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Off the grid: Environmental novelty changes hippocampal firing patterns

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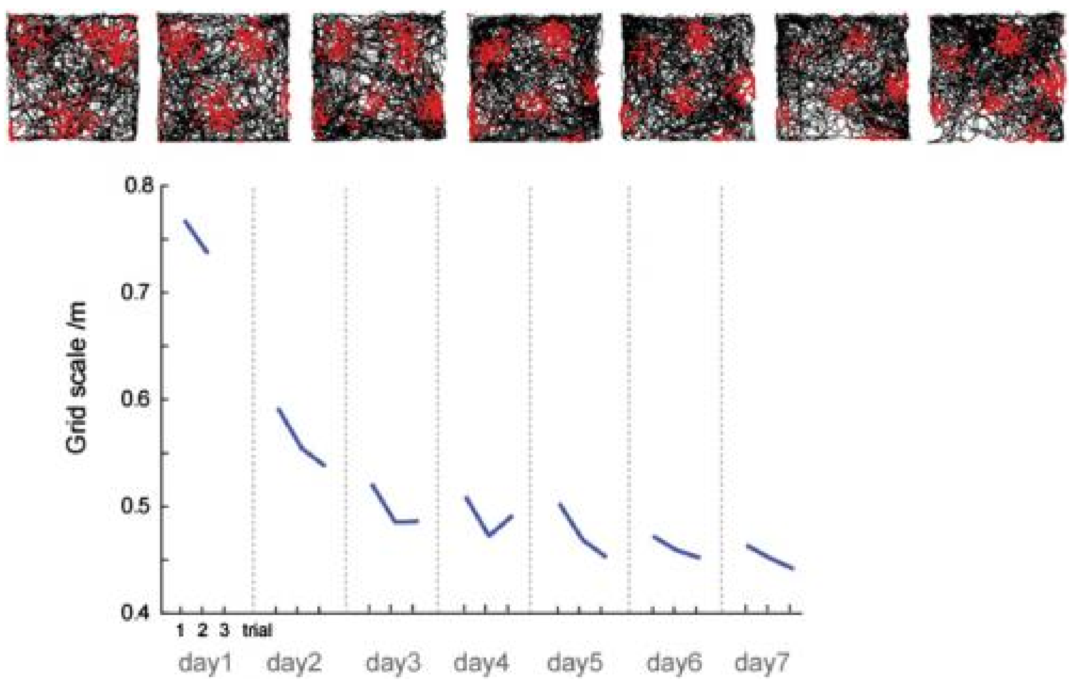

Example of a large novelty-induced increase in grid scale recorded from an animal that was not included in the main dataset (the novel arena experienced by this animal was placed in a different room from the familiar arena). The cell was present on all 7 recording days and was recorded in three novel trials per day (in addition to 2 familiar trials). The graph shows the scale of the grid in each of the three novel trials on each day (third novel trial on the first day was lost due to data corruption). The scale on the first trial is ~77 cm vs. a familiar scale (not shown) of ~42 cm. As well as a day-to-day reduction in the scale, a tendency for a reduction in the scale between adjacent trials on the same day is evident. (Upper) Unprocessed raw spike plots show the first novel trial of each day. The black lines indicate the rat’s path in a 1-m square arena, and the red points indicate superimposed action potentials. Copyright © PNAS,

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(Medical Xpress)—The brain's two hippocampal formations – one in each hemisphere's temporal lobe, medial to the inferior horn of the lateral ventricle and typically referring to the dentate gyrus, the hippocampus proper (the cornu ammonis), and the subicular cortex – are known to play essential roles in both representing an animal's location and in updating those representations by detecting novelty in the environment. While location representation processes are understood, however, those by which these representations are created and updated have remained elusive. Recently, scientists at University College London have shown that environmental novelty causes the spatial firing patterns of grid cells in the medial entorhinal cortex of freely-moving rodents to expand in scale and reduce in regularity, reverting to their usual scale as the environment again becomes familiar. The researchers conclude that grid expansion provides a potential mechanism for novelty signaling and may enhance the formation of new hippocampal representations, and that the subsequent slow reduction in scale provides a potential familiarity signal.

The research team faced a number of challenges in their study, Dr. Caswell Barry tells *Medical Xpress*. "In general, the biggest problem with this type of work is recording the neurons you are interested in," he notes. "Our system, in common with other labs, is to use bundles of very fine wires that are slowly moved through the brain region of interest. As the tips of the wires move past cells in the brain we see their electrical activity come and go. The trick is finding the right type of cell." In this study, the right cells were grid cells.

"Grid cells are remarkable – in fact, stunning," Barry adds. "For some time, we've known about cells in the brains of animals and humans that seem to mark out places in the world. The first examples, discovered in the 1970s, were for obvious reasons called place cells." A given place cell will typically fire in a single place in the animal's environment, so every time that animal goes near that place the cell responds. Different place cells have different preferred spots in the environment – so wherever the animal goes, some are always active. "Grid cells, on the other hand, discovered in 2005, also have spatial firing fields – but each grid cell will have multiple spots in the environment where it is active," Barry explains. "When you plot these points they form a very regular hexagonal pattern that covers the animal's world. This is pretty remarkable, because the animal's behavior is not regular – it runs around pretty randomly, but deep in the entorhinal cortex, these cells track its position using a coordinate system." That system is reminiscent of grid lines on a map, giving these cells their name.

"But I digress," Barry continues. "The hard thing about this experiment was that we wanted to record the same grid cells for several consecutive days, ideally up to one week. We wanted to do this because what was unclear was how that regular grid pattern forms – specifically, does it just appear the first time the animal runs across that part of the environment, or does it take some learning? So on consecutive days we started by recording grid cells and at the same time exposing the animals to a novel environment – one they hadn't been in before. On each day we put the animal in the same environment several times for 20 minutes at a time, and we repeated this on consecutive days." The result was a picture of how grid cell activity changes as the animal learns about its world.

"Just to be clear," Barry emphasizes, "the hard point here is keeping the wires we use to record next to the same cell. The sizes we're dealing with are tiny – the wires are 12-17 microns across and the cells not much bigger – so even a small movement will be problematic." This problem is compounded by the need to record from two brain regions at the same time, so the researchers also had to keep two sets of wires in place.

The important finding, Barry stresses, is that, completely unexpectedly, the scale of the grid pattern (the distance between neighboring firing fields) is initially much larger in the novel environment than it is in the familiar environment. "Indeed, as the environment becomes familiar over several days, the pattern shrinks down until the once novel environment is fully familiar. You really need those consecutive recordings to do this – it would be hard to capture the effect by looking at different times in different animals." Barry points out that this is also the case with place cells, despite their showing a much smaller effect.

"I think the key thing we did was to recognize that there had been no clear attempts to understand how firing developed in a novel environment," Barry reflects. "There are many models of grid cell formation that in their purest form would suggest that the firing patterns should appear in a novel environment just as they do in a familiar environment. However, this doesn't appear to be the case, and so probably requires some rethinking. Similarly," he adds, "because the grid firing pattern looks so regular and stable in a familiar environment, I think many researchers had hoped that it was constant metric for space, probably used to figure out distances travelled. The fact that the scale can change as we've shown - does not sit well with this view."

If grids in different parts of the entorhinal cortex expand by different amounts, this will effectively move them out of register with each other. The hippocampus, which is downstream from the entorhinal cortex, would be able to respond to this mismatch by forming a new memory. At the same time, however, the hippocampus or other brain regions that are able to compare the sizes of different grid scales, or are able to compare the scale of the expanded grid with its native size, can infer how novel an environment is from the magnitude of the mismatch in scales. "We want to test this by using environments that are very different or actually quite similar to ones that an animal has previously seen, so something really new might create a very large expansion."

Moving forward, says Barry, the team's next step will be to understand how the entire population of grid cells responds to novelty. "For example," he illustrates, "do they all increase in size by the same amount, or do some change by more than others? This is important for several reasons: In the first instance it might tell us if the animal's internal sense of scale will be changed, so people anecdotally reporting that when travelling a new route is feels shorter than a familiar route could potentially be explained by grid expansion. More importantly, if grids all change scale by differing amounts, it might function as a signal to the hippocampus, part of the brain that stores memories, that the animal has moved somewhere new and so needs to start forming new memories about the place it is in. If this is the case it would be very exciting, since we'd be looking at a trigger for new memories."

The scientists also want to understand what neural mechanisms control the grid expansion. "In some animals the grids expand by more than others," Barry explains, "so we want to identify the signal that controls this, as well as how gain is modulated. What have some ideas, one is that acetylcholine – a chemical released in the brain in response to novelty and when new memories need to be formed – might be able to change the grid scale."

Barry notes that other areas of research might benefit from their results. "This finding has a general implication for how we perceive and remember space. Potentially is could be important for how we think about designing maps and complex spaces, such as buildings. More generally," he concludes, "it helps us work towards one of the big goals of neuroscience: understanding how memories are formed, stored and recalled."

More information: Grid cell firing patterns signal environmental novelty by expansion, *PNAS*, October 23, 2012, vol. 109 no. 43, 17687–17692, doi:10.1073/pnas.1209918109

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