

reward¹⁵. Much work still needs to be done to understand how, when and where CB₂ receptors act to control cocaine intake.

In summary, Xi *et al.*⁷ suggest that previous notions of CB₂ receptors being irrelevant in the context of neuronal signaling are now 'up in smoke', and a more nuanced view of these receptors in brain function is warranted. These findings should spur efforts to determine just how wide-ranging their involvement in brain function is and to understand their precise mode of action.

COMPETING FINANCIAL INTERESTS

The author declares no competing financial interests.

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Coming up: in search of the vertical dimension in the brain

Francesco Savelli & James J Knierim

How does the brain represent space as a terrestrial animal moves in three dimensions? A study suggests that the vertical dimension is encoded with less precision than the horizontal plane.

An astronaut on board the Space Shuttle, in a moment of free time, begins to explore three-dimensional movement without the constraints of gravity. She pitches her body backward, and as her feet leave the floor, she is amused by the perception of gradually turning upside-down. When her feet are approximately 45° from the ceiling, however, she suddenly experiences a compelling illusion of three-dimensional reorientation. She no longer feels upside-down, but instead perceives the ceiling as now being the floor, herself as being right-side up and the entire chamber as now being turned upside-down. Clearly, her brain did not like the idea of being upside-down and it rotated her perception of the world instead! As this common experience of astronauts illustrates, our brains have evolved to navigate and move primarily along two-dimensional, horizontal surfaces. When we move in three dimensions, strange things can happen to our spatial perception. But these perceptions are not confined to the exotic experiences of space travel. Everyday life takes place over a manifold of vertically displaced levels. In this issue, Hayman *et al.*¹ find that certain brain regions process information about one's location along the vertical axis of space differently than the horizontal axes, thereby producing a strong anisotropy in the representation of three-dimensional space.

Over the course of a century, behavioral studies have shown that rodents keep track of

their location and memorize the spatial layout (map) of a familiar environment. This memory is critically dependent on the hippocampus, a brain region that is necessary for solving certain navigation tasks. The hippocampus is also thought to serve as a unitary framework in which non-spatial inputs are organized to support contextual learning and episodic memories². Over the last 40 years, neurophysiological studies in freely moving rats have elucidated many aspects of the neural processing underlying spatial cognition. Two classes of cells, place cells of the hippocampus and grid cells of the medial entorhinal cortex (MEC), are of particular interest here. On a horizontal surface, place cells fire in spatially confined regions of an environment (place fields). Grid cells, in contrast, fire in multiple place fields that are evenly spaced and form a regular hexagonal (or triangular) grid that tessellates the entire floor of any environment in a patchwork of equilateral triangles. Grid cells are thought to represent an infinite metric representation of space that is primarily computed through path integration (that is, the integration of self-motion cues) and anchored to salient environmental landmarks to generate an allocentric spatial map. This metric resource could then be conveniently tapped by the hippocampus place cell system, thanks to the prominent direct projections from MEC to this area. However, almost all of this diverse body of work has been concerned with spatial behavior on horizontal surfaces and tracks, and only a few studies^{3–9} have explored three-dimensional spatial orientation and mapping.

Hayman *et al.*¹ studied the manner by which place cells and grid cells represent

three-dimensional space in two tasks that are representative of how the vertical dimension is experienced by terrestrial animals. In one apparatus, a rat climbed along a vertical wall from which regularly spaced pegs protruded to provide footholds. In a second apparatus, the rat shuttled up and down a track shaped as a vertical helix (a spiral stairway) comprising five or six coils of identical diameter. The primary question was whether the place cells and grid cells represented the vertical axis (*z*) in the same way as the two horizontal axes (*x* and *y*). The authors found that, on the pegboard wall, place cells developed fields that were much more elongated vertically than would be expected from the typical field shape expressed on the horizontal platform (**Fig. 1a**). As a result, place cell firing on the wall conveyed much less information about the rat's height on the wall than about its horizontal displacement. However, some vertical information was retained, as firing rates were modulated by height. Place fields therefore appear to be shaped in three-dimensional space much like rugby balls standing on end, whose vertical sections were sampled on the wall. This phenomenon was even more marked in the recordings from grid cells; instead of developing a vertical grid, these cells produced a collection of vertical stripes that spanned the vertical extent of the wall even more broadly than did place cell fields. The grid fields seemed to grow vertically as columns rooted in the vertices of the hexagonal grid that is normally expressed in the horizontal plane (**Fig. 1b**).

The experiment on the helical track produced results that were largely consistent with this interpretation. Place fields and grid fields mostly

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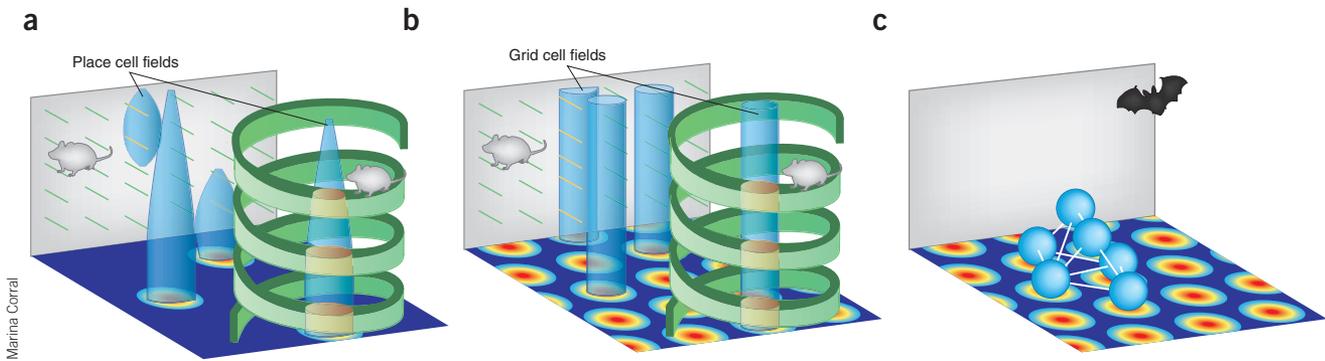


Figure 1 How does the hippocampal formation represent three-dimensional space? **(a,b)** Recordings from hippocampal place cells **(a)** and medial entorhinal grid cells **(b)** show that three-dimensional space is represented anisotropically, with the location along the *z* axis encoded with less precision than the location along the *x* and *y* axes. This anisotropy is particularly marked in the grid cells. **(c)** Future experiments in flying animals, such as bats, may reveal whether animals that move in true three-dimensional volumes encode the three axes isotropically. For example, the grid fields may populate a tetrahedral lattice, which is the natural generalization of the equilateral triangular grid. Alternative crystal-like structures, such as a lattice in which the same grid is repeated at different elevations, are also possible.

repeated their firing patterns on each coil (lap) as the rats moved through the apparatus. Place cells again proved to be more sensitive to height than grid cells in that they had less vertically elongated fields. It seems that the helix track might have 'intercepted' the grid cell's same columns or place cell's same rugby ball at varying heights. However, there are alternative explanations derived from the results of other laboratories. In a horizontal spiral track, place cells were found to often maintain a firing region in corresponding positions of each lap while resizing this region in lockstep with the increasing (or decreasing) size of each consecutive lap¹⁰. This phenomenon suggests that hippocampal cells have the ability to recognize and encode recurring similarities in the apparatus as well as in the journey of the animal^{11,12}. Substitute helix for spiral and what you get is pretty much the helical apparatus results from Hayman *et al.*¹, although grid cells were not investigated in the spiral¹⁰. Future experiments could verify whether the helix results could be explained as a form of pattern recognition or generalization over-ruling 'pure' space coding in the combined grid-place cell system. Another potential explanation, which is not mutually exclusive, comes from the boundary vector cell model, which emphasizes the importance of allocentric direction and distance to a set of prominent boundaries in forming spatial representations¹³. On the spiral and helix tracks, each time the rat completes a 360° circuit, it is facing the same direction with the nearly identical boundaries of the track to its left and right on each lap. The boundary vector cell model would then predict the firing patterns seen in these studies, at least to a first approximation, as well as the results of another study in which a track was shifted both horizontally and vertically in an environment⁷.

In conclusion, the authors found the three-dimensional encoding of place cells and grid

cells to be anisotropic. This finding can be plausibly explained by a severe limit on the ability of rats' internal path integration system to process the vertical dimension of space. This limit raises further questions. For example, would a rat be able to discriminate between different heights in similar conditions if no external cues were available to compensate for the apparent failure of vertical path integration? Would grid cells 'learn' to make true three-dimensional grids if the rat had enough motivation and training to accomplish such a discrimination?

The diminished information about height contrasts with a particular study of head direction cells, whose activity is a neural correlate of the direction pointed by the animal in the horizontal plane (yaw) irrespective of its position in space. These cells maintain their directional tuning when the rat moves from the floor up onto a wall as if the wall were a natural extension of the floor^{5,9}, providing precisely the directional signal that path integration along the vertical dimension is expected to require. In these studies, however, the rats kept their heads and bodies primarily parallel to the surface of the wall. In contrast, the rats on the pegboard track of Hayman *et al.*¹ kept their bodies and heads primarily oriented relative to the real floor (that is, relative to gravity). Notably, when rats are completely upside-down, their head direction signals become corrupted, perhaps as a neural correlate of the reorientation illusion experienced by our space traveler above⁹. Keeping the head stable relative to the gravitational plane may be a prerequisite for stable directional coding, with the consequence being that the normal path integration mechanisms that work so well during movement in the horizontal plane are unable to track motion accurately in the vertical axis under normal conditions.

A neuroethological perspective on the brain's representation of three-dimensional space should inform future investigations. Although the three-dimensional spatial encoding that Hayman *et al.*¹ found was anisotropic, the same could be said of the typical three-dimensional behavior of the animal studied: the rat is a terrestrial, non-arboreal, non-flying animal. Animals that spend a substantial part of their life moving seamlessly in three-dimensional space are ideal candidates for exploring whether the hippocampus and MEC can ever create an isotropic, three-dimensional representation of space (**Fig. 1c**). Grid cells and place cells have been documented in echolocating, walking bats (ref. 14 and M.M. Yartsev, M. Witter & N. Ulanovsky. *Soc. Neurosci. Abstr.* **203.15**, 2010). Perhaps the answer to this question will be soon delivered by wireless recordings in freely flying individuals of such species.

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