of these discoveries came from rats: animals that—aside from, say, raising themselves on their hind legs to sniff, or accidentally falling from shelves—live their lives on the horizontal. One imaginative attempt to get around this monitored rats with implanted electrodes in weightless conditions during a 1998 flight on a NASA space-shuttle, but the result was inconclusive6.

For Ulanovsky, the virtues of bats extended beyond the animals' suitability for understanding 3-D mapping: he wanted to work with a wild animal, to build a better picture of natural behaviour. He started to think that highly controlled lab experiments, so crucial to understanding some basic properties of neurons, needed a reality check. "We don't know nearly enough about how all these cells work together to map the environment that animals inhabit in the wild," he says. So he reasoned that bats caught from the wild and flown in less constrained environments would be the ideal subjects. Moreover, Ulanovsky was convinced that studying the system in something other than a lab rodent would help to identify which aspects of behaviour cut across species.

Edvard Moser agrees that studying the same skill in many species is important. "Knowing the different ways it is possible to solve the same problem will help us learn in general terms how brains, including the human brain, work."

Before Ulanovsky could put his ideas to the test, he had to find the right sort of bat, check how it explored its natural environment and, most challengingly, design instruments to collect data from the bat and its brain.

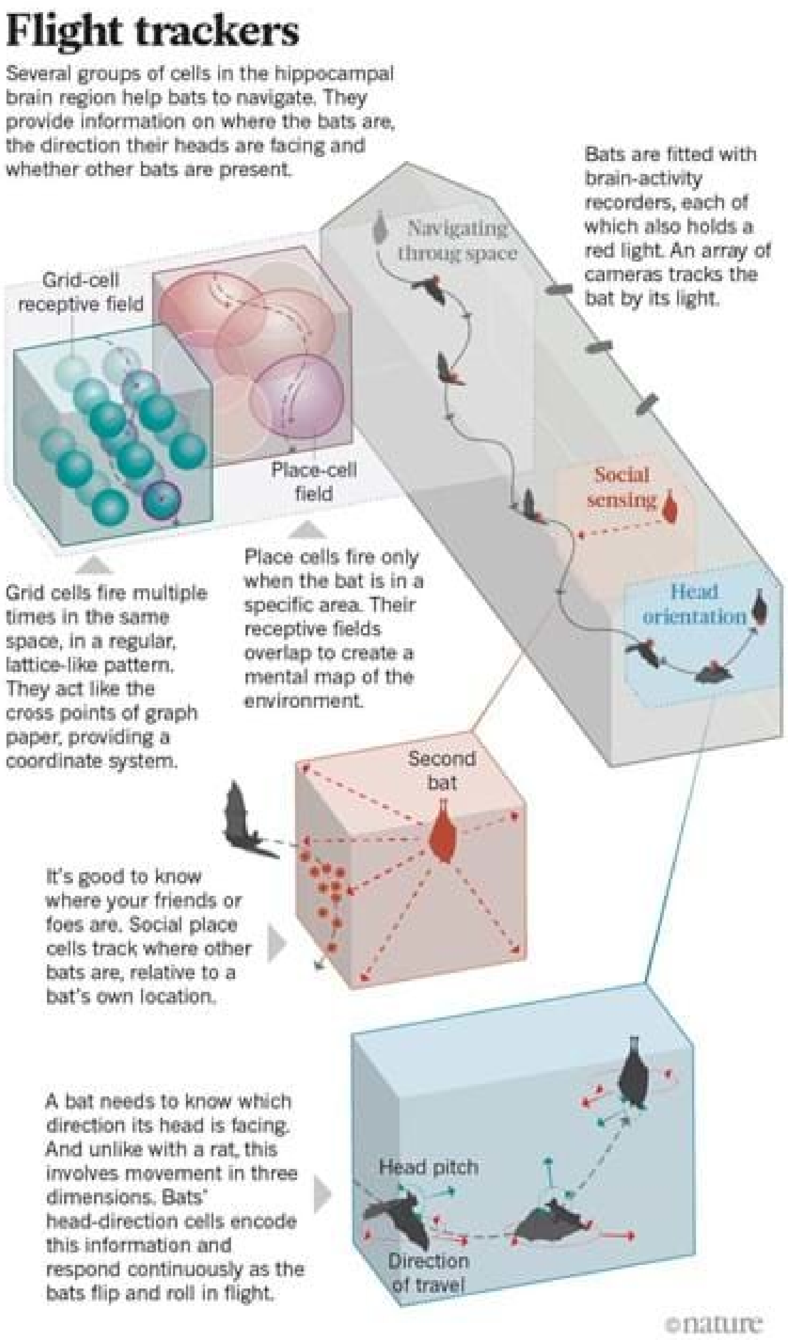
Data from the brains of rats running around small enclosures are generally picked up by implanted electrodes and transferred to computers using cables. "Clearly, that won't work in flying bats," says Ulanovsky. He set about designing wireless GPS and electrophysiology devices that are small enough for a bat to carry. It was a technical challenge, and he might not have succeeded without his army training in instrumentation and software, he says.

His GPS logger is a 5-square-centimetre device tipping the scales at 8 grams. His neural logger, with 16 spindly electrodes—each thinner than a human hair—weighs in at just 7 grams. It is sensitive enough to record several individual neurons firing, and it can store many hours' worth of data.

Tiny as they are, these loggers are too heavy for many bats to carry—including the delicate 20-gram bat Eptesicus fuscus, commonly known, ironically, as the big brown bat, and the species Ulanovsky studied when he was at Maryland. Instead, he settled on using the

Egyptian fruit bat (Rousettus aegyptiacus). It's ten times larger, approaching the size of an average laboratory rat, and common in Israel. "That was the low-tech part of my approach to miniaturization—choose a bigger bat," says Ulanovsky.

Some bats can be vicious, but Egyptian fruit bats, he says, "are easy to tame and very nice to work with". A couple of times a year, he picks up a giant net and heads out on a bat-catching safari, collecting specimens from colonies that inhabit abandoned buildings, or caves in the Judean hills.



Flight trackers

Several groups of cells in the hippocampal brain region help bats to navigate. They provide information on where the bats are, the direction their heads are facing and whether other bats are present.

Bats are fitted with brain-activity recorders, each of which also holds a red light. An array of cameras tracks the bat by its light.

Grid cells fire multiple times in the same space, in a regular, lattice-like pattern. They act like the cross points of graph paper, providing a coordinate system.

Place cells fire only when the bat is in a specific area. Their receptive fields overlap to create a mental map of the environment.

It's good to know where your friends or foes are. Social place cells track where other bats are, relative to a bat's own location.

A bat needs to know which direction its head is facing. And unlike with a rat, this involves movement in three dimensions. Bats' head-direction cells encode this information and respond continuously as the bats flip and roll in flight.

Credit: Nik Spencer/Nature

One of his earliest experiments, started in 2008, aimed to find out how far his bats chose to fly when left to their own devices. Very little was known about the natural behaviour of bats, he says, so he needed to gather some basic information. He armed 35 bats with GPS loggers and discovered that they flew 15 kilometres or more each night to find dinner—remembering the exact location of a particular heavily fruited tree7.

He also built flight rooms in his labs (see 'Flight trackers'). The largest is about 6 × 5 × 3 metres—close to half the size of a squash court—and is decked out with cameras, landing balls for the bats to hang from and feeding stations where they can be tempted with fruit. Clad in metal and a layer of black acoustic foam to shield it from external noise and electrical signals, the room is silent. The lighting can be adjusted from dim to very dim.

In the control room next door, the bats appear as tiny dots of light moving across a screen. Each bat carries a red light-emitting diode (LED), tracked by the cameras as the animals flit about the room. Their brain activity is monitored with a neural logger whose electrodes are surgically implanted into the hippocampus and whose external hardware is fixed to the skull with tiny screws. The cameras and loggers enable Ulanovsky to correlate the firing of neurons with the bats' exact position in space.

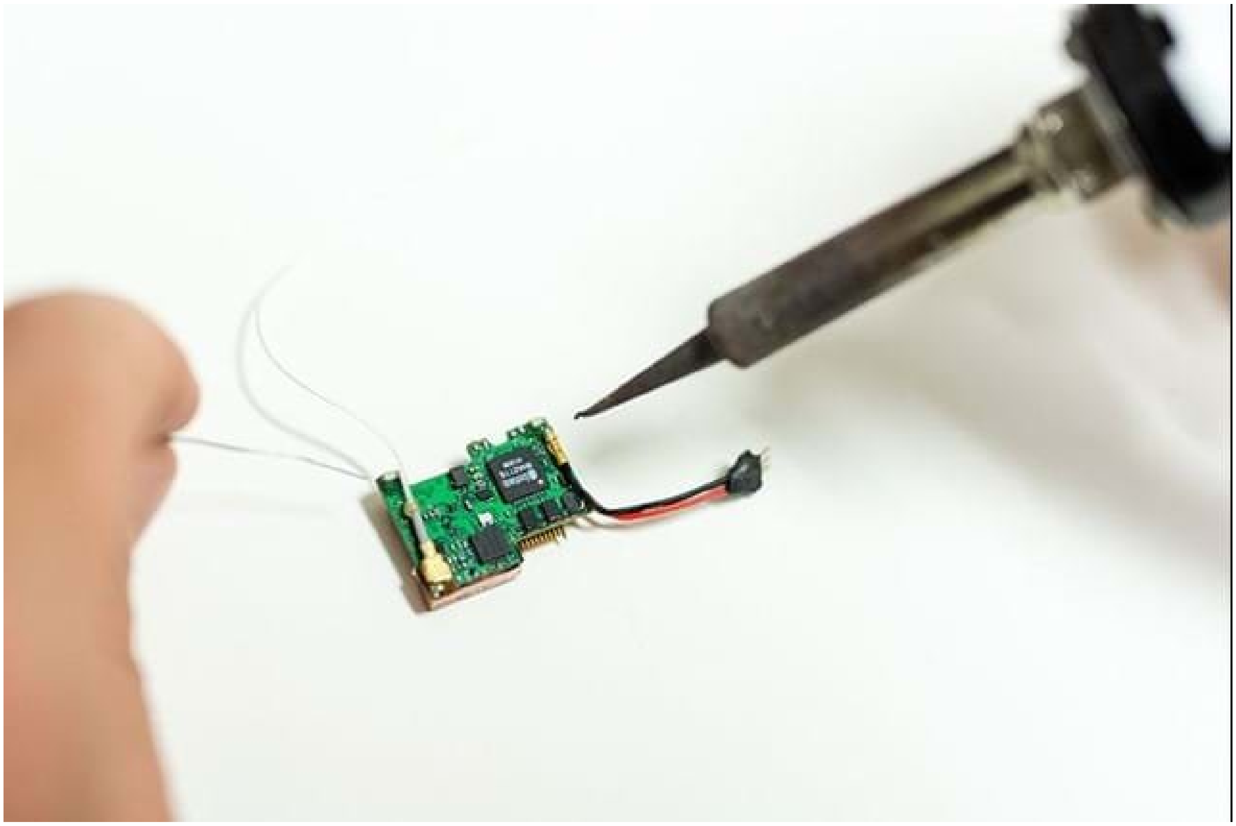
In this set-up, he has been able to reveal the 3-D territory of a typical bat-nav neuron. For example, place-cell fields—measured in rats as flat circles of a particular size—turned out in flying bats to be almost spherical8, showing none of the vertical elongation that some rat experiments had predicted9. He worked out how head-direction cells operate as a 3-D compass10, and discovered another type of navigation cell—the long-sought vector cell—which tracks angle and distance to a particular goal11. One series of experiments helped put to rest a once-popular theory from rat studies that proposed that a certain type of brain oscillation creates grid-like neural maps; the oscillation turned out to be absent in bats, and therefore not necessary for such map-building12.

He also explored the influence of a bat's social world. When he put a companion bat into the flight room, he discovered that the monitored bat had 'social place cells' that track the companion's position13. He'd imagined that such cells must exist somewhere in the brain—bats obviously need to know where their fellow bats are, as well as their predators—but was not expecting they would necessarily show up inside the hippocampus. He is now monitoring how the brains of two or three bats register the social interaction of up to ten companion bats living together in the large flight room for several months.

But Ulanovsky's burning question was how this set of navigation cells would perform outside a flight room, during more natural behaviour. It would be impossible to monitor the positions of bats in the wild—cameras would be no use because the bats' ranges are too large, and GPS would not give high enough resolution—so Ulanovsky decided that an artificial tunnel was the best option.

As a bat flies through the 200-metre tunnel, he can monitor its exact position using a tiny signalling device on the bat itself and a suite of 15 antennas placed at intervals outside the structure to pick up its radio transmissions. Each antenna sends its computed distance from the signalling tag by Wi-Fi to a workstation at the tunnel entrance, where the full 3-D movement of the bats is recreated. The whole set-up cost around 900,000 Israeli shekels (US$250,000) to construct.

From the bats' point of view, flapping through the tunnel is much easier than a 15-kilometre night-time foray to distant fruit trees. But Ulanovsky's team has tried to recreate some of the features that the brain uses as navigational aids. Graduate student Tamir Eliav collected a variety of objects and scattered them at intervals along the tunnel for the bats to use as fixed points in their internal map. Walking along the tunnel's length in the low glow of a dim LED strip light, past an old chest of drawers and a rusting bicycle rack, feels like being in an art installation.



A neural logger designed for wireless recording of neurons in flying bats. Credit: David Vaaknin for Nature

Since the inaugural flight in March 2016, Ulanovsky and his students have collected data from more than 200 neurons across different bats. These early data hint at interesting insights. For example, Ulanovsky found that a single cell would fire at one location in a small area but also at a quite different location in a large area, indicating that place cells might represent multiple spatial scales, not just one particular scale.

Researchers hadn't been able to spot this pattern in experiments in small enclosures. Ulanovsky needs more data to confirm this, but it would be in line with the predictions of some theoreticians. "If place cells all had small, laboratory-sized place fields, there would not be enough neurons in the hippocampal area to individually cover the great distances that bats travel," says Ulanovsky, "so it makes sense that some place cells respond to multiple scales."

Tunnel vision

That's motivated him to design a bigger and better tunnel. Earlier this year, a private sponsor provided half of the 9 million shekels needed to build a kilometre-long tunnel with more densely positioned, wired antennas. This will allow measurement of even larger place fields, with more precise 3-D localization. This tunnel will have a 15-metre side branch to allow the scientists to study how the same neurons respond to short and long flights, and how the brain stitches together these two scales. Air conditioning will allow experiments to run throughout the blistering summer.

The tunnel and its once-wild bats represent a useful halfway house between the real world and the lab, says Angelaki, who researches spatial navigation and decision-making in the brains of mice and monkeys.

"Behavioural neuroscientists like myself are increasingly realizing how important it is to move away from overtrained lab-animal brains," she says. In typical lab experiments, animals are trained in a very specific, usually unnatural, task. "That may not have anything to do with how that animal has evolved brain connectivity to optimize foraging in the wild," she says.

Like others around the world, Angelaki's lab is starting to use neural loggers to monitor more natural rodent behaviour, such as foraging for food scattered in their enclosures. She predicts that more researchers will start setting up their experiments with an eye on the natural world. "Over the next five years or so, results will start to emerge and there will be a big change in neuroscience practice," she says.

However, as Moser notes, Ulanovsky's bats aren't yet doing anything as clever as finding a fruit tree in the wild. "It doesn't take much thought to fly up and down a tunnel," he says. So Ulanovsky is nursing an even bigger mind-reading ambition. He is seeking funding for a maze 40 metres wide and 60 long—a little under half the size of a football pitch—to test how bat brains represent more complex environments, then plan and make decisions about how to navigate them.

The maze will be made up of interconnected tunnels in which the bat won't always be able to see its goal (usually a food treat such as a piece of banana). It will instead have to rely on memory in its cognitive map. Ulanovsky has a series of increasingly complex experiments in mind—setting up multiple goals, for example, or suddenly blocking a path that the bat had memorized. He has questions about how bats choose between several goals, or recompute a path, or how cells respond when a bat loses its way. "Do the vectors in the brain start rotating wildly?" he wonders. "These are all fascinating questions to which we have no answers."

And the bats are obliging subjects. On a good day in the tunnel, a bat can soar and wheel for thousands of metres before taking a break for its banana. "They are misunderstood creatures," says Ulanovsky, standing at the end of the tunnel and gazing at a just-landed bat with obvious tenderness. "And they will help science."

Provided by Weizmann Institute of Science

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